Meeting of the Advisory Committee on Immunization and Vaccines-related Implementation Research (IVIR-AC)

MICROSOFT TEAMS - VIRTUAL MEETING
WHO HEADQUARTERS, GENEVA, SWITZERLAND
13-16 February 2023
About the IVIR-AC pink book

This booklet contains key background documents for the meeting of the Advisory Committee on Immunization and Vaccines-related Implementation Research (IVIR-AC) 13-16 February 2022

This book will be published after the IVIR-AC meeting at the following link

https://www.who.int/groups/immunization-and-vaccines-related-implementation-research-advisory-committee
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**Current IVIR-AC – Advisory Committee Members**

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<th>Institution</th>
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<tr>
<td>Walter Orenstein (Chair)</td>
<td>Professor, Emory Global Health Institute, Emory University, Atlanta, <strong>United States of America</strong></td>
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<tr>
<td>Rakesh Aggarwal</td>
<td>Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, <strong>India</strong></td>
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<tr>
<td>Habib Hasan Farooqui</td>
<td>Additional Professor, Public Health Foundation of India, Delhi, <strong>India</strong></td>
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<tr>
<td>Alexandra Hogan</td>
<td>School of Population Health, University of New South Wales, Sydney, <strong>Australia</strong></td>
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<tr>
<td>Stefan Flasche</td>
<td>Centre for Mathematical Modelling of Infectious Diseases (CMMID), London School of Hygiene &amp; Tropical Medicine, London, <strong>United Kingdom of Great Britain and Northern Ireland</strong></td>
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<tr>
<td>Sun-young Kim</td>
<td>Global Health, School of Public Health, Seoul National University, Seoul, <strong>Republic of Korea</strong></td>
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<tr>
<td>Julie Leask</td>
<td>Professor, Susan Wakil School of Nursing and Midwifery, Sydney Nursing School, Faculty of Medicine and Health, Camperdown NSW 2050, Sydney, <strong>Australia</strong></td>
</tr>
<tr>
<td>Name</td>
<td>Affiliation</td>
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<tr>
<td>Paula M. Luz</td>
<td>Professor, Evandro Chagas Clinical Research Institute (IPEC/FIOCRUZ)</td>
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<tr>
<td>Dafrossa C. Lyimo</td>
<td>Programme Manager, Immunization and Vaccines Development</td>
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<tr>
<td>William Moss</td>
<td>International Vaccine Access Center, Johns Hopkins Bloomberg School of</td>
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<tr>
<td>Victoria Nankabirwa</td>
<td>Professor, Department of Epidemiology and Biostatics</td>
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<tr>
<td>Virginia Pitzer</td>
<td>Associate Professor, Yale School of Public Health, P.O. Box 208034, 60</td>
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<tr>
<td>Sheetal Silal</td>
<td>Centre for Tropical Medicine and Global Health, Oxford</td>
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<tr>
<td>Xuan-yi Wang</td>
<td>Research Scientist, Shanghai Medical College, Fudan University,</td>
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<tr>
<td>Joseph Wu</td>
<td>Professor, Division of Epidemiology and Biostatistics</td>
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IVIR-AC Terms of References

The IVIRAC Terms of References can be accessed at the following link:

https://www.who.int/publications/m/item/terms-of-reference-for-the-immunization-and-vaccines-related-implementatiResearch-advisory-committee-(ivir-ac)
DOI and Confidentiality undertakings
DECLARATION OF INTERESTS FOR WHO EXPERTS

WHO's work on global health issues requires the assistance of external experts who may have interests related to their expertise. To ensure the highest integrity and public confidence in its activities, WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to a potential conflict of interest related to the subject of the activity in which they will be involved.

All experts serving in an advisory role must disclose any circumstances that could represent a potential conflict of interest (i.e., any interest that may affect, or may reasonably be perceived to affect, the expert's objectivity and independence). You must disclose on this Declaration of Interests (DOI) form any financial, professional or other interest relevant to the subject of the work or meeting in which you have been asked to participate in or contribute towards and any interest that could be affected by the outcome of the meeting or work. You must also declare relevant interests of your immediate family members (see definition below) and, if you are aware of it, relevant interests of other parties with whom you have substantial common interests and which may be perceived as unduly influencing your judgement (e.g. employer, close professional associates, administrative unit or department). Please note that not fully completing and disclosing all relevant information on this form may, depending on the circumstances, lead WHO to decide not to appoint you to WHO advisory bodies/functions in the future.

Please complete this form and submit it to WHO Secretariat if possible at least 4 weeks but no later than 2 weeks before the meeting or work. You must also promptly inform the Secretariat if there is any change in this information prior to, or during the course of, the meeting or work. All experts must complete this form before participation in a WHO activity can be confirmed. Please note that not fully completing and disclosing all relevant information on this form may, depending on the circumstances, lead WHO to decide not to appoint you to WHO advisory bodies/functions in the future.

Answering "Yes" to a question on this form does not automatically disqualify you or limit your participation in a WHO activity. Your answers will be reviewed by the Secretariat to determine whether you have a conflict of interest relevant to the subject at hand. One of the outcomes listed in the next paragraph can occur depending on the circumstances (e.g., nature and magnitude of the interest, timeframe and duration of the interest).

The Secretariat may conclude that no potential conflict exists or that the interest is irrelevant or insignificant. If, however, a declared interest is determined to be potentially or clearly significant, one or more of the following three measures for managing the conflict of interest may be applied. The Secretariat (i) allows full participation, with public disclosure of your interest; (ii) mandates partial exclusion (i.e., you will be excluded from that portion of the meeting or work related to the declared interest and from the corresponding decision making process); or (iii) mandates total exclusion (i.e., you will not be able to participate in any part of the meeting or work).

All potentially significant interests will be disclosed to the other participants at the start of the activity and you will be asked if there have been any changes. A summary of all declarations and actions taken to manage any declared interests will be published in resulting reports and work products. Furthermore, if the objectivity of the work or meeting in which you are involved is subsequently questioned, the contents of your DOI form may be made available by the Secretariat to persons outside WHO if the Director-General considers such disclosure to be in the best interest of the Organization, after consulting with you. Completing this DOI form means that you agree to these conditions.

If you are unable or unwilling to disclose the details of an interest that may pose a real or perceived conflict, you must disclose that a conflict of interest may exist and the Secretariat may decide that you be totally recused from the meeting or work concerned, after consulting with you.

Name:
Institution:
Email:

Date and title of meeting or work, including description of subject matter to be considered (if a number of substances or processes are to be evaluated, a list should be attached by the organizer of the activity):

Please answer each of the questions below. If the answer to any of the questions is "yes", briefly describe the circumstances on the last page of the form.

The term "you" refers to yourself and your immediate family members (i.e., spouse (or partner with whom you have a similar close personal relationship) and your children). "Commercial entity" includes any commercial business, an industry association, research institution or other enterprise whose funding is significantly derived from commercial sources with an interest related to the subject of the meeting or work. "Organization" includes a governmental, international or non-profit organization. "Meeting" includes a series or cycle of meetings.
EMPLOYMENT AND CONSULTING

Within the past 4 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of the meeting or work?

1a Employment
Yes ☐ No ☐

1b Consulting, including service as a technical or other advisor
Yes ☐ No ☐

RESEARCH SUPPORT

Within the past 4 years, have you or has your research unit received support from a commercial entity or other organization with an interest related to the subject of the meeting or work?

2a Research support, including grants, collaborations, sponsorships, and other funding
Yes ☐ No ☐

2b Non-monetary support valued at more than US $1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.)
Yes ☐ No ☐

Support (including honoraria) for being on a speakers bureau, giving speeches or training for a commercial entity or other organization with an interest related to the subject of the meeting or work?

INVESTMENT INTERESTS

Do you have current investments (valued at more than US $5,000 overall) in a commercial entity with an interest related to the subject of the meeting or work? Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified and on which you exercise no control.

3a Stocks, bonds, stock options, other securities (e.g., short sales)
Yes ☐ No ☐

3b Commercial business interests (e.g., proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company)
Yes ☐ No ☐

INTELLECTUAL PROPERTY

Do you have any intellectual property rights that might be enhanced or diminished by the outcome of the meeting or work?

4a Patents, trademarks, or copyrights (including pending applications)
Yes ☐ No ☐

4b Proprietary know-how in a substance, technology or process
Yes ☐ No ☐

PUBLIC STATEMENTS AND POSITIONS (during the past 3 years)

5a As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of the meeting or work, for a commercial entity or other organization?
Yes ☐ No ☐

5b Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of the meeting or work?
Yes ☐ No ☐

ADDITIONAL INFORMATION

6a If not already disclosed above, have you worked for the competitor of a product that is the subject of the meeting or work, or will your participation in the meeting or work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage?
Yes ☐ No ☐

6b To your knowledge, would the outcome of the meeting or work benefit or adversely affect interests of others with whom you have substantial common personal, professional, financial or business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)?
Yes ☐ No ☐

6c Excluding WHO, has any person or entity paid or contributed towards your travel costs in connection with this WHO meeting or work?
Yes ☐ No ☐
6d Have you received any payments (other than for travel costs) or honoraria for speaking publicly on the subject of this WHO meeting or work?  
Yes □ No □

6e Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence?  
Yes □ No □

7. **TOBACCO OR TOBACCO PRODUCTS (answer without regard to relevance to the subject of the meeting or work)**

   Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity?  
Yes □ No □

**EXPLANATION OF "YES" RESPONSES:** If the answer to any of the above questions is "yes", check above and briefly describe the circumstances on this page. If you do not describe the nature of an interest or if you do not provide the amount or value involved where relevant, the conflict will be assumed to be significant.

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<tr>
<th>Nos. 1 - 4:</th>
<th>Type of interest, question number and category (e.g., Intellectual Property 4.a copyrights) and basic descriptive details.</th>
<th>Name of company, organization, or institution</th>
<th>Belongs to you, a family member, employer, research unit or other?</th>
<th>Amount of income or value of interest (if not disclosed, is assumed to be significant)</th>
<th>Current interest (or year ceased)</th>
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| Nos. 5-6: | Describe the subject, specific circumstances, parties involved, time frame and other relevant details |

**CONSENT TO DISCLOSURE.** By completing and signing this form, you consent to the disclosure of any relevant conflicts to other meeting participants and in the resulting report or work product.
DECLARATION. I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge.

Should there be any change to the above information, I will promptly notify the responsible staff of WHO and complete a new declaration of interests form that describes the changes. This includes any change that occurs before or during the meeting or work itself and through the period up to the publication of the final results or completion of the activity concerned.

Date: ___________________  Signature________________________________
Attachment 1

Memorandum of Agreement
Terms and Conditions for Temporary Advisers

I, the undersigned, in accepting to act as a Temporary Adviser to the World Health Organization (WHO), agree to the following:

1. RELATIONSHIP BETWEEN THE PARTIES

The execution of the work as Temporary Adviser does not create any employer/employee relationship as between WHO, on the one hand, and me and/or persons claiming under me, on the other hand. Thus, WHO shall not be liable to me or any other person whatsoever for any damage, loss, accident, injury, illness and/or death sustained by me in connection with, or as a result of, my assignment as Temporary Adviser to WHO, including travel.

2. TRAVEL COSTS, PER DIEM AND INCIDENTALS

I understand that my travel, per diem and incidentals will be paid by WHO, in accordance with WHO rules described in Annex 1 attached hereto.

3. CONFLICT OF INTERESTS

I agree to truthfully complete the Declaration of Interests for WHO Experts and disclose any circumstances that may give rise to a real, potential or apparent conflict of interest in relation to my work as Temporary Adviser. I will ensure that the disclosed information is correct and will truthfully declare that no other situation of real, potential or apparent conflict of interest is known to me. I undertake to promptly inform WHO of any change in these circumstances, including if an issue arises during the course of my work as Temporary Adviser. I understand and agree that this Memorandum of Agreement may be cancelled by WHO if WHO determines that the information disclosed by me in the Declaration of Interests requires modification or cancellation of the invitation extended to me to serve as Temporary Adviser to WHO.

4. INSURANCE

I agree that the insurance arrangements set forth below are being made by WHO without any prejudice whatsoever to section 1 above. Thus, I agree that WHO shall not be liable for any damage, loss, accidents, injury, illness and/or death sustained by me in connection with, or as a result of, my assignment as Temporary Adviser to WHO, including travel.

While travelling, my baggage and personal effects will be insured by WHO up to an amount of US$ 5000 (five thousand United States dollars). This insurance covers all hand baggage carried by me with the exception of documents, travel tickets, currency/cash/travellers cheques, stamps, stamped paper, identity papers, household goods and objets d'art (art works). Personal computers and accessories are also not included in WHO’s personal baggage insurance cover unless it is noted on the travel authorization that a personal computer is required during the journey. Laptops must be hand-carried on board airplanes and not checked as registered baggage. Fees to replace stolen travel tickets, credit cards and official documents may be claimed under the insurance policy.
I understand that I will also be covered by an accident and emergency* insurance policy. (A description of the coverage pursuant to this insurance policy and an information booklet containing other information, including with regard to the procedure for submission and reimbursement of claims, are available on the website of Cigna http://www.cignahealthbenefits.com Under ‘Plan members’ the standard reference number 378/WHCPVE should be entered and on the next screen the standard date of birth 31/01/1977.)

I understand that the aforementioned insurance policy does not include general 'illness insurance' (medical insurance) for which I should obtain and maintain coverage under my national, institutional or private health insurance scheme, or from the insurance provider proposed by WHO in accordance with the following paragraph, that is valid in all locations in which I shall undertake the assignment on behalf of WHO.

I understand that I may purchase additional voluntary complementary insurance coverage directly from the insurance provider proposed by WHO, for compensation in case of death due to illness and medical expenses for general (non-emergency*) illness during the contract period, and that further information concerning the voluntary complementary insurance is available on the website of Cigna: http://www.cignahealthbenefits.com. Under ‘Plan members’ the standard reference number 378/WHCPVE should be entered and on the next screen the standard date of birth 31/01/1977.

I further understand that if I opt to purchase such additional voluntary complementary insurance, I must contact the insurance company directly and pay the applicable premiums for the whole contract period prior to the start date of the contract.

Finally, I understand, with regard to both (i) the accident and emergency* illness insurance policy, and (ii) the voluntary complementary insurance coverage, referred to herein that:

- all interactions relating to such insurance coverage shall be between the insurance company and myself, without the involvement of WHO.

- any insurance claims under either of the aforementioned policies must be submitted by me directly to the insurance company, which will review and process the claim without the involvement of WHO;

- WHO assumes no responsibility for non-payment by the insurance company of all or part of a claim that may be submitted by me; and

- WHO assumes no responsibility or liability with regard to any expenses which may be incurred by me in connection with any illness contracted in the location of my assignment with WHO which exceeds the amount of the insurance coverage (compulsory and/or voluntary) referred to in this letter or as a result of any failure on my part to ensure that I have adequate insurance coverage for general (non-emergency*) illness during the contract period.

* Note: “Emergency” (as used herein) means a life-threatening situation or situation where the patient must start treatment within 48 hours and for whom travel is not possible for medical reasons.
5. SMOKING POLICY

I understand and agree that smoking is not permitted in WHO premises or in any designated meeting areas outside WHO premises.

6. CONFIDENTIALITY UNDERTAKING

I undertake to exercise the utmost discretion in all matters relating to my assignment as Temporary Adviser to WHO. In this regard, I shall treat all information and documentation (in whatever format) to which I may gain access in connection with, or as a result of, my assignment as Temporary Adviser to WHO, as confidential and proprietary to WHO and/or parties collaborating with WHO, and agree to take all reasonable measures to ensure that such information and documentation (hereinafter jointly referred to as "Information"): 

i) is not used for any purpose other than the performance of my work as Temporary Adviser to WHO; and

ii) is disclosed and provided only to persons who have a need to know for the aforesaid purpose and are bound by like obligations of confidentiality and non-use as contained in this Memorandum of Agreement.

This undertaking does not cease upon completion of my work as Temporary Adviser. However, there shall be no obligation of confidentiality if and to the extent: (i) information is publicly available, or becomes publicly available through no fault of my own; or (ii) information was already known to me (as evidenced by written records) prior to its receipt by me; or (iii) information is received from a third party not in breach of an obligation of confidentiality.

I agree to promptly return any and all copies of the aforesaid information and documentation to WHO at the conclusion of my work as Temporary Adviser to WHO or upon earlier termination of this Memorandum of Agreement.

7. INDEPENDENCE

I agree to respect the impartiality and independence required of WHO. In this regard, I shall not seek or accept instructions regarding the work performed by me as Temporary Adviser to WHO from any Government or from any authority external to WHO.

8. RIGHTS

I agree that any and all rights in the work performed by me in connection with, or as a result of, my assignment as Temporary Adviser to WHO shall be exclusively vested in WHO. I hereby irrevocably and unconditionally assign all such rights to WHO and waive any moral rights attached to such work.

I understand and agree that WHO reserves the right (a) to revise such work, (b) to use it in a different way from that originally envisaged, or (c) not to use or publish it at all.
9. COMPLIANCE WITH WHO CODES AND POLICIES

By entering into this Memorandum of Agreement, I acknowledge that I have read, and hereby accept and agree to comply with, the WHO Policies (as defined below). In connection with the foregoing, I shall not engage in any conduct that would constitute a violation of the standards of conduct, as described in the WHO Policies. Without limiting the foregoing, I shall promptly report to WHO, in accordance with the terms of the applicable WHO Policies, any actual or suspected violations of any WHO Policies of which I become aware. For purposes of this Memorandum of Agreement, the term “WHO Policies” means collectively: (i) the WHO Code of Ethics and Professional Conduct; (ii) the WHO Policy on Sexual Exploitation and Abuse Prevention and Response; (iii) the WHO Code of Conduct for responsible Research; and (iv) the WHO Policy on Whistleblowing and Protection Against Retaliation, in each case, as amended from time to time and which are publicly available on the WHO website at the following link and at http://www.who.int/about/ethics/en/

10. ZERO TOLERANCE FOR SEXUAL EXPLOITATION AND ABUSE

WHO has zero tolerance towards sexual exploitation and abuse. In this regard, and without limiting any other provisions contained herein, I undertake (i) not to engage in any conduct that would constitute sexual exploitation or abuse as described in the WHO Policy on Sexual Exploitation and Abuse Prevention and Response; and (ii) to promptly report to WHO, in accordance with the terms of the Policy, any actual or suspected violations of the Policy of which I becomes aware.

11. ANTI-TERRORISM AND UN SANCTIONS; FRAUD AND CORRUPTION

I warrant for the entire duration of my assignment as Temporary Advisor that:
(i) I am not and will not be involved in, or associated with, any person or entity associated with terrorism, as designated by any UN Security Council sanctions regime, that I will not make any payment or provide any other support to any such person or entity and that I will not enter into any employment or subcontracting relationship with any such person or entity;
(ii) I shall not engage in any illegal, corrupt, fraudulent, collusive or coercive practices (including bribery and theft) in connection with the execution of this Memorandum of Agreement; and
(iii) I shall take all necessary precautions to prevent the financing of terrorism and/or any illegal corrupt, fraudulent, collusive or coercive practices (including bribery, and theft) in connection with the execution of this Memorandum of Agreement.

12. BREACH OF ESSENTIAL TERMS

I acknowledge and agree that each of the provisions of paragraphs 9, 10 and 11 hereof constitutes an essential term of this Memorandum of Agreement, and that in case of breach of any of these provisions, WHO may, in its sole discretion, decide to:

(i) terminate this Memorandum of Agreement, and/or any other contract concluded by WHO with me, immediately upon written notice to me, without any liability for termination charges or any other liability of any kind; and/or
(ii) exclude me from entering into any future contractual or collaborative relationships with WHO.
WHO shall be entitled to report any violation of such provisions to WHO’s governing bodies, other UN agencies, and/or donors.

13. USE OF WHO NAME AND EMBLEM
Without WHO’s prior written approval, I shall not, in any statement or material of an advertising or promotional nature, refer to this Memorandum of Agreement or my relationship with WHO, or otherwise use the name (or any abbreviation thereof) and/or emblem of the World Health Organization.

14. PUBLICATION OF AGREEMENT
Subject to considerations of confidentiality, WHO may acknowledge the existence of this Memorandum of Agreement to the public and publish and/or otherwise publicly disclose my name and general information with respect to my assignment as Temporary Advisor. Such disclosure will be made in accordance with WHO’s Information Disclosure Policy and shall be consistent with the terms of this Agreement.

15. SURVIVING PROVISIONS
Those provisions of this Memorandum of Agreement that are intended by their nature to survive its expiration or earlier termination shall continue to apply.

16. SETTLEMENT OF DISPUTES
Any matter relating to the interpretation or application of this Memorandum of Agreement which is not covered by its terms shall be resolved by reference to the laws of Switzerland. Any dispute relating to the interpretation or application of this Memorandum of Agreement shall, unless amicably settled, be subject to conciliation. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the parties or, in the absence of agreement, with the rules of arbitration of the International Chamber of Commerce. The parties shall accept the arbitral award as final.
17. PRIVILEGES AND IMMUNITIES OF WHO

Nothing in or relating to this Memorandum of Agreement shall be deemed a waiver, express or implied, of any of the privileges and immunities of WHO, whether under the Convention on the Privileges and Immunities of the Specialized Agencies approved by the General Assembly of the United Nations on November 21, 1947, or otherwise, and no provision of this Memorandum of Agreement shall be interpreted or applied in a manner, or to an extent, inconsistent with such privileges and immunities.

By signing this Memorandum of Agreement, I confirm that I accept my assignment as Temporary Adviser, in accordance with and subject to the terms and conditions contained in the invitation letter and this Memorandum of Agreement and its annexes

Place and date:

Name:

Signature:

Received by WHO:

Date: _______________ Signature: _______________

Dr Philipp Lambach
Medical officer
Initiative for Vaccine Research
Annex 1 to Attachment 1 - Memorandum of Agreement
Terms and Conditions for Temporary Advisers

TRAVEL COSTS, PER DIEM AND INCIDENTALS

WHO will be responsible for my airfare and/or first-class train fare from my place of residence
to the place of the work and return. In view of the financial stringencies being faced by WHO, I
agree to cooperate in reducing airfare costs through the use of cheapest available tickets on the
most economical route.

The standard of airline accommodation for which WHO will bear the cost is:

_The lowest available economy class ticket by the least expensive route, with the
condition it does not exceed the most direct itinerary by 4 hours or more._

Should I wish to upgrade my ticket, or change the airline or route, I may do so at my own expense,
but, in accordance with WHO travel policy, WHO's liability will not exceed the limits mentioned
above.

WHO will send me the travel authorization when WHO has received the counter-signed invitation
letter and signed Memorandum of Agreement and completed and signed Declaration of Interests
for WHO Experts, and is able to send me written notification that the information disclosed by me
in the Declaration of Interests does not require modification or cancellation of WHO's invitation.

In order to take advantage of the most competitive air fares, I will make reservations as quickly as
possible through the travel agency mentioned in the invitation letter.

"WHO will provide travel cancellation insurance in the event that I am unfit to travel due to
medical reasons and a ticket purchased cannot be changed or cancelled."

If I wish to travel by private car, I will ask WHO for specific authorization in advance. In such
event, the maximum amount to be reimbursed by WHO will be according to the UN official
mileage rate to and from the destination by the most direct route. I will advise WHO if I require
details of the amount to be reimbursed. I agree that evidence must be provided that travel by car
was in fact undertaken, together with the distance travelled.

SUBSISTENCE ALLOWANCE

WHO will pay me a daily subsistence allowance (DSA), according to the UN’s standard published
DSA rates for the location concerned, for the duration of any travel during my assignment and for
travel time from my place of residence to the place of the work and return, except for the last day
of travel (for which no daily subsistence allowance will be paid). An allowance of 50% of the per
diem applicable to the city of departure will be paid to travellers for an overnight stay on an
airplane. An additional travel allowance of US$ 47* per city of departure and arrival to cover
miscellaneous expenses and local transport will also be paid. I agree and accept that the total
allowance as described herein is intended to cover all costs related to my assignment, such as
accommodation, meals and all other incidental expenses. Accordingly, charges for airport taxes,
ground transportation from airport to hotel or vice versa will not be separately reimbursed, and I
am not required to submit a travel claim.
WHO policy on the reimbursement of accommodation depends upon whether the traveller stays in a hotel, or other commercial establishment, or makes his or her own private arrangements and does not incur lodging costs. Travellers staying in a hotel will receive the full applicable DSA; travellers that do not incur expenses for lodging will receive 50% of the applicable DSA rate.

I agree to advise WHO which of the above accommodation options I decide upon and will provide details of my bank account if I would like the payment for DSA to be made to this account.

WHO HOTEL PROGRAMME

WHO has implemented a Preferred Hotel Programme in 20 cities:

In all of the above cities, WHO has selected and agreed rates with selected properties. WHO travellers going to any of these cities must stay at one of the preferred hotels:

The list of available hotels and descriptions at each location are accessible using the following link: https://hoteldirectory.lanyon.com/Login.aspx?authToken=6fc76fd9-fe20-47f0-88d4-e2c7bf10408f.

As a result of the preferential room rates in the selected hotels, travellers to these cities will receive an adjusted DSA.

SWITZERLAND

Applicable rates

WHO will pay a daily subsistence allowance (DSA), according to the official WHO daily subsistence allowance rates in force, at the date of the Travel, as per current policy, up to a maximum ceiling of CHF 3,000 per month, i.e. per consecutive periods of 30 calendar days. The DSA would then be applied at a rate of CHF 100 per extra day during my assignment and for travel time from my place of residence to Switzerland and return, except for the last day of travel (for which no DSA will be paid). An allowance of 50% of the DSA applicable to the city of departure will be paid to travellers for an overnight stay on an airplane. An additional travel allowance of US$ 47 per city of departure and arrival, and return* to cover miscellaneous expenses and local transport will also be paid.

Other provisions:

a. Only one month’s DSA will be advanced to me at a time. The following month’s DSA will only be advanced if I provide WHO, proof of accommodation charges incurred (such as copy of a hotel booking, proof of payment, or other suitable evidence) for the previous TR period.

b. Any excess DSA paid will be adjusted on the next Travel Request (TR).

c. The final month’s DSA will only be paid once accommodation receipts have been received by WHO, evidencing the DSA entitlement for all prior months.

d. Travel Claim(s) will be submitted if an adjustment to the previously paid amount on TR
needs to be made.

e. If DSA has been paid for the city where I am assigned primarily, DSA paid for any travel
to another duty station during the same period must be adjusted to ensure that no double
payment occurs, and DSA already paid must be deducted if I take leave for personal reasons
during the period.

I agree and accept that the total allowance as described above is intended to cover all costs related
to my assignment, such as accommodation, meals and all other incidental expenses. Accordingly,
charges for airport taxes, ground transportation from airport to hotel or vice versa will not be
separately reimbursed, and I am not required to submit a travel claim.

WHO policy on the reimbursement of accommodation depends upon proof of accommodation
charges incurred (such as copy of a hotel booking/commercial establishment, proof of payment,
or other suitable evidence) for the previous TR period. Or whether the traveller makes his or her
own private arrangements and does not incur lodging costs. Travellers staying in a hotel will
receive the full applicable DSA; travellers that do not incur expenses for lodging will receive 50%
of the applicable DSA rate.

* The travel allowance for New York is $ 78.
For a return trip, travel allowances are payable on both ways. e.g. departure Washington - $47,
- US$ 188)
Agenda and List of Participants
Meeting of the Advisory Committee on Immunization and Vaccines-related Implementation Research (IVIR-AC)

Microsoft Teams
Geneva, Switzerland
13 to 16 February 2023

Agenda

Background reading materials available at:
SharePoint page - IVIR-AC Meeting - 13 to 16 February 2023

Chair: Walt Orenstein

13 February

<table>
<thead>
<tr>
<th>Duration</th>
<th>Title</th>
<th>Content</th>
<th>Purpose</th>
<th>Proposed speaker</th>
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</thead>
<tbody>
<tr>
<td>12:00 - 12:05 5’</td>
<td>Opening of Meeting</td>
<td>• Update on global strategies and issues of relevance to WHO</td>
<td>For information</td>
<td>K. O’Brien, Director, Department of Immunization, Vaccines and Biologicals</td>
</tr>
</tbody>
</table>
| 12:05 - 12:15 10’ | Introduction/     | • Administrative issues
• Objectives of IVIR-AC meeting and outline of the 1st day       |                                | P. Lambach
W. Orenstein, Chair                                      |
<table>
<thead>
<tr>
<th>Time</th>
<th>Objective</th>
<th>Content</th>
</tr>
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</table>
| 12:15 - 12:25 10’ | Background | Priority questions of the WHO SAGE WG on COVID-19 vaccines currently include (a full list is provided in the background material)  
- Shifting vaccination priorities with high infection-derived immunity,  
- Cost-effectiveness of COVID-19 vaccines (compared to other vaccines) and  
- Impact of VoC (Variants of Concern) on vaccination priorities  
- How to include COVID-19 vaccines in routine immunization programmes  
- This session serves to discuss WHO-supported modelling efforts that have been made in follow-up to the last IVIR-AC meeting’s session on COVID-19 vaccine modelling  
- Three research groups have been funded and will present their progress and plans |
| 12:25 - 12:45 20’ | A flexible immunity model-based framework for evaluation of likely impacts of emerging variants and vaccines | Feedback from IVIR-AC is requested on the following questions:  
- Shifting vaccine priorities with high infection derived immunity  
- Assess the impact of Variants of Concern on vaccination priorities  
- Potential public health impact of a variant adapted booster?  
- Cost-effectiveness of COVID-19 vaccines (compared to other vaccines)  
- What is the cost-effectiveness of routine annual COVID-19 booster doses in different populations and age groups given high background infection exposure, immune waning and escape?  
- Future booster strategy – frequency/interval, priority population, CEA |

S. Flasche, A. Wilder-Smith, Y Sim, J. McVernon
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Details</th>
<th>Presenter(s)</th>
</tr>
</thead>
</table>
| 12:45-13:05 20’ | Prioritising vaccine deployment with high infection-derived immunity | • COVID-19 vaccination priorities are likely to change in settings with high infection-derived immunity compared to earlier in the pandemic; we are using mathematical modelling to investigate how vaccine deployment should be prioritised  
• Presentation of results from a global model of SARS-CoV-2 transmission and vaccination that are used to explore how vaccines should be prioritised now that there is a background of high infection-derived immunity  
• Feedback from IVIR-AC is requested on the following questions:  
  o Overall: How should vaccines be prioritised both locally and globally now that there has been a substantial amount of transmission (i.e. significant infection-derived immunity)?  
  o What are the current highest relevance questions that the model should be adapted to answer?  
• Q&A (clarifications) | R. Thompson, S. Moore, I. Bouros                                           |
| 13:05-13:25 20’ | Technical presentation 3                                                | • Assess how immunological history (prior infection and/or vaccination) and ongoing evolution influences optimal vaccine policy based on severity of infection and mortality  
• Assess how immune imprinting (e.g., variant specific history) and specific cross reactions between COVID-19 serotypes influences optimal vaccine policy  
• Feedback from IVIR-AC is requested on the following questions:  
  o What current policy questions could this model be adapted to answer?  
  o To what extent are country-specific simulations beneficial compared to more general models with sensitivity on key parameters (i.e., level of prior infection)? | A. Kraay, P. Martinez Vargas |
### Dengue disease impact and cost-effectiveness: Optimizing public health impact

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Description</th>
<th>Speaker(s)</th>
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</thead>
<tbody>
<tr>
<td>13:25-13:45 20’</td>
<td>Q&amp;A and Discussion</td>
<td>Expectations to IVIR-AC:</td>
<td>V. Pitzer, S. Silal, S. Flasche</td>
</tr>
<tr>
<td>13:45-13:50</td>
<td>Break</td>
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</tr>
<tr>
<td>13:50-14:00 10’</td>
<td>Rationale and Background</td>
<td>Following completion of TAK003’s Phase 3 trials, this vaccine is currently undergoing evidence review in preparation of policy issuance in Q4 2023</td>
<td>A. Wilder-Smith</td>
</tr>
<tr>
<td>14:00-14:15 15’</td>
<td>Technical presentation</td>
<td>Presentation:</td>
<td>R. Hanley, J. Shen</td>
</tr>
<tr>
<td>14:15-14:35 20’</td>
<td>Q&amp;A and Discussion</td>
<td>Questions to IVIR-AC:</td>
<td>P. Luz, J. Wu, S. Sillal</td>
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</tbody>
</table>

### Dengue disease impact and cost-effectiveness: Benefit-risk assessments

<table>
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<tr>
<th>Time</th>
<th>Session</th>
<th>Description</th>
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<tr>
<td>13:25-13:45 20’</td>
<td>Q&amp;A and Discussion</td>
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<td>13:45-13:50</td>
<td>Break</td>
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<tr>
<td>13:50-14:00 10’</td>
<td>Rationale and Background</td>
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<tr>
<td>14:00-14:15 15’</td>
<td>Technical presentation</td>
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<td>14:15-14:35 20’</td>
<td>Q&amp;A and Discussion</td>
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<tr>
<td>14:35 – 14:50</td>
<td>Information request from SAGE</td>
<td>Efficacy data and the negative efficacy data for serotypes 3 and 4. • epidemiological understanding of the serotype specific burden and force of infection, as well as the disease severity pyramid for the different serotypes in primary and secondary infection (as you mention) (and maybe infectivity) • interpreting the trial results (that I know your team are doing) • scenarios</td>
<td>A Wilder Smith</td>
</tr>
<tr>
<td>14:50 – 15:10</td>
<td>Q&amp;A and Discussion</td>
<td>Questions to IVIR-AC 1. Estimates of population-level and individual-level benefit/risk over 10 and 20 years, stratified by age of recipient, serostatus of recipient and by average transmission intensity in a setting. Transmission intensity is best quantified by average force of infection, though average seroprevalence in a specific age group (e.g. 11-year-olds) can be used as a proxy. A range of year-by-year serotype dominance scenarios should be examined, informed by surveillance data from a range of settings, as well as a range of vaccine efficacy (or lack of) by serotype and serostatus and serotype specific infectivity and disease severity. 2. Cost-benefit of vaccination programmes without pre-vaccination screening, or by pre-vaccination screening dependent upon seroprevalence in a specific age group (e.g. pre-vaccination screening in low seroprevalence settings, and no pre-vaccination screening in high seroprevalence settings). Threshold seroprevalence for screening determined by when such an effort becomes either cost-effective or has the most favorable benefit-risk ratio.</td>
<td>For decision P. Luz, J. Wu, S. Sillal</td>
</tr>
<tr>
<td>15:10 - 15:15</td>
<td>Wrap up</td>
<td>• Summarize day’s findings and request any follow up from WHO Secretariat/IVIR-AC FPs for closed session</td>
<td>For information</td>
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<td>Time</td>
<td>Session</td>
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<tr>
<td>12:00 - 12:05 5’</td>
<td>Introduction</td>
<td>• Recap of previous day and objectives for the day</td>
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<td></td>
<td>For information</td>
<td>W. Orenstein, Chair</td>
<td></td>
</tr>
<tr>
<td>12:05 – 12:10 5’</td>
<td>Background</td>
<td>• Countries that have completed the implementation of their activities request WHO and UNICEF to independently verify elimination through the lot quality assurance-cluster sampling (LQA-CS) survey method</td>
<td></td>
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<tr>
<td></td>
<td>For information</td>
<td>N. Yusuf</td>
<td></td>
</tr>
<tr>
<td>12:10 – 12:25 15’</td>
<td>Technical presentation</td>
<td>• Description of MNTE validation methods for assessments in conflict areas developed by a MNTE Expert Working Group</td>
<td></td>
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<tr>
<td></td>
<td>For information</td>
<td>F. Gasse, M. Deming</td>
<td></td>
</tr>
<tr>
<td>12:25 – 12:45 20’</td>
<td>Q&amp;A and Discussion</td>
<td>• IVIR-AC discusses presentation, clarifies on content and acknowledges main issues</td>
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<tr>
<td></td>
<td>For information</td>
<td>H.H. Farooqui, Dafrossa Lyimo, W. Orenstein, Chair</td>
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</table>

**MNTE validation methods for assessments in conflict areas**

- Countries that have completed the implementation of their activities request WHO and UNICEF to independently verify elimination through the lot quality assurance-cluster sampling (LQA-CS) survey method.
- In the 12 countries that are yet to eliminate maternal and neonatal tetanus, the poorest performing districts are most likely to be those with conflicts and other access constraining factors. The existing LQA-CS survey method and tools do not take into consideration, community access related challenges.
- A WHO-led MNTE Expert Group proposes to the IVIR-AC for decision on alternative options for validating MNTE in conflict affected areas.
- Identifying the most appropriate option for validating MNTE in conflict areas will help refine elimination M&E and accelerate the global goal of eliminating MNT by 2025.

Questions to IVIR-AC:
- Do you consider the two options proposed by the MNTE Expert Group appropriate to address the challenges to MNTE assessment in conflict affected areas?
<table>
<thead>
<tr>
<th>Time</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:45-13:00</td>
<td>Tea break</td>
</tr>
<tr>
<td>13:00 - 13:10 10’</td>
<td><strong>Background</strong>&lt;br&gt;• Background to the session: Introduction to the WHO programme on the role of vaccines in reducing AMR&lt;br&gt;&lt;br&gt;<strong>Background reading materials:</strong> see Sharepoint</td>
</tr>
<tr>
<td>13:10 - 13:30 20’</td>
<td><strong>Technical presentation 1</strong>&lt;br&gt;• The value of vaccines in reducing health burden associated with drug-resistant infections</td>
</tr>
<tr>
<td>13:30 - 13:50 20’</td>
<td><strong>Technical presentation 2</strong>&lt;br&gt;• The value of vaccines in reducing antibiotic use</td>
</tr>
<tr>
<td>13:50 - 14:20 20’</td>
<td><strong>Technical presentation 3</strong>&lt;br&gt;• The value of vaccines in reducing economic burden associated with drug-resistant infections</td>
</tr>
<tr>
<td>14:20 - 14:50 30’</td>
<td><strong>Q&amp;A and discussion to inform IVIR-AC recommendations</strong>&lt;br&gt;Questions to IVIR-AC&lt;br&gt;• Does IVIR-AC agree that the presented analyses are technically appropriate to inform prioritisation of development and use of vaccines in reducing AMR?&lt;br&gt;• Does IVIR-AC agree with the draft recommendations to be included in the report on the value of vaccines in reducing AMR?&lt;br&gt;• What are IVIR-AC's suggestions for ensuring that the value of vaccines in reducing AMR is systematically incorporated into policy decisions?</td>
</tr>
<tr>
<td>14:50 - 15:00 10’</td>
<td><strong>Wrap up</strong>&lt;br&gt;• Summarize day’s findings and request any follow up from WHO Secretariat/IVIR-AC FPs for closed session</td>
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</table>

For decision:
- M. Hasso-Agopsowicz
- K. Abbas C. Kim
- N. Davies
- N. Naylor
- V. Pitzer, H.H. Farooqui, P. Luz, X. Wang

For information:
- W. Orenstein, Chair
<table>
<thead>
<tr>
<th>15 February</th>
<th>Introduction</th>
<th>Vaccine Impact Modelling</th>
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<tr>
<td>12:00 - 12:05</td>
<td>5’ Introduction</td>
<td>• Recap of previous day and objectives for the day</td>
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<td>For information</td>
<td>For information W. Orenstein, Chair</td>
</tr>
<tr>
<td>12:05 - 12:15</td>
<td>10’ Background</td>
<td>W. Orenstein, Chair</td>
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<td></td>
<td>For information</td>
<td>Y Sim</td>
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**Vaccine Impact Modelling**

- The Vaccine Impact Modelling Consortium (VIMC) is a multinational collaboration of many research groups funded by Gavi, the Vaccine Alliance, the Wellcome trust and the Bill & Melinda Gates Foundation (BMGF).
- In collaboration with VIMC, WHO IVB generated IA2030 vaccine impact estimates in 2021 which have served as the Impact Goal Indicator 1.1 “Number of future deaths averted through immunization” as part of the IA2030 Monitoring & Evaluation framework.
- WHO IVB is strengthening its collaboration with VIMC to address other key priority questions for the Immunization Agenda 2030.
- Due to the complementary nature of ongoing work on vaccine impact modelling, we would like to present a combined session for vaccine impact modelling. This session will consist of a main presentation from VIMC and a short update from the IA2030 vaccine impact estimates project team.
<table>
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<tr>
<th>Time</th>
<th>Session</th>
<th>Details</th>
<th>Presenter(s)</th>
</tr>
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</table>
| 12:15 – 12:35 | Vaccine Impact Modelling       | • Three aims of VIMC analysis on impact of COVID-19 related disruptions for immunization are to model vaccine impact estimates (deaths, cases and DALYs averted) that show:  
  o Where the 2020-2021 disruption has left us  
  o What can be done to recoup losses in coverage  
  o What could be achieved if we met aspirational goals (with and without disruption)  
  • **Background reading materials: see Sharepoint** | K Gaythorpe  |
| 20’          | Consortium (VIMC)              |                                                                                                                                        |              |
| 12:35-12:45  | IA2030 vaccine impact         | • WHO’s IA2030 vaccine impact estimates project team is developing a novel analytical framework to generate estimates of future deaths averted through vaccination against Polio and Influenza from 2021-2030.  
  • **Background reading materials: see Sharepoint** | A Carter     |
| 10’          | estimates                    |                                                                                                                                        |              |
| 12:45-13:05  | Q&A and Discussion            | • IVIR-AC is asked to:  
  o *(VIMC)* Review and provide feedback the final results from the analysis on the impact of COVID-19 disruptions for immunization particularly around communicating results  
  o *(IA2030)* Provide feedback on proposed approaches to generating vaccine impact estimates on the incidence and health burden of Polio and influenza  
  • IVIR-AC discusses presentation, clarifies on content and acknowledges main issues | J. Wu, P Luz, S Kim |
| 20’          |                                |                                                                                                                                        |              |
| 13:05-13:15  | Tea break                     |                                                                                                                                        |              |
|              | **Typhoid Conjugate Vaccine   | **Typhoid Conjugate Vaccine Micro Array Patches (TCV-MAP) FVVA**  
  **Overview of TCV-MAP FVVA** - As part of the VIPS Alliance roadmap on vaccine MAPs, the TCV-MAP FVVA was initiated in 2022 to evaluate the potential broad socio-economic and public health impact of MAPs for TCV delivery from the | G. Giersing  |
| 13:15 - 13:20 | Micro Array Patches (TCV-MAP) |                                                                                                                                        |              |
| 5’           | Background                    |                                                                                                                                        |              |
|              |                                |                                                                                                                                        |              |
perspective of countries (including LMICs), funders and industry
- The FVVA will also inform potential future investments in the development of TCV-MAPs and be a model to develop a methodology that could be replicated for other vaccine product delivery innovations

| 13:20 - 13:35 15’ | Technical presentation TCV-MAP FVVA – Review of Quantitative Methodology | **Background reading materials:**
See SharePoint
TCV-MAP FVVA background slides including overview of quantitative analyses |
|-------------------|-------------------------------------------------|--------------------------------------------------|

| 13:35 - 13:55 20’ | Q&A and Discussion | **IVIR-AC is asked to provide recommendations to improve the analysis of equity impact**
**IVIR-AC is asked to provide feedback on the planned next steps of the project** |
|-------------------|-------------------|--------------------------------------------------|

<table>
<thead>
<tr>
<th>13:55 - 14:05 10’</th>
<th>Wrap up</th>
<th><strong>Summarize day’s findings and request any follow up from WHO Secretariat/IVIR-AC FPs for closed session</strong></th>
</tr>
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</table>

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<tr>
<th>14:05 - 14:10 05’</th>
<th>Closing of meeting</th>
<th><strong>Follow up to meeting and next steps</strong></th>
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T. Scarna,
M. Mvundura
M. Antillon

V. Pitzer, D. Lyimo,
J. Leask

For information
W. Orenstein

For information
P. Lambach
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<th>16 February</th>
<th>Closed session: IVIR-AC members only</th>
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<tr>
<td>12:00 - 16:00</td>
<td>IVIR-AC reporting/recommendations</td>
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Meeting of the Advisory Committee on Immunization and Vaccines-related Implementation Research (IVIR-AC)

Microsoft Teams
Geneva, Switzerland
13 to 16 February 2023

Draft list of participants

Background reading materials available at:
SharePoint page - IVIR-AC Meeting - 13 to 16 February 2023

Advisory Committee Members

Rakesh Aggarwal, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

Habib Hasan Farooqui, College of Medicine, Qatar University, Doha, Qatar

Alexandra Hogan, School of Population Health, University of New South Wales, Sydney, Australia.

Stefan Flasche, Centre for Mathematical Modelling of Infectious Diseases (CMMID), London School of Hygiene & Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland

Sun-young Kim, Global Health, School of Public Health, Seoul National University, Seoul, Republic of Korea

Julie Leask, Susan Wakil School of Nursing and Midwifery, Sydney Nursing School, Faculty of Medicine and Health, Sydney, Australia

Paula M. Luz, Evandro Chagas Clinical Research Institute, Oswaldo Cruz Foundation (IPEC/FIOCRUZ), Rio de Janeiro, Brazil

Dafrossa C. Lyimo, Immunization and Vaccines Development, Ministry of Health, Community Development, Gender, Elderly & Children, Dar es salaam, United Republic of Tanzania
William Moss, International Vaccine Access Center Johns Hopkins Bloomberg School of Public Health, USA

Walter Orenstein (Chair), Emory Global Health Institute, Emory University, Atlanta, United States of America

Virginia Pitzer, Yale School of Public Health, New Haven, United States of America

Sheetal Silal, Modelling and Simulation Hub, Africa (MASHA), University of Cape Town, Cape Town, South Africa

Xuan-yi Wang, Shanghai Medical College, Fudan University, Shanghai, People’s Republic of China

Joseph Wu, Division of Epidemiology and Biostatistics, School of Public Health, The University of Hong Kong, Hong Kong SAR, People’s Republic of China

Participants

Kaja Abbas, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland

Marina Antillon, Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland

Austin Carter, University of Washington, Seattle, Washington, United States of America

Nicholas Davies, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland

Michel Deming, Independent Consultant to WHO

Ijeoma Edoka, Health Economics and Epidemiology Research Office (HE2RO), University of the Witwatersrand, Johannesburg, South Africa

Francois Gasse, Independent Consultant to WHO

Chaelin Kim, International Vaccine Institute, Seoul, South Korea

Jodie McVernon, Doherty Institute, University of Melbourne, Melbourne, Australia

Sam Moore, School of Life Sciences and Mathematics Institute, University of Warwick, Warwick, United Kingdom of Great Britain and Northern Ireland

Mercy Mvundura, PATH, Seattle, United States of America

Nichola Naylor, UK Health Security Agency, London, United Kingdom of Great Britain and Northern Ireland
Neil Fergusson, Imperial College London, London, United Kingdom of Great Britain and Northern Ireland

Katy Gaythorpe, Imperial College London, London, United Kingdom of Great Britain and Northern Ireland

Riona Hanley, Takeda Vaccines Business Unit, Takeda Pharmaceutical, Tokyo, Japan

Mark Jit, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland

Alicia Kraay, College of Applied Health Sciences, University of Illinois, Illinois, United States of America

Kathleen Morales, Sierra Strategy Group, LLC. Texas, United States of America

Tiziana Scarna, Gavi, the Vaccine Alliance, Global Health Campus, Geneva, Switzerland.

Jing Shen, Takeda Vaccines Business Unit, Takeda Pharmaceutical Company Limited, Tokyo, Japan

Robert Steinglass, Independent Immunization Technical Advisor

Robin Thompson, Associate Professor of Mathematical Epidemiology, Mathematics Institute, University of Warwick, United Kingdom of Great Britain and Northern Ireland

Observers/Standing participants

Sharon Achilles, BMGF, Bill and Melinda Gates Foundation, Seattle, United States of America

James Alexander, Centers for Disease Control and Prevention, Atlanta, United States of America

Paula Barbosa, International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), Geneva, Switzerland

Eduardo Azziz Baumgartner, Centers for Disease Control and Prevention, Atlanta, United States of America

Laetitia Bigger, International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), Geneva, Switzerland

Iona Bouros, University of Warwick, United Kingdom of Great Britain
and Northern Ireland

Joseph Brezee, Taskforce for Global Health, Georgia, United States of America

Mike Brison, Bill and Melinda Gates Foundation, Seattle, United States of America

Megan Carey, Cambridge Infections Diseases, University of Cambridge, Cambridge, United Kingdom of Great Britain and Northern Ireland

Laura Craw, Gavi, the Vaccine Alliance, Geneva, Switzerland

Emily Dansereau, Bill and Melinda Gates Foundation, Seattle, United States of America

Ilia Gorodnichev, PwC, New York, United States of America

Dan Hogan, Gavi, the Vaccine Alliance, Geneva, Switzerland

Edward Hill, University of Warwick, United Kingdom of Great Britain and Northern Ireland

Matt Keeling, University of Warwick, United Kingdom of Great Britain and Northern Ireland

Katrina Kretsinger, Centers for Disease Control and Prevention, Atlanta, United States of America

Supriya Kumar, Bill and Melinda Gates Foundation, Seattle, United States of America

Dr Chia-Lin Lee

Peter McIntyre, (SAGE liaison), Women’s and Children’s Health University of Otago, Te Whare Wānanga o Otāgo, Otāgo, New Zealand

Meg McCarron, Centers for Disease Control and Prevention, Atlanta, United States of America

Nelly Mejia, Centers for Disease Control and Prevention, Atlanta, United States of America

Todi Mengistu, Gavi, the Vaccine Alliance, Geneva, Switzerland

Jonathan Mosser, Institute for Health Metrics and Evaluation (IHME), University of Washington, Washington, United States of America

Sonia Pagliusi, Developing Countries Vaccine Manufacturers Network International (DCVMN), Geneva, Switzerland

Sarah Pallas, Centers for Disease Control and Prevention, Atlanta, United States of America
Minal Patel, Centers for Disease Control and Prevention, Atlanta, United States of America

Tanya Shewchuk, Bill and Melinda Gates Foundation, Seattle, United States of America

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WER summary of last IVIRAC
**Meeting of the Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC), September 2022**

The IVIR-AC recommendations are based on technical discussions during a hybrid (in-person/virtual) meeting of the IVIR-AC, held on 12–14 September 2022. Nine groups presented to IVIR-AC on vaccine impact modelling, vaccine introduction and demand generation and the Full value of vaccine assessments (FVV A). Several sessions provided updates on how IVIR-AC’s previous recommendations are reflected in the presenters’ current work.

**COVID-19 vaccine impact modelling**

To ensure that WHO’s COVID-19 vaccine policies and guidance align to reflect changing COVID-19 disease and transmission patterns, host immunity factors (vaccine-induced and/or naturally acquired immunity), and COVID-19 vaccine choices, uptake and coverage, the SAGE working group subgroup on vaccine impact modelling for COVID-19 (SG COVID-19) identified 3 core areas to which mathematical modelling studies are crucial to inform vaccination strategies. These areas are: shifting vaccine prioritization in the presence of high infection-derived immunity, cost-effectiveness of COVID-19 vaccination compared to other vaccines, and COVID-19 vaccine impact modelling.

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2 Full value of vaccine assessments (FVVAs) expand vaccine value to include the broader socioeconomic benefit or impact of a vaccine.
the impact of variants of concern on vaccination priorities.

To inform the SG COVID-19’s upcoming presentations to SAGE and to stimulate dialogue on future challenges and questions around COVID-19 vaccination, 2 WHO-funded modelling groups presented preliminary results and next steps to address a subset of the priority modelling questions developed by SG COVID-19 in those 3 core areas. The 2 presentations addressed: 1) the utility of seroprevalence thresholds to guide the timing of additional COVID-19 vaccine doses; and 2) the cost-effectiveness of a second booster dose in the United States. IVIR-AC was asked to provide feedback on each group’s work, their proposed plans, and key messages to SAGE relating to the ability of the analyses to inform the priority questions.

**IVIR-AC recommendation highlights**

Recommendations relating to the seroprevalence threshold analysis:

- While understanding that trends in seroprevalence are a valuable adjunct to regional and global policy considerations, there is still insufficient evidence to support the use of population-based seroprevalence thresholds to inform country-level vaccine recommendations at this time.

- To further evaluate the utility of seroprevalence surveys for informing the timing of additional vaccine doses, the seroprevalence modelling analysis should clarify and revisit assumptions regarding the waning of natural and vaccine-induced immunity and the relative risk of (re)infection for seropositive versus seronegative persons and should relate these assumptions to data on the relationship between vaccine effectiveness and quantity of binding and/or neutralizing antibodies.

- As with all COVID-19 modelling studies, it is crucial to define the primary outcome clearly (e.g. hospital burden or percentage of deaths averted) in order to determine the utility of a seroprevalence threshold and to use that as a benchmark to compare future scenarios.

Recommendations relating to the cost-effectiveness of a second booster dose analysis:

- The economic analysis could potentially inform the cost-effectiveness of a second booster dose in the United States population aged 50 years and over, but further work is needed to assess the robustness of this evidence, particularly by incorporating transmission from all age groups.

**Points saillants des recommandations de l’IVIR-AC**

Recommandations relatives à l’analyse du seuil de séroprévalence:

- Bien que les tendances de la séroprévalence constituent un complément d’information précieux pour étayer les considérations politiques régionales et mondiales, les données probantes actuellement disponibles n’ont pas encore de plaidoirie en faveur d’une utilisation des seuils de séroprévalence en population pour éclairer les recommandations vaccinales dans les pays.

- Afin d’évaluer plus précisément dans quelle mesure les enquêtes de séroprévalence sont utiles pour décider du moment opportun d’administrer des doses supplémentaires de vaccin, l’analyse de modélisation de la séroprévalence devrait clarifier et réexaminer les hypothèses relatives au déclin de l’immunité (naturelle ou induite par la vaccination) et au risque relatif de (ré)infection des personnes séropositives par rapport aux personnes séronégatives, et devrait relier ces hypothèses aux données sur la relation entre l’efficacité des vaccins et la quantité d’anticorps de liaison et/ou neutralisants.

- Comme pour toutes les études de modélisation de la COVID-19, il est primordial de définir clairement le critère de jugement principal (par exemple, charge hospitalière ou pourcentage de décés évités) à appliquer pour déterminer l’utilité d’un seuil de séroprévalence et de s’en servir comme référence pour comparer les scénarios futurs.

Recommandations relatives à l’analyse du rapport coût-efficacité d’une deuxième dose de rappel:

- L’analyse économique est susceptible de fournir des renseignements sur le rapport coût-efficacité d’une deuxième dose de rappel chez les personnes âgées de 50 ans et plus aux États-Unis d’Amérique, mais des travaux supplémentaires sont nécessaires pour évaluer la fiabilité de ces données, en particulier en incluant la transmission par des sujets de toutes les tranches d’âge.

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1. Subset questions: a) Is there potential for serological data to inform re-vaccination timing? b) Are second booster doses cost-effective in older adults?

2. Sous-questions: a) Pourrait-on se servir des données sérologiques pour déterminer le moment opportun pour la revaccination? b) L’administration d’une deuxième dose de rappel présente-t-elle un bon rapport coût-efficacité chez les personnes âgées?
IVIR-AC recommendation highlights

- The current approach for incorporating transmission from younger age groups using a scaling parameter that is multiplied by the prevalence of infection in older adults is inappropriate and is likely to overestimate the reduction in transmission associated with a second booster dose in older adults; the contribution of younger individuals to transmission should instead be additive, constant over time, and subject to sensitivity analysis.

- The cost-effectiveness model should account for waning immunity from the second booster dose since vaccine effectiveness studies suggest that the protection against infection from a second booster dose may be short-lived. Variability in the timing of subsequent waves of infection should also be explored in sensitivity analyses.

- An extension of the work to assess the cost-effectiveness of a fourth dose in younger adults and the incremental cost-effectiveness of a primary series and subsequent boosters for children would be important additions to the evidence base; future analyses should consider characteristics of bivalent and other novel vaccines.

Full value of improved influenza vaccine assessment

FVVA* expand “vaccine value” beyond individual health benefit to include the broader socioeconomic benefit or impact of a vaccine. WHO is developing a “Full value of improved influenza vaccines assessment” (FVIVA) to illustrate the value of current seasonal influenza vaccines and the potential added value of future “improved vaccines*”, which may address the needs of low- and middle-income countries (LMICs). The FVIVA includes 3 interconnected workflows on 1) vaccine research, development and supply; 2) demand; and 3) impact. Data from the 3 workflows feed into the final analysis on “improved vaccine” characteristics as a mediator of impact, demand, supply and vice versa. IVIR-AC was asked to review the proposed methods to develop the FVIVA and provide technical insights to strengthen the approach.

Évaluation de la pleine valeur des vaccins antiviraux améliorés

La FVVA (évaluation de la pleine valeur des vaccins)* élargit la notion de valeur d’un vaccin au-delà des avantages qu’il présente pour la santé individuelle, en tenant compte également de ses avantages ou de son impact sur le plan socioéconomique. L’OMS prépare actuellement une «évaluation de la pleine valeur des vaccins antiviraux améliorés» (FVIVA) destinée à étudier la valeur des vaccins antiviraux saisonniers actuels et la valeur ajoutée potentielle des futurs «vaccins améliorés», qui pourraient répondre aux besoins des pays à revenu faible ou intermédiaire. L’évaluation FVIVA comprend 3 axes de travail interconnectés sur 1) la recherche, la mise au point et l’approvisionnement des vaccins; 2) la demande; et 3) l’impact. Les données issues de ces 3 axes de travail viennent alimenter l’analyse finale des caractéristiques des vaccins améliorés qui sont susceptibles d’influencer sur l’impact, la demande et l’approvisionnement, et vice versa. L’IVIR-AC a été invité à examiner les méthodes proposées pour l’élaboration de la FVIVA et à fournir des conseils techniques sur les moyens de renforcer cette approche.

Points saillants des recommandations de l’IVIR-AC

- Préciser si les cadres relatifs aux scénarios d’utilisation et aux archétypes de pays doivent tenir compte de l’hétérogénéité des vaccins antiviraux (par exemple vaccin trivalent ou quadrivalent, vaccin à dose standard ou à dose élevée).
- Préciser comment la demande de vaccins est définie (par exemple achat, intention, ou adoption réelle) et définir la période d’équilibre entre l’offre et la demande (par exemple, équilibrer annuellement afin d’atteindre avec les vaccins actuels;
current vaccines; populations with different seasonality might have different time frames).
- Retrospectively validate the demand and supply forecast framework against historical data.
- In the health economic evaluation, clarify which clinical outcome the vaccine protects against (i.e. protection against infection, symptomatic disease, or hospitalization and death). Effectiveness against severe clinical outcomes should be a priority.
- The 3 workstreams should work together interactively. However, data exchange across workstreams and cross-workstream analyses should be aware of the risk of compounding error. Given the multi-level nature of the FVIVA with respect to model outputs as inputs for other models, micro-validation and sensitivity analyses are recommended at each level of analysis. For instance, where proxies are used for key data inputs, such as vaccine uptake and delivery platforms for user groups, performance of the proxies should be evaluated for those countries where data are available. This is particularly important for LMICs where vaccine uptake is notably lower with a disincentive to record data.

Influenza vaccine global demand forecasting tool
Global influenza vaccine supply potential far exceeds demand, especially in LMICs. In 2019, 50% of the world's population accessed only 6% of available seasonal influenza vaccine doses.6

Seasonal influenza vaccine planning and prioritization remain a challenge for LMICs due to yearly re-vaccination requirements, costs and the lack of demand forecasting capability to fulfill the advanced funding commitment required to secure vaccine supply in advance of the upcoming influenza season.

To strengthen and support seasonal influenza vaccine planning and prioritization and dually support pandemic preparedness efforts, Ready2Respond7 developed a long-range influenza vaccine demand forecasting tool8 which helps countries to: 1) simulate yearly demand for seasonal influenza vaccines up to 5 years ahead, and 2) document pandemic influenza vaccine demand scenarios. IVIR-AC was asked for ways to expand access to the tool, to strengthen its use with périodes susceptibles d'être différentes pour les populations soumises à des schémas saisonniers différents).
- Valider rétrospectivement le cadre de prévision de l'offre et de la demande au regard des données historiques.
- Pour l'évaluation sanitaire économique, préciser l'issue clinique contre laquelle le vaccin confère une protection (à savoir protection contre l'infection, contre les formes symptomatiques de la maladie ou contre les hospitalisations et les décès). La priorité doit être accordée à l'efficacité des vaccins contre les issues cliniques graves.
- Il convient qu'il y ait une collaboration interactive entre les 3 axes de travail. Cependant, il faut être conscient du risque d'erreur cumulée pouvant découler de l'échange de données et des analyses croisées entre les axes de travail. Compte tenu de la structure à plusieurs niveaux de la FVIVA, les données de sortie d'un modèle étant utilisées comme données d'entrée d'autres modèles, il est recommandé de mener des analyses de microvalidation et de sensibilité à chaque niveau. Par exemple, lorsque des indicateurs indirects sont utilisés en tant que données d'entrée essentielles, comme l'adoption des vaccins ou les plateformes d'administration chez les groupes d'utilisateurs, la performance de ces indicateurs indirects doit être évaluée pour les pays où les données correspondantes sont disponibles. Cela est particulièrement important pour les pays à revenu faible ou intermédiaire dans lesquels le taux d'adoption des vaccins est nettement plus faible, ce qui dissuade l'enregistrement des données.

Outil de prévision de la demande mondiale de vaccins antigrippaux
L'offre mondiale potentielle de vaccins antigrippaux dépasse largement la demande, en particulier dans les pays à revenu faible ou intermédiaire. En 2019, 50% de la population mondiale n'a utilisé que 6% des doses disponibles de vaccin contre la grippe saisonnière.6

La planification et l'établissement des priorités en matière de vaccination antigrippale saisonnière demeurent un défi pour les pays à revenu faible ou intermédiaire. Ces difficultés s'expliquent par la nécessité d'une revaccination annuelle, les coûts associés et l'absence de moyens permettant de prévoir la demande et ainsi de satisfaire aux exigences de financement anticipé pour garantir l'approvisionnement requis en vaccins avant la prochaine saison grippale.

Pour renforcer et soutenir la planification et l'établissement des priorités en matière de vaccination contre la grippe saisonnière et appuyer les efforts de préparation aux pandémies, Ready2Respond7 a mis au point un outil de prévision à long terme de la demande de vaccins antigrippaux8 qui aide les pays à: 1) simuler la demande annuelle de vaccins contre la grippe saisonnière jusqu'à 5 ans à l'avance, et 2) documenter les scénarios de demande de vaccins contre la grippe pandémique. L'IVIR-AC a été invité à formuler des suggestions pour élargir l'accès à

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moniae is the most common cause of bacterial pneumonia in humanitarian crisis settings. Streptococcus pneumoniae can spread rapidly in densely populated areas, as well as unpredictable social mixing and overcrowding, which can fuel the spread of acute respiratory infections, leading to increased rates of pneumonia.

Humanitarian crisis settings provide a perfect environment for spreading pneumonia, and the IVIR-AC (International Vaccine Information Resource) has made recommendations for the use of the pneumococcal conjugate vaccine to prevent pneumonia. Points to consider when expanding to next-generation influenza vaccines include:

- To enhance access to the tool, create awareness of its availability: develop a communications plan and formally launch the tool (e.g., partner with the Global Influenza Surveillance and Response System (GISRS) which has been working with 124 WHO Member States on global influenza surveillance for decades).
- Promote the tool to those who can motivate decision-makers (e.g., National Immunization Technical Advisory Groups (NITAGs), professional associations etc.) and those who can support programme managers (e.g., WHO regional offices, SABIN Boost, PATH).
- When focusing on motivation for programme managers to use the tool, provide information about the full burden of influenza in the context of competing priorities. This includes the health, social and economic burdens.
- When advocating for use of the tool, incorporate the experience and lessons learned from other vaccine forecasting tools. Ensure there is a clear description of this tool, with a demonstration of its use. Consider case studies of usage by a small number of countries.
- Use an implementation framework such as the Behavior Change Wheel to guide activities.
- When expanding to next-generation influenza vaccines, partner with the London School of Hygiene and Tropical Medicine (LSHTM) team which is leading the vaccine impact workstream of WHO’s FVIVA to elucidate how potential improvements in vaccine effectiveness, broader and/or longer protection in next-generation influenza vaccines may influence archetypes and future demand.
- Simplify communication to elucidate the benefits of next generation vaccines scenarios.
- Consider developing a mobile app version of the tool.

Use of pneumococcal conjugate vaccine in humanitarian settings

Humanitarian crisis settings provide a perfect environment for soaring rates of acute respiratory infection and transmission. Social mixing and overcrowding within a dense population, as well as unpredictable nutrition and hygiene circumstances, may sustain such risk for the extent of the crisis. Streptococcus pneumoniae is the most common cause of bacterial pneumonia.


References

Améliorer l’accès à l’outil en diffusant des informations sur sa disponibilité: élaborer un plan de communication et procéder à un lancement officiel de l’outil (par exemple en partenariat avec le Système mondial de surveillance de la grippe et de riposte (GISRS), qui collabore avec 124 États Membres de l’OMS pour assurer une surveillance mondiale de la grippe depuis des décennies).

Promouvoir l’outil auprès des entités qui sont en mesure d’inciter les décideurs (par exemple groupes consultatifs techniques nationaux sur la vaccination, associations professionnelles, etc.) ou de soutenir les administrateurs de programmes (par exemple, bureaux régionaux de l’OMS, SABIN Boost, PATH).

Lors des activités visant à encourager les administrateurs de programmes à utiliser l’outil, fournir des informations sur la charge totale de la grippe, c’est-à-dire sa charge aussi bien sanitaire que sociale et économique, dans un contexte de priorités concurrentes.

Lors des activités de promotion de l’outil, intégrer les expériences et les leçons tirées de l’utilisation d’autres outils de prévision de la demande de vaccins. Fournir une description claire de cet outil, avec une démonstration de son utilisation. Envisager de recourir à des études de cas portant sur l’utilisation de l’outil dans un petit nombre de pays.

Utiliser un cadre de mise en œuvre tel que la «Behavior Change Wheel» (roue de changement des comportements) pour guider les activités.

Pour étendre la fonctionnalité de l’outil aux vaccins antigrippaux de nouvelle génération, collaborer avec l’équipe de la London School of Hygiene and Tropical Medicine (LSHTM) responsable de l’axe de travail sur l’impact des vaccins de la FVIVA de l’OMS afin de déterminer dans quelle mesure les améliorations susceptibles d’être apportées aux vaccins antigrippaux de nouvelle génération (efficacité accrue, protection plus longue et/ou plus longue) influenceront sur les archétypes et la demande future.

Simplifier la communication pour mettre en lumière les avantages présentés par les scénarios d’utilisation des vaccins de nouvelle génération.

Envisager de mettre au point une version de l’outil sous forme d’application mobile.

Utilisation du vaccin antipneumococcique conjugué dans les contextes humanitaires

Les situations de crise humanitaire créent un environnement particulièrement propice à la transmission et à l’envolée des infections respiratoires aiguës. Le surpeuplement et les contacts sociaux au sein d’une population dense, ainsi que des conditions de nutrition et d’hygiène imprévisibles, peuvent faire perdurer ce risque pendant toute la durée de la crise. Streptococcus pneumoniae est le principal agent responsable des pneu-
monia and one of the most common causes of meningitis in children under 5 years of age in unvaccinated populations. Despite the high prevalence of risk factors for disease and transmission, pneumococcal conjugate vaccines (PCV) are rarely used in humanitarian settings, partly because of a lack of evidence to optimize their use in those contexts, outside of the traditional Expanded Programme on Immunization (EPI). Additional studies are needed to fill the evidence gap and inform the development of clearer guidance on PCV use in humanitarian settings.

To address this need, LSHTM, Save the Children, the Republic of Somaliland Ministry of Health and Development and Murdoch Children's Research Institute collected social contact and nasopharyngeal carriage data in a camp for internally displaced persons (IDPs) in Somaliland and used these data to model simulated PCV vaccination strategies. The findings suggest that, in the absence of routine immunization, PCV campaigns can effectively interrupt transmission and can have an impact on pneumococcus-related morbidity and mortality in the short-to-medium term in this and similar humanitarian settings. The second phase of the project includes a follow-up Phase IV vaccine trial to evaluate the impact of a PCV campaign in children under 5 years of age in the IDP camp over the 2-year period following vaccination. IVIR-AC was asked to comment on the robustness of the second phase of the project, the overall methods of approach and what, if any, additional information would strengthen the subsequent intervention study.

IVIR-AC recommendation highlights

- IVIR-AC agrees with the proposed study design/methodological approach to identify optimal vaccination strategies for PCV use in humanitarian emergency settings, and acknowledges:
  - the importance of the Phase IV study to validate modelling results;
  - that primary data on key model parameters is a major strength of the model.

- In order to strengthen the findings of the modelling analysis and allow for extrapolation to other settings, the group should conduct additional sensitivity and scenario analyses related to vaccine coverage, rate of migration, frequency of campaigns, and time horizon of the analysis.

- The research team should consider adding an additional carriage survey in the non-displaced population in Somaliland at 24 months following vaccination in the internally displaced population to assess trends in the counterfactual population.

- The group could consider additional sensitivity analysis for the impact of the intervention, depending on:

Points saillants des recommandations de l’IVIR-AC

- L’IVIR-AC approuve la structure/méthodologie d’étude proposée pour identifier les stratégies optimales de vaccination avec le VPC dans les situations d’urgence humanitaire, et convient:
  - que l’étude de phase IV est importante pour valider les résultats de la modélisation;
  - que les données primaires sur les paramètres clés du modèle constituent un atout majeur du modèle.

- Pour consolider les résultats de l’analyse de modélisation et permettre leur extrapolation à d’autres contextes, le groupe devrait effectuer des analyses de sensibilité et de scénarios supplémentaires portant sur la couverture vaccinale, le taux de migration, la fréquence des campagnes et l’horizon temporel de l’analyse.

- L’équipe de recherche devrait envisager de mener une enquête supplémentaire sur le portage dans la population non déplacée au Somaliland, 24 mois après la vaccination des personnes déplacés à l’intérieur de leur propre pays, afin d’évaluer les tendances dans la population contrefactuelle.

- Le groupe pourrait envisager d’effectuer une analyse de sensibilité supplémentaire pour étudier l’impact de l’intervention en fonction des éléments suivants:
- efficacy of a single-dose versus 2-dose schedule;
- vaccine serotype coverage;
- rate of serotype replacement;
- rate of decline of efficacy (i.e. duration and breadth of protection).

● It would be helpful to present the results of the modelling analysis disaggregated by:
  - direct versus indirect effects;
  - vaccine type / non-vaccine type / colonization with both.

Measles case fatality ratio estimation
Robust, transparent and dynamic age- and country-specific measles case fatality ratios (CFRs) are critical for updating WHO’s measles mortality estimates. IVIR-AC previously reviewed several iterations\(^\text{10}\) of the analytical framework and methodology for CFR estimation. To address IVIR-AC’s latest March 2022 recommendations\(^\text{11}\) and seek final appraisal on the revised CFR framework, the LSHTM and the Harvard T.H. Chan School of Public Health presented new measles CFR estimates generated from the framework, on behalf of a working group of experts. They elaborated on the considerations when addressing IVIR-AC’s previous recommendations in the revised framework, and on future plans and considerations for applying the model framework to explore the impact of the COVID-19 pandemic on the measles mortality burden. The team requested IVIR-AC’s endorsement of the current revised measles CFR estimation framework, for recommendations on applying the model framework to COVID-19, and on appropriate measles CFR use cases for the open access framework.

IVIR-AC recommendation highlights:
● The updated effort adequately responds to several previous recommendations, in particular: 1) the criteria for selecting the final set of indicators and including them in the model, as well as the approach to the decomposition analysis, were clearly described; 2) collinearity of indicators was assessed within mechanistic groups; 3) model validation was performed in and out of sample with new/unpublished data; and 4) sensitivity analyses around case definitions and study quality were performed. We also praise the improved age-modelling methodology – an important addition that improved model fit.

- l’efficacité d’un schéma à dose unique par rapport à un schéma à 2 doses;
- la couverture sérotypique des vaccins;
- le taux de remplacement des sérotypes;
- le taux de déclin de l’efficacité (durée et étendue de la protection).

● Il serait utile de présenter les résultats de l’analyse de modélisation ventilés comme suit:
  - effets directs/indirects;
  - colonisation par le type vaccinal/non-vaccinal/les deux.

Estimation du taux de létalité de la rougeole
Pour mettre à jour ses estimations de la mortalité due à la rougeole, il est indispensable que l’OMS dispose d’estimations du taux de létalité de la rougeole qui soient fiables, transparentes, dynamiques et ventilées par âge et par pays. L’IVIR-AC a déjà examiné plusieurs itérations\(^\text{10}\)\(^\text{11}\) du cadre analytique et de la méthodologie d’estimation du taux de létalité. Pour donner suite aux recommandations les plus récentes de l’IVIR-AC, émises en mars 2022,\(^\text{12}\) et solliciter une évaluation finale du cadre révisé d’estimation du taux de létalité, la LSHTM et la Harvard T.H. Chan School of Public Health ont présenté de nouvelles estimations du taux de létalité de la rougeole produites au moyen de ce cadre, pour le compte d’un groupe de travail d’experts. Les intervenants ont décrit les éléments pris en compte pour appliquer les recommandations précédentes de l’IVIR-AC dans le cadre révisé, ainsi que les plans et possibilités futures d’utiliser le cadre de modélisation pour étudier l’impact de la pandémie de COVID-19 sur la charge de mortalité de la rougeole. L’équipe a demandé à l’IVIR-AC d’approuver le cadre révisé actuel d’estimation du taux de létalité de la rougeole et de formuler des recommandations sur l’application du cadre de modélisation à la COVID-19, ainsi que sur les scénarios d’utilisation appropriés du taux de létalité de la rougeole pour le cadre en libre accès.

Points saillants des recommandations de l’IVIR-AC
● Les mises à jour effectuées satisfont à plusieurs recommandations précédentes, en particulier: 1) les critères régissant la sélection de l’ensemble final d’indicateurs et leur inclusion dans le modèle, de même que la méthode utilisée pour l’analyse de décomposition, ont été clairement décrits; 2) la colinéarité des indicateurs a été évaluée au sein des groupes mécanistes; 3) la validation du modèle a été effectuée, à la fois en échantillon et hors échantillon, à l’aide de données nouvelles ou non publiées; et 4) des analyses de sensibilité axées sur les définitions de cas et la qualité des études ont été réalisées. Nous saluons également la méthode améliorée adoptée pour la modélisation selon l’âge: il s’agit d’un ajout important qui a permis un meilleur ajustement du modèle.


● Moving forward, as these results will soon serve as a basis for mortality estimates/calculations, it should be emphasized that: 1) (as in prior studies) the methodology excludes literature on specific populations (i.e. displaced populations) and therefore may not be applicable to these settings; and 2) the estimates account only for short-term (less than 30 days) mortality due to measles.

● We strongly encourage the inclusion of random effects terms in the Bayesian meta-regression model given the failure of the model to account fully for the stochastic nature of the data; this will allow for separate reporting of 95% prediction intervals in addition to 95% credible intervals for the mean CFR, which may have different use cases.

● When examining the short- and long-term impact of the COVID-19 pandemic on measles mortality, the researchers should consider the potential impact of the pandemic on the relationship between indicators of the measles CFR and the CFR, particularly for non-causal indicators that are proxies rather than being mechanistically related to the CFR.

● We concur that, for the open access framework, the final set of indicators should be predefined and updated on an annual basis with no refitting of the model to new primary data.

● To facilitate use of the R package, we suggest creating a detailed vignette with a problem statement and one complete application of the methodology in a step-by-step manner (e.g. for one country, including data on all indicators).

Tuberculosis full value of vaccine assessment

The tuberculosis (TB) vaccine development pipeline has a number of late-stage candidates with the potential to address the needs of LMICs and ultimately to reduce the global disease burden of TB. However, vaccine development is long and expensive and there remains little market incentive for investment in diseases of poverty, especially in LMICs, thus supporting the need to undertake an FVV A to inform decision-making on investment, introduction and use.

To illustrate the broader value of novel TB vaccines, the TB FVV A framework assesses the combined health and socioeconomic benefit of novel TB vaccines that fulfill the WHO preferred product characteristics in multiple delivery scenarios within 105 LMICs. IVIR-AC was asked to review and comment on the approach and outcome of the analysis and to recommend additional studies which may complement or broaden these initial analyses.

IVIR-AC recommendation highlights for future iterations

● IVIR-AC commends the FVV A approach taken and confirms the choice of model and approach as

● Pour l’avenir, étant donné que ces résultats serviront bientôt de base aux estimations/calculs de la mortalité, il convient de souligner que: 1) (comme dans les études précédentes) la méthodologie exclut la littérature traitant de populations particulières (notamment les populations déplacées) et peut donc ne pas être applicable à ces contextes; et 2) les estimations reflètent uniquement la mortalité à court terme (moins de 30 jours) imputable à la rougeole.

● Nous encourageons vivement l’inclusion de termes à effets aléatoires dans le modèle de métarégression bayésienne étant donné que le modèle ne rend pas pleinement compte de la nature stochastique des données; cela permettra de présenter séparément les intervalles de prédiction à 95% et les intervalles de crédibilité à 95% du taux de léthalité moyen, qui peuvent avoir des scénarios d’utilisation différents.

● Lorsqu’ils étudient l’impact à court et à long terme de la pandémie de COVID-19 sur la mortalité due à la rougeole, les chercheurs devraient tenir compte des effets potentiels de la pandémie sur la relation entre le taux de léthalité de la rougeole et les indicateurs utilisés pour le mesurer, en particulier pour les indicateurs de type non causal qui sont des indicateurs indirects plutôt que des indicateurs ayant un lien mécaniste avec le taux de léthalité.

● Pour le cadre en libre accès, nous convenons que l’ensemble final d’indicateurs devrait être prédéfini et actualisé chaque année sans réajustement du modèle aux nouvelles données primaires.

● Pour faciliter l’utilisation du paquet R, nous suggérons de préparer une vignette détaillée présentant un énoncé de problème et une description complète de l’application de la méthode étape par étape (par exemple pour un pays, avec des données sur tous les indicateurs).

Évaluation de la pleine valeur des vaccins contre la tuberculose

La filière de développement des vaccins antituberculeux compte plusieurs vaccins candidats à un stade avancé qui pourraient répondre aux besoins des pays à revenu faible ou intermédiaire et, à terme, réduire la charge de morbidité mondiale due à la tuberculose. Cependant, la mise au point des vaccins est un processus coûteux et de longue haleine et le marché n’incite guère à investir dans les maladies de la pauvreté, en particulier dans les pays à revenu faible ou intermédiaire, d’où la nécessité de mener une évaluation FVVA pour éclairer les décisions relatives aux investissements et à l’introduction et à l’utilisation des vaccins.

Pour illustrer la valeur plus globale des nouveaux vaccins antituberculeux, le cadre d’évaluation FVVA pour la tuberculose examine les avantages à la fois sanitaires et socioéconomiques des nouveaux vaccins antituberculeux présentant des caractéristiques conformes aux «caractéristiques à privilégier» définies par l’OMS, selon plusieurs scénarios d’administration dans 105 pays à revenu faible ou intermédiaire. L’IVIR-AC a été invité à examiner la méthode et les résultats de l’analyse, à faire part de ses commentaires et à recommander des études supplémentaires susceptibles de compléter ou d’étoffer ces premières analyses.

Points saillants des recommandations de l’IVIR-AC pour les futures itérations

● L’IVIR-AC salue l’approche adoptée pour la FVVA et confirme que le modèle et la méthode choisis seront globa-
generally suitable for addressing questions about the epidemiological and economic impacts of novel TB vaccines, once they become available.

- To further improve the robustness of the epidemiological impact model, the model could be calibrated to time series data rather than a set of indicators in a single year. Alternatively, a validation analysis comparing a time trend in model estimates and observed data could be conducted for all countries or country archetypes, with further details on data sources and their underlying variability.

- To increase the relevance of the findings to individual countries, the modelled vaccine coverage could be specific to each country’s coverage rates based on age-appropriate vaccines, including by wealth quintile in the health equity analysis.

- In future iterations, consider expanding the health equity analysis to include a wide and representative set of country data.

- To guard against potential misinterpretation of findings, clearly specify limitations of assumptions underlying the long-term projections of economic benefits extending to 2080.

- To further understand the impact of price, the study could calculate a threshold price at which TB vaccine would be cost-effective in the scenarios considered.

- To enhance the communication of results, make a comparison across other vaccine interventions for which the health budgets will ultimately need to prioritize spend. Results should be benchmarked against TB targets and other relevant comparators.

- To broaden the scope and impact of the work, extend the set of scenarios to introduce the infant vaccine and adolescent/adult vaccine in isolation and simultaneously at different timepoints.

**MR-MAP initial full value of vaccine assessment (MR-MAP ifVVa)**

Measles and rubella vaccination prevent the highest number of vaccine-preventable deaths in children and provide the highest return on investment in public health. A measles-rubella (MR) micro-array patch (MAP) vaccine can expand measles and rubella vaccination coverage by reducing LMIC operational barriers associated with needle/syringe formulations, especially in hard-to-reach populations that remain critical to global measles and rubella eradication efforts.

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14. The micro-array patch (MAP) is an innovative, needle-free vaccine presentation and administration technology consisting of an array of micro-projections on a patch.
To capture the broad potential benefit of MR-MAPs and inform and encourage future investment, an initial FVVA (iFVVA) was developed by UNICEF in collaboration with the Vaccine Innovation and Prioritization Strategy (VIPS) working group. The iFVVA includes several analyses that illustrate the combined health and economic benefits of MR-MAPS, including demand forecasting in the context of various use cases, impact studies on disease burden, mortality, DALYs and cost-effectiveness analyses. The collective results suggest that MR-MAPs are likely to reduce morbidity and mortality significantly and to be cost-effective in all countries. IVIR-AC was asked to provide feedback on the results, overall framework, and priorities for next steps.

IVIR-AC recommendation highlights

- On the basis of the results of the economic analysis, IVIR-AC recommends further optimization of the use cases by refining the different scenarios of MCV immunization in each country, expanding and clarifying the target population to promote the integration with the EPI programme at global, regional and country levels. In addition, to strengthen the case for MR-MAP, IVIR-AC suggests a clearer account of product characteristics, such as the immunological characteristics and types of microneedles.

- Because of the global promotion of MMR to replace MCV in EPI programmes, in countries that already use MMR the demand forecasting calculation should account for future MMR use, the possibility of adopting MR-MAP to replace MMR, and potential application in populations other than EPI populations.

- Perform a threshold analysis to assess the range of prices at which MR-MAPs would be cost-effective. If feasible, assess a coverage threshold under which MR-MAPs would be cost-effective in all settings. Additionally, expand sensitivity analyses to evaluate the impact of parameter uncertainty.

- To approach a more appropriate estimate of cost-effectiveness, incorporate decreased human resources costs, decreased wastage, and health benefits from rubella when using MR-MAPs. Clarify model parameters and inputs (including sources for costs) in a table.

- Review the terminology used to describe low and high coverage scenarios to reflect assumptions more clearly: 2019-stagnant coverage and 2019-relative increased coverage. In addition, clarify ratio-

Afin de mesurer les avantages globaux potentiels des patches à micro-aiguilles pour la vaccination antirougeoleuse-antirubéoleuse et de guider et d’encourager les investissements futurs, une évaluation FVVA initiale (iFVVA) a été élaborée par l’UNICEF, en collaboration avec le groupe de travail de la Stratégie d’établissement des priorités en matière d’innovation vaccinale (VIPS). L’évaluation iFVVA comprend plusieurs analyses visant à illustrer les avantages à la fois sanitaires et économiques de ces patches, notamment des prévisions de la demande dans différents scénarios d’utilisation, des études d’impact sur la charge de morbidité, la mortalité et les années de vie ajustées sur l’incapacité (DALY) et des analyses coûtefficacité. Les résultats combinés de ces analyses indiquent que les patchs vaccinaux à micro-aiguilles contre la rougeole et la rubéole sont susceptibles de réduire la morbidité et la mortalité de manière significative et de présenter un bon rapport coûtefficacité dans tous les pays. L’IVIR-AC a été invité à faire part de ses commentaires sur les résultats obtenus, le cadre général et les priorités pour les prochaines étapes.

Points saillants des recommandations de l’IVIR-AC

- Sur la base des résultats de l’analyse économique, l’IVIR-AC recommande de procéder à une optimisation supplémentaire des scénarios d’utilisation en affinant les différents scénarios de vaccination contre la rougeole dans chaque pays et en élargissant et en définissant plus clairement la population cible afin d’encourager l’intégration de cette intervention avec le Programme élargi de vaccination aux niveaux mondial, régional et national. En outre, pour renforcer l’argumentaire en faveur de l’utilisation des patches, l’IVIR-AC suggère de fournir une description plus détaillée des caractéristiques du produit, notamment des caractéristiques immunologiques et des types de micro-aiguilles.

- Compte tenu des efforts déployés à l’échelle mondiale pour promouvoir le remplacement du vaccin à valence rougeole (MCV) par le vaccin ROR dans les programmes élargis de vaccination, dans les pays qui utilisent déjà le ROR, le calcul de présaison de la demande devrait tenir compte de l’utilisation future du ROR, de la possibilité d’adopter le patch à micro-aiguilles pour remplacer le ROR et de son application potentielle dans les populations non couvertes par le Programme élargi de vaccination.

- Effectuer une analyse de seuil afin de déterminer la fourchette de prix dans laquelle les patchs vaccinaux à micro-aiguilles contre la rougeole et la rubéole présenteraient un rapport coût-eficacité favorable. Si possible, déterminer le seuil de couverture en dessous duquel ces patchs auraient un bon rapport coût-eficacité quel que soit le contexte. Étendre en outre les analyses de sensibilité pour évaluer l’impact de l’incertitude des paramètres.

- Pour obtenir une estimation plus juste du rapport coût-eficacité, tenir compte de la baisse des coûts associés aux ressources humaines, de la réduction du gaspillage et des avantages sanitaires liés au fait que les patchs offrent une vaccination contre la rubéole. Préciser les paramètres et les données d’entrée du modèle (y compris les sources des coûts) dans un tableau.

- Revoir la terminologie utilisée pour décrire les scénarios de couverture faible et élevée afin d’indiquer plus clairement les hypothèses: couverture stagnante par rapport à 2019 et couverture relative accrue par rapport à 2019.
nale for choosing 2019 coverages (as opposed to post-COVID-19).
- For communicating the use case to non-technical stakeholders, use plain language, minimize acronyms, consider simpler naming (e.g. patches) and demonstrate absolute reductions using appropriate graphics. Draw on the evidence base for communicating rates to lay audiences.
- To increase demand for MAPs and raise confidence in the feasibility of their use, provide and share evidence and/or insights of EPI managers’ experience and perspectives on their utility, and provide supporting literature which illustrates the acceptability and feasibility of MAPs.
- In the equity case, communicate the use case for population groups where there is needle-related hesitancy (e.g. children and teens with intellectual disability).
- Monitor for emerging misinformation. Draw on the evidence base for addressing misinformation, including pre-bunking (warning about upcoming misinformation) and other techniques.18
- Develop a communication strategy and seek to understand the potential demand and use case for MR-MAPs in countries not currently using a rubella-containing vaccine. Clearly present the risks and benefits, demonstrating how higher coverage for both M and R could be achieved with MR-MAPs as opposed to needle and syringe.

Vaccine impact estimates for Immunization Agenda 2030 (IA 2030) – update

IVIR-AC previously reviewed16–19 several iterations of the vaccine impact modelling methodology and preliminary vaccine impact estimates, as part of the WHO Immunization Agenda 2030 (IA 2030): A global strategy to leave no one behind.20 The first iteration of estimates from 2021 initiated the ongoing iterative process to strengthen, improve and refine the model’s estimates, explaining in detail why the coverage rates of 2019 were chosen (instead of those of the post-COVID-19). For communicating the use case to non-technical stakeholders, use plain language, minimize acronyms, consider simpler naming (e.g. patches) and demonstrate absolute reductions using appropriate graphics. Draw on the evidence base for communicating rates to lay audiences.

Estimations de l’impact des vaccins dans le cadre du Programme pour la vaccination à l’horizon 2030 – mise à jour

L’IVIR-AC a précédemment examiné16–19 plusieurs itérations de la méthode de modélisation de l’impact des vaccins, ainsi que les estimations préliminaires correspondantes, dans le cadre du Programme pour la vaccination à l’horizon 2030 de l’OMS (IA2030).20 Les estimations issues de la première itération en 2021 ont été le point de départ du processus itératif en cours visant à renforcer, à améliorer et à affiner les estimations du

16 Meeting of the immunization and vaccine-related implementation research advisory committee (IVIR-AC), September 2020. Wkly Epidemiol Rec. 2020;95(49):609–23 [https://apps.who.int/iris/handle/10665/337346, accessed March 2022].
17 Meeting of the immunization and vaccine-related implementation research advisory committee (IVIR-AC), March 2021. Wkly Epidemiol Rec. 2021;96(17):133–44 [https://apps.who.int/iris/handle/10665/341059, accessed March 2022].
which serve as targets for Impact Goal Indicator 1.1, Number of future deaths averted through immunization, as part of the IA 2030 Monitoring & Evaluation framework.

The IA 2030 team provided a detailed update on implementation of previous recommendations, illustrating how the current model reflects those changes. IVIR-AC was asked to review the final results of the expanded uncertainty analysis and model validation steps, previously requested by IVIR-AC, on approaches to tracking annual progress against vaccine targets, and on planned next steps.

Recommendations centered around modelling uncertainty and broad considerations with respect to communicating and reporting annual progress.

**IVIR-AC recommendation highlights**

On the uncertainty analyses
- The main steps presented for the uncertainty analysis are consistent with IVIR-AC’s previous recommendations, including both the incorporation of both model uncertainty (from estimated regression coefficients) and input parameter uncertainty (implemented via Latin hypercube sampling).
- Provide further documentation regarding implementation, including the types of distributions assigned to the input parameters and their (in-)dependence, and how uncertainty from vaccine impact Modelling Consortium/Institute for Health Metrics and Evaluation (VIMC/IHME) death estimates was incorporated.

On annual progress reporting
- To avoid confusion in terminology, replace “observed deaths” with “estimated deaths” and clarify that this is the product of updated WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) vaccine coverage and impact ratio (deaths averted per fully vaccinated person) from the IA 2030 vaccine impact estimates.
- Report on a few (2–3) metrics. In addition to absolute levels of deaths averted, we suggest reporting absolute levels of deaths and death rates (e.g. deaths and deaths averted per 100 000 population). We also suggest using rates of change across 2 time points (e.g. percentage increase in deaths averted per year).
- Carefully consider repercussions which may arise from communication strategies tracking and reporting annual progress against vaccination targets. Utilize existing knowledge and experience to better understand any potential complications which may arise from communication choices. Initiate efforts with WHO to prepare for possible changes in reporting in the near future.

model, qui servent de cibles pour l’indicateur relatif à l’objectif d’impact 1.1, à savoir le nombre de décès futurs évités grâce à la vaccination, dans le cadre de suivi et d’évaluation du programme IA2030.

L’équipe du programme IA2030 a fait le point sur la mise en œuvre des recommandations précédentes, montrant comment ces modifications ont été intégrées au modèle actuel. L’IVIR-AC a été invité à examiner les résultats définitifs de l’analyse d’incertitude et les étapes de validation du modèle, précédemment demandées par l’IVIR-AC, et de faire part de ses commentaires sur les méthodes de suivi des progrès annuels au regard des cibles vaccinales et sur les prochaines étapes prévues.

Les recommandations ont essentiellement porté sur l’incertitude de la modélisation et sur les considérations générales relatives à la communication et à la notification des progrès annuels.

**Points saillants des recommandations de l’IVIR-AC**

Concernant les analyses de l’incertitude
- Les principales étapes présentées pour l’analyse de l’incertitude sont conformes aux recommandations précédentes de l’IVIR-AC, notamment la prise en compte à la fois de l’incertitude du modèle (à partir des coefficients de régression estimés) et de l’incertitude des paramètres d’entrée (au moyen d’un échantillonnage par hypercube latin).
- Fournir une documentation plus détaillée sur la mise en œuvre, en précisant notamment les types de distributions appliqués aux paramètres d’entrée et leur (in)dépendance, ainsi que la manière dont l’incertitude des estimations de décès provenant du Consortium de modélisation de l’impact des vaccins et de l’Institute for Health Metrics and Evaluation (VIMC/IHME) a été incorporée.

Concernant la notification des progrès annuels
- Pour éviter toute confusion d’ordre terminologique, remplacer «décès observés» par «décès estimés» et préciser qu’il s’agit du produit des estimations OMS/UNICEF actualisées de la couverture vaccinale nationale (WUENIC) et du ratio d’impact (décès évités par personne entièrement vaccinée) tiré des estimations de l’impact des vaccins du programme IA2030.
- Rendre compte de quelques paramètres (entre 2 et 3). Outre le nombre absolu de décès évités, nous suggérons d’indiquer le nombre absolu de décès ainsi que les taux relatifs aux décès (par exemple, les décès et les décès évités pour 100 000 habitants). Nous proposons également de faire état des variations entre 2 points temporaires différents (par exemple, augmentation en pourcentage du nombre de décès évités par an).
- Examiner attentivement les répercussions que peuvent avoir les stratégies de communication en termes de suivi et de notification des progrès annuels au regard des cibles vaccinales. S’appuyer sur les connaissances et les expériences existantes pour mieux comprendre les complications qui peuvent résulter des choix faits en matière de communication. En collaboration avec l’OMS, entreprendre des efforts pour se préparer à des changements possibles des modalités de notification dans un avenir proche.
As with previous IVIR-AC recommendations, we continue to endorse the importance of strengthening synergies with other major groups (e.g. VIMC) as critical.

Vaccine impact modelling consortium

The VIMC is a multinational collaboration of 21 research groups working to deliver a more sustainable, efficient and transparent approach to generating estimates of disease burden and vaccine impact for 12 vaccine-preventable diseases (VPDs). Phase 1 of VIMC, termed VIMC 1.0, ends in 2022 following completion of the latest consortium-wide manuscript (pre-print) examining coverage disruptions due to COVID-19 and related increases in disease burden and vaccine impact.

VIMC presented an update on the status of the third consortium-wide publication and elaborated on future activities proposed for VIMC’s next phase – VIMC 2.0. IVIR-AC was asked to provide feedback on VIMC 2.0 and on priority questions for the next period, specifically with regard to optimizing the use of current vaccines or future challenges around control of VPDs.

IVIR-AC recommendation highlights

The next phase of modelling should consider priority questions related to:

- optimising the use of current vaccines, such as:
  - vaccine coverage as a function of vaccine delivery infrastructure improvements or vaccine hesitancy reduction efforts from evidence-informed approaches,
  - definition of the most appropriate vaccine regimens for different groups, such as fewer doses for the general population (e.g. human papillomavirus), or
  - expanded use of adjuvanted vaccines in individuals with impaired or reduced immunological response;
- future challenges around VPD control, such as climate change impact beyond VPDs, using a One Health approach.

Comme dans ses recommandations précédentes, l’IVIR-AC souligne qu’il est crucial de renforcer les synergies avec d’autres grands groupes (par exemple le VIMC).

Consortium de modélisation de l’impact des vaccins

Le VIMC est une collaboration multinationale réunissant 21 groupes de recherche dont l’objectif est de proposer une méthode plus durable, efficace et transparente de production des estimations de la charge de morbidité et de l’impact des vaccins pour 12 maladies à prévention vaccinale. La première phase des travaux du VIMC, appelée VIMC 1.0, se termine en 2022 suite à la finalisation du dernier manuscrit rédigé par l’ensemble du consortium (en préimpression), qui examine les perturbations de la couverture vaccinale occasionnées par la COVID-19 et leurs conséquences en termes d’augmentation de la charge de morbidité et d’impact des vaccins.

Le VIMC a fait le point sur l’état d’avancement de la troisième publication du consortium et a présenté les activités proposées pour la prochaine phase de ses travaux, VIMC 2.0. L’IVIR-AC a été invité à faire part de ses commentaires sur la phase VIMC 2.0 et sur les questions à aborder en priorité lors de la prochaine période, en particulier les moyens d’optimiser l’utilisation des vaccins actuels et les défis qui se poseront à l’avenir en matière de lutte contre les maladies à prévention vaccinale.

Points saillants des recommandations de l’IVIR-AC

La prochaine phase de la modélisation devra aborder les questions prioritaires suivantes:

- l’optimisation de l’utilisation des vaccins actuels, notamment:
  - la couverture vaccinale en fonction des améliorations apportées à l’infrastructure d’administration des vaccins ou des efforts déployés pour réduire la réticence à la vaccination selon des approches fondées sur des données probantes;
  - la définition des schémas vaccinaux les plus appropriés pour différents groupes, comme l’utilisation d’un nombre réduit de doses pour la population générale (par exemple pour le papillomavirus humain); ou
  - l’utilisation plus large des vaccins adjuvants chez les personnes dont la réponse immunologique est altérée ou réduite;
- les défis futurs en matière de lutte contre les maladies à prévention vaccinale, notamment l’impact des changements climatiques au-delà de ces maladies, conformément à l’approche "Une seule santé".
● national vaccination policies as a potential mediator of vaccine uptake and determinant of coverage, and possibly impact, as well as a contributor to the wider aspects of vaccine implementation (e.g. supply chain).

When formulating and prioritizing modelling questions, IVIR-AC suggested clarifying and communicating all methods used in the process and considering utilization of a multi-criteria decision analysis tool when multi-stakeholder groups with divergent agendas and priorities are involved.

Progress towards regional measles elimination – worldwide, 2000–2021

Anna A. Minta,1 Matt Ferrari,2 Sebastien Antoni,3 Allison Portnoy,4 Alyssa Sbarra,6 Brian Lambert,8 Sarah Haury sky,9 Cynthia Hatcher,10 Yoann Nedelec,11 Deblina Datta,11 Lee Lee Ho,12 Claudia Steulet,13 Marta Gacic-Dobo,14 Paul A. Rota,15 Mick N. Mulders,16 Anindya S. Bose,7 William Perea Caro8 and Patrick O’Connor1

All 6 WHO regions have committed themselves to eliminate measles. The aim of the Immunization Agenda 2021–2030 (IA2030)12 is to achieve regional targets as a core indicator of impact. Measles is positioned as a tracer of the ability of a health system to deliver essential childhood vaccines. IA2030 highlights the importance of ensuring rigorous surveillance systems for measles to document gaps in immunity and achieve 95% coverage with 2 timely doses of measles-containing vaccine (MCV) among children. This report describes progress towards measles elimination during 2000–2021 and updates a previous report.3

During 2000–2021, estimated global coverage with a first MCV dose (MCV1) increased from 72% to a peak of 86% in 2019 but decreased during the COVID-19 pandemic to 83% in 2020 and to 81% in 2021, the lowest MCV1 coverage recorded since 2008. All countries conducted measles surveillance, but only 47 of 135 countries (35%) that reported discarded cases3 achieved the sensitivity indicator target of ≥22 discarded cases per 100 000 population in 2021, indicating underperformance of surveillance systems in some countries. Annual reported

1 Measles elimination is defined as the absence of endemic measles virus transmission in a region or other defined geographical area for ≥12 months in the presence of a high-quality surveillance system that meets the targets of key performance indicators.

2 IA2030 is the global vision and strategy to extend the benefits of vaccines to everyone, everywhere, developed by immunization stakeholders and endorsed by the World Health Assembly in 2020 (https://www.who.int/immunization/immunization_agenda_2020/en/).

3 No.45, 2022, pp.549–556.

4 A discarded case is defined as a suspected case that has been investigated and determined to be neither measles nor rubella by 1 laboratory testing in a proficient laboratory or 2 epidemiological linkage to a laboratory-confirmed outbreak of a communicable disease that is not measles or rubella. The discarded case rate is used to measure the sensitivity of measles surveillance.

Progrès accomplis dans le monde en vue de l’élimination régionale de la rougeole, 2000–2021

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Les 6 Régions de l’OMS se sont toutes engagées à éliminer la rougeole. L’objectif fixé dans le Programme pour la vaccination à l’horizon 2030 (IA2030)12 est d’atteindre les cibles régionales, qui servent d’indicateur de base de l’impact de la vaccination. La rougeole est utilisée comme un indicateur de la capacité d’un système de santé à administrer les vaccins essentiels destinés aux enfants. Le programme IA2030 souligne qu’il est essentiel d’assurer une surveillance rigoureuse de la rougeole afin de mettre en évidence les lacunes de l’immunité et d’atteindre une couverture de 95% par 2 doses de vaccin à valence rougeole (MCV) administrées en temps utile chez les enfants. Le présent rapport décrit les progrès accomplis vers l’élimination de la rougeole au cours de la période 2000–2021, et actualise les informations fournies dans le rapport précédent.3

Au cours de la période 2000–2021, la couverture mondiale estimée par la première dose de MCV (MCV1) a d’abord augmenté, passant de 72% à un pic de 86% en 2019, mais a ensuite régressé pendant la pandémie de COVID-19, s’établissant à 83% en 2020 et à 81% en 2021, soit son taux le plus faible enregistré depuis 2008. Tous les pays ont mené des activités de surveillance de la rougeole, mais seuls 47 (35%) des 135 pays ayant signalé des cas écartés3 ont atteint la cible de l’indicateur de sensibilité (≥22 cas écartés pour 100 000 habitants) en 2021, ce qui est révélateur d’une performance insuffisante des systèmes de surveil-
measles incidence decreased by 88% during 2000–2016, from 145 to 18 cases per 1 million population, then rebounded to 120 in 2019 during a global resurgence,\(^5\) before decreasing to 21 in 2020 and to 17 in 2021. Large and disruptive outbreaks were reported in 22 countries in 2021. During 2000–2021, the estimated annual number of measles deaths decreased by 83%, from 761,000 to 128,000; an estimated 56 million measles deaths were averted by vaccination. To regain progress and achieve regional measles elimination targets during the COVID-19 pandemic, accelerating targeted efforts is necessary to reach all children with 2 MCV doses, while implementing robust surveillance and identifying and closing immunity gaps to prevent cases and outbreak.

### Immunization activities

WHO and the United Nations Children’s Fund (UNICEF) use data from 1) administrative coverage (calculated by dividing the number of vaccine doses administered by the estimated target population, reported annually), 2) country estimates\(^6\) and 3) vaccination coverage surveys to estimate MCV1 and second dose MCV (MCV2) coverage through routine immunization services (i.e., not mass campaigns).\(^7\) During 2000–2010, estimated MCV1 coverage increased worldwide from 72% to 84%; however, coverage stagnated at 84 to 86% during 2010–2019, decreased to 83% in 2020 during the COVID-19 pandemic and decreased further to 81% in 2021. Although there was regional variation, all 6 WHO regions reported decreased MCV1 coverage since 2019, only the European Region experiencing a plateau between 2020 and 2021 (Table 1).

Of the 194 WHO Member States, 91 (47%) achieved ≥90% MCV1 coverage in 2021; however, only 24 (26%) of those countries reported an MCV1 coverage of ≥80% in all districts. In 2021, 24.7 million infants did not receive MCV1 from routine immunization services, an increase of 2.4 million (11%) from 2020. The 10 countries with the highest number of infants who did not receive MCV1 were Nigeria (3.1 million), India (2.5 million), the Democratic Republic of the Congo (1.7 million), Ethiopia (1.7 million), Indonesia (1.2 million), Pakistan (1.2 million), the Philippines (1.0 million), Angola (0.8 million), Brazil (0.7 million) and the United Republic of Tanzania (0.5 million). These countries accounted for 59% of all children who did not receive MCV1. Estimated MCV2 coverage quadrupled

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5 See No. 46, 2022, pp. 564–572.

6 Estimates based on administrative data and any other available information on factors that affect immunization coverage, including private sector or nongovernmental organization contributions to immunization, insufficient demographic data and incomplete reporting.


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5 Voir N°46, 2022, pp. 564-572.

6 Estimations fondées sur les données administratives et toute autre information disponible sur des facteurs ayant une incidence sur la couverture vaccinale, y compris les contributions du secteur privé ou des organisations non gouvernementales à la vaccination, l’insuffisance des données démographiques et la soumission incomplète de données.

### Table 1
Estimates of coverage with the first and second doses of measles-containing vaccine administered through routine immunization services, reported measles cases and incidence, by WHO Region – Worldwide, 2000, 2010, 2016, 2019, 2020 and 2021

<table>
<thead>
<tr>
<th>WHO Region/year (no. of countries in region) – Région OMS (nombre de pays dans la catégorie)/année</th>
<th>Coverage with MCV1 (%) – Couverture par MCV1 (%)</th>
<th>Countries with ≥90% MCV1 coverage (Pays avec couverture par MCV1 ≥90%)</th>
<th>Coverage with MCV2 (%) – Couverture par MCV2 (%)</th>
<th>Reporting countries with &lt;5 measles cases/million (%) – Pays déclarants avec &lt;5 cas de rougeole par million (%)</th>
<th>No. of reported measles cases – Nombre de cas de rougeole notifiés</th>
<th>Measles incidence (per million people) – Incidence de la rougeole (en millions de personnes)</th>
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<tbody>
<tr>
<td><strong>African – Région africaine</strong></td>
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<tr>
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<td>53</td>
<td>9</td>
<td>5</td>
<td>6</td>
<td>520 102 (60.9)</td>
<td>832</td>
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<tr>
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<td>72</td>
<td>36</td>
<td>5</td>
<td>30</td>
<td>199 174 (57.9)</td>
<td>232</td>
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<tr>
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<td>68</td>
<td>34</td>
<td>22</td>
<td>49</td>
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<tr>
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<td>34</td>
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<tr>
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<td>72</td>
<td>89</td>
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<td>6 769 (4.3)</td>
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<td>48</td>
<td>77</td>
<td>52</td>
<td>26 089 (21.0)</td>
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<tr>
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<td>77</td>
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<td>91</td>
<td>91</td>
<td>99 (0.1)</td>
<td>0.1</td>
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<td><strong>South-East Asia – Région de l’Asie du Sud-Est</strong></td>
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<tr>
<td>2000 (10)</td>
<td>62</td>
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<td>0</td>
<td>78 558 (9.2)</td>
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<td>75</td>
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<td>2020 (11)</td>
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<td>45</td>
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<tr>
<td>2021 (11)</td>
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<td>55</td>
<td>78</td>
<td>55</td>
<td>6 448 (5.2)</td>
<td>3</td>
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from 17% in 2000 to 72% in 2020, then decreased slightly, to 71% in 2021. The number of countries offering MCV2 increased by 92%, from 95 (50%) in 2000 to 182 (94%) in 2021. Three countries (Comoros, Côte d’Ivoire and Equatorial Guinea) introduced MCV2 in 2021.  

Approximately 150 million people received MCV during supplementary immunization activities (SIAs)\(^6\) in 18 countries in 2021. An additional 4 million received MCV during responses to measles outbreaks. As of December 2021, 25 MCV campaigns that had been

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\(^a\) See \(\text{https://immunizationdata.who.int/pages/coverage/mcv.html}\); data as of 29 September 2022.

\(^b\) Denominator is the number of WHO member states. – Le dénominateur est le nombre d’États Membres de l’OMS.

\(^c\) Population data from United Nations, Department of Economic and Social Affairs, Population Division, 2022. Any country not reporting measles cases for that year was removed from both the numerator and denominator in calculating incidence. – Données démographiques provenant des Nations Unies, Département des affaires économiques et sociales, Division de la population, 2022. Tous les pays qui n’ont pas fourni de données sur les cas de rougeole pour cette année-là ont été retirés du numérateur et du dénominateur.

\(^d\) Cases per 1 million people. – Cas pour 1 million de personnes.

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\(^6\) Generally, SIAs are conducted for 2 target age ranges. Initial catch-up SIAs are for children aged 9 months–4 years to eliminate susceptibility to measles in a population. Periodic follow-up SIAs then target children aged 9–59 months born since the previous SIA. Follow-up SIAs are generally conducted nationwide every 2–4 years to eliminate susceptibility to measles in recent birth cohorts because of low MCV coverage and to protect children who did not respond to MCV1. Data on SIAs by country are available at \(\text{https://immunizationdata.who.int/listing.html}\). Countries may provide additional data to WHO, and data are updated retrospectively.


\(^9\) Les AVS sont généralement réalisées en clôtant 2 tranches d’âge différentes. Des AVS initiales de rattrapage sont menées auprès des enfants âgés de 9 mois à 14 ans pour éliminer la sensibilité à la rougeole dans une population donnée. Des AVS réguliers de suivi clôtent ensuite les enfants âgés de 9-59 mois qui sont nés depuis l’AVS précédente. Les AVS de suivi sont généralement réalisées à l’échelon national tous les 2 à 4 ans afin d’éliminer toute sensibilité à la rougeole apparue dans les dernières cohortes de naissance en raison d’une faible couverture par le MCV et de protéger les enfants dont la réponse au MCV1 n’a pas été satisfaisante. Les données par pays concernant les AVS sont disponibles à l’adresse \(\text{https://immunizationdata.who.int/listing.html?topic=&location=}\). Il est possible que des pays transmettent des données supplémentaires à l’OMS, dans quel cas les données sont mises à jour rétrospectivement.
Reported measles incidence and surveillance performance

The WHO Global Measles and Rubella Laboratory Network (GMRLN) supports countries in providing standardized, quality-controlled laboratory testing for measles and rubella. Of the 135 (70%) countries that reported discarded cases, 47 (35%) achieved the sensitivity indicator target of ≥2 discarded cases per 100 000 population in 2021, as compared with 45 (31%) of 143 countries that reported in 2020. GMRLN laboratories received 122 735 specimens for testing in 2021, as compared with 122 116 specimens in 2020.

Countries report the number of incident measles cases to WHO and UNICEF annually, on the Joint Reporting Form.10 During 2000–2016, the number of reported measles cases decreased by 84%, from 853 479 to 132 490. The number reported peaked at 873 022 in 2019, then decreased to 159 073 in 2020 and 123 981 in 2021. Between 2000 and 2016, the annual measles incidence decreased by 88%, from 145 to 18 cases per 1 million population; the incidence then increased to 120 cases per million in 2019 and decreased by 82% to 21 in 2020 and 22% to 17 in 2021. In 2021, 22 countries in 2 WHO regions were affected by large, disruptive outbreaks;11 18 (82%) outbreaks occurred in countries in the African Region and 4 (18%) in the Eastern Mediterranean Region.

The genotypes of measles cases were reported by 27 (33%) of the 82 countries that reported at least 1 measles case in 2021, as compared with 45 (39%) of 115 countries in 2020. The number of genotypes reported decreased from 13 in 2002 to 6 in 2014, 3 in 2020 and 2 in 2021. In 2020, 1615 sequences were reported; of 648 reported sequences in 2021, 221 (34%) were D8, and 426 (66%) were B3.

Estimated numbers of measles cases and deaths

A previously described model13 for estimating the numbers of measles cases and deaths was updated with data for 2021 and United Nations population estimates.
for 2000–2021. Case fatality ratios (CFRs) from an updated systematic review and a suite of covariates known to be related to CFRs were used in a Bayesian meta-regression modelling framework to estimate CFRs for measles. The updated estimates reflect heterogeneity among countries, years and ages. The revised model and 2021 data show that the estimated number of measles cases decreased by 72%, from 34,013,000 in 2000 to 9,484,000 in 2021, and the estimated annual number of deaths due to measles decreased by 83%, from 761,000 to 128,000 (Table 2). The numbers of both cases and deaths were higher in 2021 than in 2020. During 2000–2021, in comparison with no measles vaccination, measles vaccination prevented an estimated 56 million deaths globally (Figure 1).

Regional verification of measles elimination

By the end of 2021, 76 (39%) countries had been verified by independent regional commissions as having achieved or maintained measles elimination. No WHO region had achieved or sustained elimination, and no country in the African Region has yet been verified as having eliminated measles. The WHO Region of the Americas achieved verification of measles elimination in 2016; however, endemic measles transmission was reestablished in the Bolivarian Republic of Venezuela (2016) and Brazil (2018). Since 2016, endemic transmission has been reestablished in 8 countries in other regions that had previously achieved verification of measles elimination (Albania, Cambodia, Czechia, Lithuania, Mongolia, Slovakia, the United Kingdom and Uzbekistan).

Discussion

All WHO regions remain committed to measles elimination; however, none has achieved or sustained elimination targets. Drops in MCV1 coverage and in surveillance performance that started or continued during the COVID-19 pandemic persisted in 2021. Of all the WHO regions, the South-East Asia Region had the highest number of deaths due to measles, shedding light on the importance of maintaining strong vaccination programmes.

Vérification régionale de l’élimination de la rougeole


Discussion

Toutes les Régions de l’OMS maintiennent leur engagement en faveur de l’élimination de la rougeole. Toutefois, aucune n’a atteint ou maintenu les cibles d’élimination. La couverture par le MCV1 et les performances de la surveillance ont commencé ou continué de se régresser pendant la pandémie de COVID-19, et cette tendance a persisté en 2021. De toutes les Régions de
largest decrease in MCV1 coverage between 2019 and 2021 (from 94% to 86%), and only the European Region maintained MCV1 coverage between 2020 and 2021. None of the WHO regions has recovered the coverage levels with MCV1 or MCV2 of 2019, which were still below the 95% coverage necessary to attain and sustain measles elimination.20

SIAs represent an opportunity to reach children who missed MCV doses in routine immunization programmes

### Table 2 Estimated number of measles cases and deaths, by WHO Region – worldwide, 2000 and 2021

<table>
<thead>
<tr>
<th>WHO Region/year (no. of countries in region) – Région OMS (nombre de pays dans la catégorie)</th>
<th>Estimated no. of measles cases (95% CI) – Nombre estimé de cas dus à la rougeole (IC à 95%)</th>
<th>Estimated no. measles deaths (95% CI) – Nombre estimé de décès dus à la rougeole (IC a 95%)</th>
<th>Estimated mortality reduction, 2000–2021 (%) – Estimation de la baisse de la mortalité, 2000-2021 (%)</th>
<th>Cumulative measles deaths averted by vaccination, 2000–2021 – Nombre cumulé de décès dus à la rougeole évités par la vaccination, 2000-2021</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>African – Région africaine</strong></td>
<td></td>
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</tr>
<tr>
<td>2000 (46)</td>
<td>10 965 152 (7 134 948–14 649 839)</td>
<td>356 299 (227 304–488 539)</td>
<td>81</td>
<td>19 499 793</td>
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<td>66 229 (38 811–106 293)</td>
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<td><strong>Americas – Région des Amériques</strong></td>
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<tr>
<td>2000 (35)</td>
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<td>NA – SO b</td>
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<tr>
<td><strong>Eastern Mediterranean – Région de la Méditerranée orientale</strong></td>
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<tr>
<td>2000 (21)</td>
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<td>2000 (52)</td>
<td>911 710 (733 732–1 353 344)</td>
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<td>97</td>
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<td>132 (34–352)</td>
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<td>10 230 (8 328–13 538)</td>
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<td>4 723 119</td>
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<td>2021 (27)</td>
<td>958 395 (331 831–2 320 863)</td>
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<td><strong>Total (all regions) – Totaux (pour l’ensemble des Régions)</strong></td>
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<td>127 656 (74 444–197 500)</td>
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The measles mortality model used to generate estimated measles cases and deaths is rerun each year using the new and revised annual WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) data, as well as updated surveillance data. In addition, in 2021, the model was revised with respect to correlations in coverage among different measles-containing vaccine delivery methods; therefore, the estimated cases and mortality estimates in this report might differ from those in previous reports. – Le modèle utilisé pour estimer le nombre de cas et de décès dus à la rougeole est réexécuté chaque année avec les nouvelles estimations OMS/UNICEF de la couverture vaccinale nationale (WUENIC) et les données de surveillance actualisées. En outre, en 2021, ce modèle a été révisé pour intégrer la corrélation entre la couverture et les différentes méthodes d’administration du vaccin antirougeoleux; par conséquent, les estimations du nombre de cas et de la mortalité associée qui apparaissent dans ce rapport peuvent légèrement différer de celles des rapports précédents.

Estimated measles mortality was too low to allow reliable measurement of mortality reduction. – La mortalité rougeoleuse estimée était trop faible pour permettre de mesurer de manière fiable la réduction de la mortalité.


and close gaps in immunity. In 2021, implementation of 25 campaigns that had been delayed due to COVID-19 indicated some recovery from the pandemic; however, the 18 SIAs that had not yet been conducted as of December 2021 present a risk for measles outbreaks.

The observed decrease in measles incidence in 2020 and 2021 could reflect true changes related to increased immunity following a 2017–2019 global resurgence of measles, reduced viral transmission associated with COVID-19 mitigation measures, or limited detection resulting from surveillance system underperformance, or a combination of several factors. The sensitivity of measles surveillance remained low in 2021, with few specimens received for laboratory testing and few cultures.

The Measles Outbreaks Strategic Response Plan 2021–2023 envisions a world in which all countries are equipped with robust measles outbreak prevention, preparation, and response systems. It contains 4 objectives: 1) improved coordination for outbreak preparedness and response; 2) expanded vaccination in vulnerable communities through resource mobilization for risk-based national plans; 3) enhanced national capacity for outbreak preparedness in priority countries (including robust surveillance); and 4) better timeliness and effectiveness of investigation and response to measles outbreaks (https://apps.who.int/iris/handle/10665/340657 and the Measles Outbreak Guide https://apps.who.int/iris/handle/10665/360891).

Deaths prevented by vaccination were estimated by the area between estimated numbers of deaths with vaccination and those without vaccination (cumulative total of 56 million deaths prevented during 2000–2021). Vertical bars represent upper and lower 95% confidence limits around the point estimate – Les décès évités par la vaccination sont estimés par la zone comprise entre le nombre estimé de décès avec la vaccination et le nombre estimé de décès sans vaccination (total cumulé de 56 millions de décès évités entre 2000 et 2021). Les barres verticales représentent les limites supérieure et inférieure de l’intervalle de confiance à 95% autour de l’estimation ponctuelle.

Le Plan stratégique de riposte aux flambées de rougeole 2021–2023 a pour vision de parvenir à un monde dans lequel tous les pays disposent de systèmes solides de prévention, de préparation et d’intervention en cas de flambées épidémiques de rougeole. Il comporte 4 objectifs: 1) une meilleure coordination des activités de préparation et de riposte aux flambées; 2) l’intensification de la vaccination dans les communautés vulnérables en mobilisant les ressources nécessaires aux plans nationaux fondés sur les risques; 3) le renforcement des capacités nationales de préparation aux flambées épidémiques dans les pays prioritaires (y compris une surveillance robuste); et 4) une mise en œuvre plus rapide et plus efficace des enquêtes et des interventions en cas de flambée épidémique de rougeole (https://apps.who.int/iris/handle/10665/355148 et Guide sur les flambées épidémiques de rougeole https://apps.who.int/iris/handle/10665/360891).

La baisse de l’incidence rougeoleuse observée en 2020 et 2021 pourrait être le reflet d’une évolution réelle liée à une augmentation de l’immunité à la suite de la résurgence mondiale de la maladie en 2017-2019, à une transmission virale réduite associée aux mesures de lutte contre la COVID-19, à une détection limitée résultant de la performance insuffisante des systèmes de surveillance, ou à une combinaison de tous ces facteurs.

La sensibilité de la surveillance de la rougeole est restée faible en 2021, et permettent de combler les lacunes de l’immunité. En 2021, la mise en œuvre de 25 campagnes qui avaient été retardées en raison de la COVID-19 est le signe d’un certain relèvement après la pandémie; toutefois, 18 AVS n’avaient toujours pas été menées en décembre 2021, ce qui entraîne un risque de flambées épidémiques de rougeole.
tries achieving the indicator of surveillance sensitivity. Sustained decreases in surveillance affect not only timely detection of cases and outbreaks but also undermine the ability of a programme to use measles to highlight gaps in the overall immunization system.

The findings reported are subject to at least 3 limitations. First, not all countries report complete, or any, data on SIAs and outbreak response activities; therefore, the numbers on these activities provided in this report could be underestimated. Secondly, the method for modelling estimates was updated this year, obviating comparison with the estimates for previous years. Finally, the number of specimens submitted for genotyping represents only a fraction of measles cases, so that the data presented in this report might not reflect the actual global distribution of genotypes.

Decreasing routine MCV coverage and delays in SIAs in 2021 left millions of children with 0 or only 1 dose of MCV. In the absence of a high-performing surveillance system to detect cases promptly, a growing population of susceptible children is at risk for measles and outbreaks. In alignment with IA2030, the Measles and Rubella Strategic Framework 2021–2030 outlines strategies for countries to build robust case-based surveillance for measles to detect immunity gaps and outbreaks, identify the causes of under-vaccination and develop targeted solutions, including catch-up vaccination for those who missed their routine doses during the pandemic, to reach all children with 2 doses of MCV. Accelerating these measures will help regain past progress towards regional measles elimination.

Acknowledgements
Country surveillance and immunization programme staff members.

Author affiliations
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Le déclin de la couverture de la vaccination systématique par le MCV et les retards enregistrés dans la mise en œuvre des AVS en 2021 signifient que des millions d’enfants ont reçu seulement 0 ou 1 dose de MCV. En l’absence d’un système de surveillance efficace permettant une détection rapide des cas, un nombre croissant d’enfants sensibles se trouve exposé au risque de rougeole et de flambées épidémiques de la maladie. Conformément au programme IA2030, le cadre stratégique de lutte contre la rougeole et la rubéole 2021-2030 décrit des stratégies pouvant être adoptées par les pays pour mettre en place une surveillance robuste de la rougeole basée sur les cas afin de détecter les lacunes immunitaires et les flambées épidémiques, d’identifier les causes de la sous-vaccination et d’élaborer des solutions ciblées, notamment la vaccination de rattrapage des personnes ayant manqué des doses du calendrier de vaccination systématique pendant la pandémie, afin que tous les enfants puissent bénéficier de 2 doses de MCV. L’accélération de ces mesures permettra de relancer les progrès vers l’élimination régionale de la rougeole.

Remerciements
Membres du personnel de surveillance et des programmes de vaccination dans les pays.

Affiliations des auteurs
* Département Vaccination, vaccins et produits biologiques, Organisation mondiale de la Santé, Genève (Suisse); * Centre for Infectious Disease Dynamics, Pennsylvania State University, University Park, PA (États-Unis d’Amérique); * Center for Health Decision Science, Harvard T.H. Chan School of Public Health, Boston, MA (États-Unis d’Amérique); * Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Londres (Royaume-Uni); * Global Immunization Division, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, GA (États-Unis d’Amérique); * Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA (États-Unis d’Amérique) (auteur correspondant: Anna A. Minta, mintaa@who.int).


24 The aim of the Measles and Rubella Strategic Framework 2021–2030 is to provide high-level guidance for developing regional and national strategies and operational plans to achieve “a world free from measles and rubella”. It is meant to serve as a disease-specific strategy under the IA2030 structure and is aligned with other key strategy documents, including WHO’s Thirteenth General Programme of Work 2019–2023; the UNICEF Immunization Roadmap 2018–2030; and Gavi, the Vaccine Alliance’s 2021–2025 strategy (https://www.who.int/publications/i/item/measles-and-rubella-strategic-framework-2021-2030).
Background information to the sessions
Session 1
COVID 19 vaccine impact modelling
Technical presentation 1
A flexible immunity model-based framework for evaluation of likely impacts of emerging variants & vaccines

Project coordination and oversight – team 0: Profs. Jodie McVernon, Ivo Mueller, James Wood

Shifting vaccine priorities – team 1: Christopher M. Baker, Thao P. Le, Isobel Abell, Camelia Walker

Impacts of VoCs – team 2: Eamon Conway, Yasmine McDonough, Trish Campbell, Michael Lydeamore

Variant boosters – team 3: Nick Golding, Gerry Ryan, Freya Shearer, Deborah Cromer, Alexandra Hogan

Cost effectiveness – team 4: Natalie Carvalho, Edifofon Akpan, Cyan Wang, Mackenzie Bourke, Patrick Abraham

13th February 2023
Motivating questions

• Shifting vaccine priorities with high infection derived immunity
• Assess the impact of Variants of Concern on vaccination priorities
• Cost-effectiveness of COVID-19 vaccines (compared to other vaccines)

• What is the cost-effectiveness of routine annual COVID-19 booster doses in different populations and age groups given high background infection exposure, immune waning and escape?
• How should this inform future booster strategy – optimum frequency/interval, priority populations, cost-effectiveness analysis
• In the era of Omicron and high population immunity, do we still need to offer primary vaccination schedules for unvaccinated healthy children and adolescents)?
• Do we need to offer booster doses to children and adolescents who did receive the primary series?
'older' vs 'younger'

Age distribution

Vaccination coverage and distribution schedule

primary coverage 20/50/80%

timing/age targeting

Contact matrices

as per SOCRATES or Prem et al

Transmission potential

prior AR variable

any VoC/vaccine combination

Immunological model

Agent Based Model
(with infection transmission)

Simulation infection histories

Clinical Pathways Model

severity by VoC

Clinical outcomes for infected individuals

Vaccine cost

Disease management cost

Vaccine cost-effectiveness

for exemplar country contexts

Disability weights & life tables

Multi-strain extension

Epidemiological model

for exemplar country contexts
There is a clear increase in trend in neutralising antibodies due to boosting and infection (Khoury et. al. medRxiv, and unpublished).

Our VE model has been modified to incorporate this trend, below is a qualitative scenario where the number of vaccine doses plus infection continues to increase NAbs (other immune mechanisms implicit but not quantifiable in ‘cumulative’ baseline protection).

*Example for BA1/2 curves
Vaccine procurement and delivery costs in Western Pacific region

### Vaccine dose price by income group

<table>
<thead>
<tr>
<th>Population</th>
<th>Base (all vaccines)</th>
<th>Lower (AZ)</th>
<th>Higher (Pfizer/Moderna)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older population, high coverage</td>
<td>$14.2</td>
<td>$3.9</td>
<td>$25.2</td>
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<tr>
<td>Younger population, high coverage</td>
<td>$7.8</td>
<td>$4.0</td>
<td>$12.5</td>
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<tr>
<td>Younger population, low coverage</td>
<td>$7.8</td>
<td>$4.1</td>
<td>$10.0</td>
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</tbody>
</table>

### Delivery (operational) cost per dose

#### "Older population", high primary vaccination coverage
Japan and Australia: estimated based on government budgets; Korea, Rep. and Hong Kong: from local studies; wastage rate assumed

<table>
<thead>
<tr>
<th>Delivery cost (US$)</th>
<th>Wastage rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case value (lower, higher)</td>
<td>$23.2 (11.08, 33.6)</td>
</tr>
</tbody>
</table>

#### Younger population, “leveraging scenario” in two UNICEF reports, delivery costs to get to 70% coverage (20% coverage for low primary vaccination group), wastage rate = 10% 2-3

<table>
<thead>
<tr>
<th>Delivery cost (US$)</th>
<th>Wastage rate</th>
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</thead>
<tbody>
<tr>
<td>Base case value (lower, higher)</td>
<td>$13.4 (0.7, 29.3)</td>
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</tbody>
</table>

#### "Younger population", high primary vaccination coverage (80%; 50%)

<table>
<thead>
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<th>Delivery cost (US$)</th>
<th>Wastage rate</th>
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<tbody>
<tr>
<td>Base case value (lower, higher)</td>
<td>$7.7 (2.5, 10.5)</td>
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</table>

#### "Younger population", low primary vaccination coverage (20%)

<table>
<thead>
<tr>
<th>Delivery cost (US$)</th>
<th>Wastage rate</th>
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<tbody>
<tr>
<td>Base case value (lower, higher)</td>
<td>$7.8 (2.5, 10.5)</td>
</tr>
</tbody>
</table>

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1. World Health Organization (2022). C-19 Vaccine price data from public source and as reported by countries to WHO
3. UNICEF (2022) Costs and predicted financing gap to deliver COVID-19 vaccines in 133 low- and middle-income countries
### Disease management costs in Western Pacific region

**“Younger countries”**

Modelled costs (2019 US$) of clinical case management for COVID-19 across 79 LMICS\(^1\) inflated to 2020 US$; Japan and Australia: referred to 2020 national medical fee schedules and adopted costing method of Torres-Rueda S\(^1-4\); Korea, Rep. and Hong Kong: referred to local studies 5-6.

<table>
<thead>
<tr>
<th>Country</th>
<th>Home-based care per case (2020 US$)</th>
<th>Home-based care per case (inflated to 2020 US$)</th>
<th>General ward care per day (2020 US$)</th>
<th>General ward care per day (inflated to 2020 US$)</th>
<th>ICU ward care per day (2019 US$)</th>
<th>ICU ward care per day (additional 20% inflated to 2020 US$)</th>
<th>Death per case (2019 and 2020 US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micronesia, Fed. Sts.</td>
<td>31.4 (28, 34.8)</td>
<td></td>
<td>40.8 (39.9, 41.7)</td>
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<td>347.1 (340.9, 353.4)</td>
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<td>64.5</td>
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<tr>
<td>Kiribati</td>
<td>44.8 (20.8, 131.1)</td>
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<td>47.5 (34.3, 99.0)</td>
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<td>399.5 (295.1, 1272.7)</td>
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<td>64.5</td>
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<td>Vanuatu</td>
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<tr>
<td>Fiji</td>
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<tr>
<td>Lost coverage</td>
<td>54.0 (53.5, 114.7)</td>
<td>267.0 (208.7, 657.2)</td>
<td>2120.5 (825.0, 4284.3)</td>
<td></td>
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</tbody>
</table>

-500.00 $0.00 $1’000.00 $2’000.00 $3’000.00 $4’000.00 $5’000.00 $6’000.00

**“Older countries”**

Japan and Australia: referred to 2020 national medical fee schedules and adopted costing method of Torres-Rueda S\(^1-4\); Korea, Rep. and Hong Kong: referred to local studies 5-6.

![Graph showing costs in different countries]

Population and vaccine coverage assumptions
(80% primary uptake, 11% booster coverage\(^\text{^1}\), rollout over 3 months)

\(^{1}\)11,000 doses per 100,000 pop

- No more boosting
- Pediatric boosting
- High risk boosting
- Random boosting

\(^{2}\)Pediatric (ages 5-15)

\(^{3}\)*ages 65+ first, but also includes ages 60+, then 55+ due to lack of 65+ population

Random (among all previously vaccinated individuals)
Time of variant emergence varies relative to prior infection/vaccine exposures, and booster program

Different BA.4/5-like (immune escape variant) emergence times

Different boosting times (if boosting)

Main vaccination program

* Focus on scenarios with emergence at 1.5 OR 2.5 years
** Booster campaign starts at 2 years
*** Additional scenario with 6 monthly high-risk boosting

*All scenarios shown here assume ancestral vaccine strain
Infection curves (older pop’n, immune escape 1.5/2.5 yrs, 80% coverage, boost from 2 yrs)

* Modest impact of any strategy on infection dynamics (low coverage), high risk targeting mitigates severe outcomes

* Infection peak and overall burden higher than early escape scenario, but high-risk boosting still averts severe disease

*results presented per 100,000 pop
Cost-effectiveness plane

• High transmission potential (TP)
• Boosting at 2 years
• Points show immune escape at 1.5 or 2.5 years

Summary:
• Timing of boosting matters (relative to immune escape): More cost-effective when boosting occurs prior to immune escape
• High risk boosting cost-saving or cost-effective
• Pediatric boosting not cost-effective

# High risk boosting may be CE in younger (LMIC) populations, depending on WTP threshold and other model inputs.
Infection curves (older population, immune escape at 1.5 or 2.5 yrs, 6 monthly booster)

Escape 1.5 yrs
- Timing of booster dose relative to emergence influences impact
- Half yearly boosting consistently achieves fewer severe outcomes

Escape 2.5 yrs
- Results presented per 100,000 pop
Cost-effectiveness planes: older population, high initial coverage, high risk boosting at different time points, or 6-monthly intervals (compared to no further boosting)

- Cost-effectiveness of high-risk boosting varies according to immune escape timing but *generally very cost-effective or cost-saving in older (HIC) population*
- 6-monthly boosting *cost-effective but more expensive than annual boosting*, not cost-saving (unlikely CE in younger pop)
Increasing primary coverage from low baseline (20/50%)

Target groups (for each baseline coverage):
- No further vaccination
- New pediatric primary vaccination
- High risk boosting (65+, remaining doses given out as boosters to younger age groups)
- New primary vaccination (according to original scheme)
- Total: 11k doses (among 100k population)
Infection curves (immune escape 2.0 yrs, boosting 2 yrs, initial coverage 50% or 20%)

50% primary coverage

* New pediatric vaccination has little or no impact on severe outcomes, some gains from increased adult coverage

20% primary coverage

* High risk boosting remains best strategy even with low primary uptake, although impact is reduced
Cost-effectiveness plane

- High transmission potential (TP)
- Immune escape at 2 years
- Boosting starts at 2 years
- Comparing 20% and 50% initial vaccination coverage

Summary:
- High risk boosting strategies best
- High risk boosting may be CE for younger (LMIC) countries with highest WTP thresholds, depending on unit costs
- New primary pediatric vaccination and new primary vaccination unlikely to be CE
Summary and conclusions

• Paediatric programs (primary series, boosting) are not cost-effective

• Given consistent age-dependency to date of severe disease risk, elder-targeted strategies are most likely to be cost-effective or even cost saving across a broad range of uncertainties

• Absolute harms averted are influenced by:
  • Age and risk profile of the population
  • Prior immune landscape (infection exposure history, vaccination rollout)
  • Timing of emergence of an immune escape variant in relation to boosting

• 6 monthly ‘high risk’ booster programs may be cost effective in older (HIC) populations, but not those with younger demographics (LMIC)
Questions for IVIR-AC

• We assume that even in populations with low primary vaccine uptake, elders will have been immunised first and are thus eligible for boosters. Are there specific primary vaccine approaches that should be explored in these age groups if primary uptake was low?

• We have prepared outputs to compare 6 monthly immunisation of ‘high risk’ with a single campaign delivered over 3 months. Are there other feasible implementation scenarios that should be considered?

• At present we vary coverage of the primary series between 20 and 80%, but fix booster uptake at around 10% of the total population (targeted variously to older or younger ages, or randomly). Is higher recurring coverage considered achievable or worth exploring?
Additional slides

Sensitivity analyses on key assumptions

A. Impact of boosting on ‘older’ population in settings with reduced transmission (population density, climate factors, etc)
B. Impact of boosting on ‘younger’ population with different baseline primary course uptake (80/50/20%) and high/low transmission
Results – older population 80% initial vaccination coverage, low TP

Representative WPR countries: Australia, Hong Kong, Japan, New Zealand, Republic of Korea, Singapore
Infection curves (older pop’n, low transmission, immune escape 1.5/2.5 yrs, 80% coverage)

* Low exposure pre-variant emergence - protection mostly vaccine derived, little hybrid immunity, reduced vaccine impact

* Booster delivered prior to variant emergence, high risk booster strategy mitigates against severe impacts

*results presented per 100,000 pop
Cost-effectiveness plane

- Low transmission potential (TP)
- Boosting at 2 years
- Points show immune escape at 1.5 or 2.5 years

Summary:
- High risk boosting CE especially if immune escape happens at 2.5 years
- Random boosting CE
- Pediatric boosting not CE

One-way sensitivity analysis
One-way sensitivity analysis

Scenario: Older population (80% initial coverage), further boosting high risk, low TP, boosting at 2 years, immune escape starts at 1.5 years

**Interpretation:**

**Vaccine delivery cost and unit cost per dose** most influential costing parameters
Results – younger population
80% initial vaccination coverage

Representative WPR countries: Fiji, Samoa, Tonga, Mongolia, Cambodia, Lao PDR, Philippines, Vanuatu, Kiribati, Fed Sts Micronesia
Minor differences between the different boosting groups, in terms of infections, lower deaths overall than older pop’n

Clearer differences between total deaths by vaccine group, less natural immunity at time of emergence

*results presented per 100,000 pop
Cost-effectiveness plane

- High transmission potential (TP)
- Boosting at 2 years
- Points show immune escape at 1.5 or 2.5 years

Summary:
- Pediatric boosting scenarios are not cost-effective, and show increased DALYs*
- High risk boosting may be cost-effective or cost-saving in younger (LMIC) populations, depending on WTP threshold and other model inputs
- No other strategies clearly CE

*stochastic variation?
One-way sensitivity analysis: costing input parameters

Scenario: Younger population 80% initial coverage, further boosting high risk, high TP, boosting at 2.0 (year), immune escape starts 2.5 (year)

Interpretation:
Vaccine delivery cost, home based care cost, and unit cost per dose most influential costing parameters
Infection curves (younger population, immune escape at 1.5 or 2.5 yrs, 6 monthly booster)

Escape 1.5 yrs
- Severe outcomes overall fewer than in older population

Escape 2.5 yrs
- Differential benefit of 6 monthly boost depends on variant timing
Cost-effectiveness planes: younger population, high initial coverage, high risk boosting at different time points, or 6-monthly intervals (compared to no further boosting)

- Cost-effectiveness of high-risk boosting varies by immune escape timing and willingness to pay threshold
- 6-monthly boosting **not cost-effective for younger (LMIC) countries with high initial coverage (80%)**
Results – younger population
50% initial vaccination coverage

Representative countries: Fiji, Samoa, Tonga, Mongolia, Cambodia, Lao PDR, Philippines, Vanuatu, Kiribati, Fed Sts Micronesia
Infection curves (younger pop’n, immune escape 2 yrs, 50% coverage, high v low transmission)

**High Transm’n**

* High risk boosting remains most impactful strategy

**Low Transm’n**

* Vaccine impact more marked in setting of lower prior infection
Cost-effectiveness plane

• High and low transmission potential
• Immune escape at 2 years
• Boosting starts at 2 years

Summary:
• High risk boosting in low transmission potential scenario may be CE for countries with high WTP thresholds
• Random boosting and further primary pediatric vaccination not CE
Results – younger population
20% initial vaccination coverage

Representative countries: Solomon Islands; PNG
Infection curves (younger pop’n, immune escape 2 yrs, 20% coverage, high v low transmission)

*Low primary coverage equates to low booster coverage, minimal impact in this scenario by strategy, high risk remains superior

High Transm’n

![High Transmission Infection Curve]

- Younger population
  - No further boosting
  - New pediatric vaccination (ages 5-15)
  - High risk boosting (95% first)
  - New primary vaccinations
  - Circulating BA.1
  - Circulating BA.4.5
  - Main vaccination program
  - Further vaccination program

Low Transm’n

![Low Transmission Infection Curve]

- Younger population
  - No further boosting
  - New pediatric vaccination (ages 5-15)
  - High risk boosting (95% first)
  - New primary vaccinations

*Vaccine impact more marked in setting of lower prior infection

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Median</th>
<th>95% Quantiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>No further boosting</td>
<td>16.0</td>
<td>(9.0, 25.0)</td>
</tr>
<tr>
<td>New pediatric vaccination (ages 5-15)</td>
<td>16.0</td>
<td>(9.0, 25.0)</td>
</tr>
<tr>
<td>High risk boosting (95% first)</td>
<td>11.0</td>
<td>(5.0, 17.0)</td>
</tr>
<tr>
<td>New primary vaccinations</td>
<td>14.0</td>
<td>(8.0, 22.0)</td>
</tr>
</tbody>
</table>
Cost-effectiveness plane

• High and low transmission potential
• Immune escape at 2 years
• Boosting starts at 2 years

Summary:
• No boosting strategies CE regardless of transmission potential
• Further primary pediatric vaccination clearly not CE
A flexible immunity model-based framework for evaluation of likely impacts of emerging variants & vaccines

Technical Report

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1 Introduction

Since the emergence of SARS-CoV-2 (COVID-19), there have been multiple waves of infection and multiple rounds of vaccination rollouts. Both prior infection and vaccination can prevent future infection and reduce severity of outcomes, combining to form hybrid immunity against COVID-19 at the individual and population level.

This report provides results from the modelling used to address the following issues concerning current vaccines on shifting vaccination priorities with high infection-derived immunity:

- The incremental benefit of a first, second, booster, or second booster vaccine dose (J&J + others) in a population with a high prevalence of past infection;
- The use groups to be vaccinated in high seroprevalence settings (what use group derives little benefit from vaccination);
- The vaccine-preventable disease burden in different priority-use groups and how it compares to other vaccine-preventable diseases;
- The serological data needed to formulate serology informed national policy on vaccination;
- The cost-effectiveness of routine annual COVID-19 booster doses in different populations and age groups given high background infection exposure, immune waning and escape;
- Future booster strategies - optimum frequency/interval, priority populations, and cost-effectiveness;
- Primary, and booster, vaccination for unvaccinated health children and adolescents in the context of Omicron and high population immunity.

To address these questions, we will do the following things:

- We will configure two agent based model (ABM) populations, representing typical ‘younger’ and ‘older’ demographics within the Western Pacific Region (WPR);
- We will simulate single strain COVID-19 epidemics within these populations according to a range of vaccine coverage (with initial primary coverage of 20, 50, 80%) and attack rate (20-80%) scenarios;
- In populations with differing levels of prior primary vaccine coverage and timing and attack rates of epidemics, we will assess the incremental benefit of additional vaccine doses (1st, 2nd, 3rd, 4th as relevant) using currently available formulations against contemporaneously circulating Omicron subtypes. Assuming a first wave of BA1/2 we will consider likely protection against a subsequent BA1/2 or BA4/5 wave;
- We will use symptomatic infection outputs from the ABM to provide inputs to a clinical pathways model that determines likely progression to disease (and length of stay) based on an individual’s history of exposure, vaccination, age and other identifiable clinical risk factors;
• Output projections will include anticipated hospitalisations, ICU bed occupancy and deaths for different levels of population vaccine coverage and age targeting (i.e. paediatric vs elder programs). These outcomes and their mitigation by vaccination will be reported in each of the populations characterised, for the various prior exposure scenarios explored;

• We will use the outputs as described above to estimate years of life lost from premature deaths (YLLs), years of life lived with disability (YLDs) and calculate disability-adjusted life years (DALYs) associated with all scenarios explored. Alongside vaccination program costs and disease management costs, we will estimate the incremental cost-effectiveness of additional vaccination scenarios targeting various population groups, for different groups of representative countries.

In particular, this report details the results presented to IVIRAC on the 13th of February 2023. Further modelling details and assumptions can be found in [1] and [2]. The code used to generate the model figures in this report can be found at https://github.com/spectrum-spark/covid_singlestrain_scenarios. Further details on the cost effectiveness analysis can be found in [3] at https://github.com/spectrum-spark/covid-CEA.
2 Scenario definition

In our scenarios, we vary population type, immune escape, transmission potential (TP), vaccine coverage and boosting strategy. For more details on how scenarios are defined, please see [2].

Population types

- **“Older” population**: representative of high-income countries (HIC) in the WPR, where the “older” population distribution is averaged from China, Hong Kong SAR, Macao SAR, Japan, Republic of Korea, Singapore, Australia, New Zealand, New Caledonia, Guam, and French Polynesia.

- **“Younger population**: representative of mostly lower-middle income and some upper-middle income countries (MIC) in the WPR, where the “younger” population distribution is averaged from Mongolia, Brunei Darussalam, Cambodia, Lao People’s Democratic Republic, Philippines, Fiji, Papua New Guinea, Solomon Islands, Vanuatu, Kiribati, Micronesia (Fed. States of), Samoa, and Tonga.

Transmission potential

Transmission potential (TP) reflects different populations’ intrinsic transmission which is dependent on a variety of factors such as demographic, weather/climate, housing, population density etc. In general, populations with high TP have high past attack rate and populations with low TP have low past attack rate. We consider scenarios with:

- High TP, and
- Low TP.

Vaccine coverage

- **High coverage**: 80% primary vaccine coverage after the first year (88% primary vaccine coverage by 1.5 years) in both “older” and “younger” populations.

- **Low coverage**: 20% or 50% primary vaccine coverage (22% and 55% primary vaccine coverage by 1.5 years respectively) in the “younger” population only. Note that 20% primary vaccine coverage applies to a subset of “younger” populations where this scenario is relevant (such as Papua New Guinea and the Soloman Islands)

Immune escape

An immune escape variant emerges either

- **1.5 years**, or
- **2.0 years**, or
• **2.5 years**

after the start of the main vaccination program.

**Boosting strategies**

Three boosting strategies are considered, with 11,000 vaccine doses administered in all scenarios:

• **Pediatric boosting,**
• **High risk boosting,** and
• **Random boosting.**

Furthermore, we consider boosters starting at either a fixed point (e.g. from 2 years) or delivered routinely (e.g. every 6 months from 2 years).

![Figure 1: Older population demographic and 88% primary vaccination coverage breakdown.](image)
Figure 2: Younger population demographic and 88% primary vaccination coverage breakdown.
Figure 3: Boosting strategies for the older population scenarios given 88% primary vaccination coverage.
Figure 4: Boosting strategies for the younger population scenarios given 88% primary vaccination coverage.

(a) Pediatric boosting  (b) High risk boosting  (c) Random boosting

Figure 5: Timing of variant emergence considered relative to prior infection/vaccine exposures and booster program

Different BA.4/5-like (immune escape variant) emergence times

Different boosting times (if boosting)
3 Cost-effectiveness analysis

The cost-effectiveness analysis was conducted from a healthcare system perspective, including direct medical costs only. All costs are reported in 2020 United States dollars (USD). Health outcomes are presented in terms of disability-adjusted life years (DALYs) using disability weights from the Global Burden of Disease study (GBD)[4, 5, 6, 7, 8, 9], assumptions on the duration of illness from prior studies, and estimates of life years lost due to premature mortality from WHO life tables. Future costs and health outcomes are discounted by 3%.

There are two cost categories:

- Programmatic costs related to the vaccination intervention, including vaccine dose costs, wastage, and delivery costs;
- Disease management costs at home, in outpatient and inpatient settings for symptomatic COVID-19 related illness.

3.1 Defining exemplar country contexts for cost-effectiveness analysis

The representative ‘exemplar’ countries groupings are as follows, with full details provided in the cost-effectiveness appendix [3]:

- **Group A**: High income country (HIC), ‘older’ population with strong health systems capacity and high (∼80%) prior primary vaccine coverage. High unit costs for vaccine delivery and disease management. *(Countries in this group include Japan, Australia, Republic of Korea, and Hong Kong, and are representative of other WPR HICs such as New Zealand.)*

- **Group B**: Upper- and lower- middle income country (MIC), ‘younger’ population with varying levels health systems capacity and prior primary vaccine coverage (∼80% and ∼50%). Low-to-high unit costs for vaccine delivery (depending on geography and population size) and low-to-middle unit costs for disease management. *(Countries in this group include Fiji, Samoa, Tonga, Mongolia, Cambodia, Philippines, Lao, Vanuatu, Kiribati, Micronesia, Papua New Guinea, and Solomon Islands.)*

- **Group C**: Lower-middle income country, younger population with weaker health systems capacity and low (∼20%) prior primary vaccine coverage. Low unit costs for vaccine delivery and disease management. *(Countries in this group, a subgroup of Group B, include Papua New Guinea and Solomon Islands.)*

Some WPR countries are not included in these representative ‘exemplar’ country groupings (for example, those with demographics that classify as neither ‘older’ nor ‘younger’, or those with demographics that match to ‘older’ or ‘younger’ categorisation, but per-capita income level does not). The implications for these countries would need to be considered in light of the findings for Groups A and B.
4 Results

4.1 Scenarios 1 and 2: Older population, high TP, 80% initial vaccination coverage, immune escape 1.5/2.5 years, *boosting from 2 years*

In Scenario 1 we see modest impact of any strategy on infection dynamics. However, high risk targeting helps mitigate severe outcomes.

While the infection peak and overall burden is higher in Scenario 2 (late escape) compared to Scenario 1 (early escape), high-risk boosting still averts severe disease.

![Figure 6: Infections and deaths for Scenario 1: older population, high TP, immune escape 1.5 years, 80% initial vaccination coverage, boosting from 2 years scenario.](image)

Figure 6: Infections and deaths for Scenario 1: older population, high TP, immune escape 1.5 years, 80% initial vaccination coverage, boosting from 2 years scenario.
Figure 7: Infections and deaths for Scenario 2: older population, high TP, 80% initial vaccination coverage, immune escape 2.5 years and boosting from 2 years scenario.
4.2 Cost-effectiveness for Scenarios 1 and 2

We find that boosting is more cost-effective when it occurs prior to immune escape. High risk boosting is likely to be highly cost-saving or cost-effective, while pediatric boosting is not cost-effective. Cost-effectiveness of high-risk boosting is driven primarily by vaccine program (delivery and dose) costs, followed by disease management costs in general ward.

Furthermore, high risk boosting may be cost-effective or even cost-saving in younger (MIC) populations, depending on willingness to pay (WTP) thresholds and other model inputs. These results are driven primarily by home-based care cost inputs, and vaccine delivery costs, which remain highly uncertain in these settings (see Fig. 23).

Figure 8: Cost-effectiveness plane for Scenarios 1 and 2: Older population, high TP, 80% initial vaccination coverage, immune escape 1.5/2.5 years, and boosting from 2 years.
4.3 Scenarios 3 and 4: Older population, high TP, 80% initial vaccination coverage, immune escape at 1.5/2.5 years, 6 monthly boosting

Scenarios 3 and 4 show that the timing of booster dose relative to emergence influences the impact of vaccination. Furthermore, 6 monthly boosting consistently achieves far fewer severe outcomes when compared to no further boosting (Scenarios 1 and 2).

Figure 9: Infections and deaths for Scenario 3: older population, high TP, 80% initial vaccination coverage, immune escape at 1.5 years, 6 monthly boosting

<table>
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<th>Time (years)</th>
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<th>95% quantiles</th>
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<td>(25.0, 45.0)</td>
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<td>(22.48, 44.0)</td>
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<td>2.5</td>
<td>40.0</td>
<td>(28.0, 51.0)</td>
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<tr>
<td>Half yearly boosters</td>
<td>31.0</td>
<td>(20.0, 41.0)</td>
</tr>
</tbody>
</table>
Figure 10: Infections and deaths for Scenario 4: older population, high TP, 80% initial vaccination coverage, immune escape at 2.5 years, 6 monthly boosting
4.4 Cost-effectiveness for Scenarios 3 and 4

The cost-effectiveness of high-risk boosting varies according to immune escape timing, but generally is very cost-effective or cost-saving in the older (HIC) population. 6-monthly boosting remains highly cost-effective, but more expensive than annual boosting.

Furthermore, 6-monthly boosting has uncertain cost-effectiveness in the younger (MIC) population. Again, results are driven by home-based care costs (lower costs indicate 6-monthly boosting is unlikely to be cost-effective) and vaccine program costs (lower costs, for example, donated vaccine, would mean 6-monthly boosting may be very cost-effective or cost-saving) (see Fig. 27 and Fig. 28).

Figure 11: Cost-effectiveness plane for Scenario 3: older population, high TP, 80% initial vaccination coverage (88% total vaccination coverage), immune escape at 1.5/2.5 years, with 6 monthly boosting.
Figure 12: Cost-effectiveness plane for Scenario 4: older population, high TP, 80% initial vaccination coverage (88% total vaccination coverage), immune escape at 1.5/2.5 years, with 6 monthly boosting.
4.5 Scenarios 5 and 6: Younger population, high TP, 20%/50% initial vaccination coverage, immune escape at 2 years, boosting from 2 years

We now consider scenarios for younger populations with lower primary vaccine coverage (20% or 50% initial vaccine coverage after 1 year). We consider three boosting strategies targeting different groups:

- New pediatric primary vaccination,
- High risk boosting (older first),
- New primary vaccinations.

We fix immune escape variant emergence at the ‘best case scenario’, i.e. 2 years.

![Diagram](image)

Figure 13: Boosting strategies for the younger population scenarios given 20% initial primary vaccination coverage. The same approach is used for the 50% initial vaccination coverage scenarios.
Scenarios 5 and 6 show new pediatric vaccination has little or no impact on severe outcomes, however we see some gains from increased adult coverage. High risk-boosting remains the best strategy even with low primary uptake, although impact is reduced in this case.

Figure 14: Infections and deaths for Scenario 6: younger population, high TP, 50% initial vaccine coverage, immune escape at 2 years.
Figure 15: Infections and deaths for Scenario 6: younger population, high TP, 20% initial vaccine coverage, immune escape at 2 years.
4.6 Cost-effectiveness for Scenarios 5 and 6

Again, we find that high risk boosting strategies are best. High-risk boosting may be cost-effective for younger (MIC) countries with high WTP thresholds, but this depends on unit cost inputs, in particular home-based care costs and vaccine program costs. New primary pediatric vaccination and new primary vaccination are unlikely to be cost-effective.

Figure 16: Cost-effectiveness plane for Scenarios 5 and 6: younger population, high TP, 20%/50% initial vaccination coverage, immune escape at 2 years, boosting from 2 years.
5 Conclusions

Overall, given consistent age-dependency to date of severe disease risk, elder-targeted strategies (high-risk boosting in our scenarios) are most likely to be cost-effective (or even cost-saving) across a broad range of uncertainties. In particular, paediatric programs (primary series or boosting) are not cost-effective. Absolute harms averted are influenced by: age and risk profile of the population, prior immune landscape (infection exposure history, vaccination rollout), and timing of emergence of an immune escape variant in relation to boosting. 6 monthly ‘high risk’ booster programs may be cost effective in older (HIC) populations, but cost-effectiveness is much more uncertain in younger demographics (MIC), driven primarily by assumptions surrounding home-based care and vaccine program costs.

Furthermore, in the scenarios we considered, we found that:

- If there is a steady stream of infection importation, resurgent waves are anticipated every 6-12 months without emergence of variants.
- In the ‘no vaccine’ case where immunity is based solely on epidemic cycles, such populations also suffer from synchronous waning, leading to sharp peaks (oscillations) of waves.
- Populations with high vaccine coverage have damped/extended/delayed peaks in comparison.
- The timing of emergence of variants relative to recent infections/immunisation campaigns influences the magnitude of subsequent waves and related clinical impacts (shorter intervals are better).
- Population demographics: both have similar infection numbers, but older populations have consistently more severe outcomes.
- Transmission potential effects: Populations with low past waves will have low future waves, and populations with high past waves will have high future waves.
- Transmission potential has the greatest effect on older population deaths.
- Vaccination coverage: high vaccination coverage reduces the peak/infections, reduces severe outcomes, and delays waves.
- Further (“reactive”) vaccination effects: Reduces infections, severe disease, and can delay “wave 4” (the wave that emerges at the very end of the simulation), and is also useful in the low transmission scenario.
- BA.4/5 introduction timing: if BA.4/5 was introduced earlier, then “wave 3” infections and deaths are lower. Also, reactive vaccination makes a bigger difference when BA.4/5 was introduced earlier.
References


6 Additional Results

6.1 Older population, high coverage, low TP

Representative WPR older countries: Australia, Hong Kong, Japan, New Zealand, Republic of Korea, Singapore.

Scenarios 7 and 8: Older population, low TP, 80% initial vaccination coverage, immune escape at 1.5/2.5 years, boosting from 2 years

In the scenario of low exposure pre-variant emergence, we find protection is mostly vaccine derived. However, with little hybrid immunity, vaccine have reduced impact. In Scenario 8, we see boosters delivered prior to vaccine emergence and in this case the high-risk booster strategy mitigates against severe impacts.

Figure 17: Infections and deaths for Scenario 7: older population, low TP, 80% initial vaccine coverage, immune escape at 1.5 years.
Figure 18: Infections and deaths for Scenario 8: older population, low TP, 80% initial vaccine coverage, immune escape at 2.5 years.
Cost-effectiveness for Scenarios 7 and 8

For Scenarios 7 and 8, high-risk boosting remains cost-effective, especially if immune escape happens at 2.5 years (Scenario 8). Furthermore, while random boosting is cost-effective, pediatric boosting is not cost-effective.

Figure 19: Cost-effectiveness plane for Scenarios 7 and 8: older population, low TP, 80% initial vaccination coverage, immune escape at 1.5/2.5 years, boosting from 2 years.
One-way sensitivity analysis for Scenario 7

We consider Scenario 7: Older population, low TP, 80% initial vaccination coverage, immune escape at 1.5 years, boosting from 2 years with a high-risk boosting strategy.

We find that vaccine delivery cost and unit cost per dose are the most influential costing parameters for older population scenarios.

![One-way sensitivity analysis for Scenario 7](image)

Figure 20: One-way sensitivity analysis for Scenario 7.
6.2 Younger population, high coverage, high TP


Scenarios 9 and 10: Younger population, high TP, 80% initial vaccination coverage, immune escape at 1.5/2.5 years, boosting from 2 years.

Figure 21: Infections and deaths for Scenario 9: younger population, high TP, 80% initial vaccination coverage, immune escape at 1.5 years, boosting from 2 years.
Figure 22: Infections and deaths for Scenario 10: younger population, high TP, 80% vaccine coverage, immune escape at 2.5 years, boosting from 2 years.
Cost-effectiveness for Scenarios 9 and 10

In these scenarios, pediatric boosting scenarios are not cost-effective and in our simulations show increased DALYs (this may be due to stochastic variation). High-risk boosting may be cost-effective or cost-saving in younger (LMIC) populations depending on WTP threshold and other model inputs. We found no other strategies were clearly cost-effective.

Figure 23: Cost-effectiveness plane for Scenarios 9 and 10.
One-way sensitivity analysis for Scenario 10

We consider Scenario 10: younger population, high TP, 80% initial vaccination coverage, immune escape at 2.5 years, boosting from 2 years with a high-risk boosting strategy.

We find that home-based care cost, vaccine delivery cost, and vaccine cost per dose are the most influential costing parameters.

Figure 24: One-way sensitivity analysis for Scenario 10.
Scenarios 11 and 12: Younger population, high TP, 80% initial vaccination coverage, immune escape at 1.5/2.5 years, 6 monthly boosting

We find that severe outcomes are overall fewer than in the older population, but the differential benefit of 6 monthly boosting depends on variant timing.

Figure 25: Infections and deaths for Scenario 11: younger population, high TP, 80% initial vaccine coverage, immune escape at 1.5 years, 6 monthly boosting.
Figure 26: Infections and deaths for Scenario 12: younger population, high TP, 80% vaccine coverage, immune escape at 2.5 years, 6 monthly boosting.
Cost effectiveness for Scenarios 11 and 12

We find the cost-effectiveness of high-risk boosting in younger populations with high initial vaccine coverage varies by timing of the emergence of an immune escape variant by is likely to be cost-effective or even cost saving. 6-monthly boosting is unlikely to be cost-effective for younger (LMIC) countries with high initial vaccine coverage (80%) unless vaccine is donated. Again, if home-based care costs are assumed to be 0, results shift away from being cost-effective, especially 6-monthly boosting.

Figure 27: Cost-effectiveness plane for Scenario 11.
Figure 28: Cost-effectiveness plane for Scenario 12.
6.3 Younger population, low coverage, high/low TP


Scenarios 13 and 14: Younger population, high/low TP, 50% initial vaccination coverage, immune escape at 2 years, boosting from 2 years

High-risk boosting remains the most impactful strategy, with vaccine impact more marked in settings of lower prior infection.

Figure 29: Infections and deaths for Scenario 13: younger population, high TP, 50% initial vaccine coverage, immune escape at 2 years, boosting from 2 years.
Figure 30: Infections and deaths for Scenario 14: younger population, low TP, 50% initial vaccine coverage, immune escape at 2 years, boosting from 2 years.
Cost effectiveness for Scenarios 13 and 14

For younger countries with lower (50%) initial vaccination coverage, high-risk boosting may be cost-effective for countries with high WTP thresholds. However, random boosting and further primary pediatric vaccination strategies are not cost-effective.

Figure 31: Cost-effectiveness plane for Scenarios 13 and 14.
Scenarios 15 and 16: Younger population, high/low TP, 20% initial vaccination coverage, immune escape at 2 years, boosting from 2 years

As low primary coverage equates to low booster coverage, we see minimal impact by strategy in this scenario. However, high-risk boosting remains superior. As for Scenario 14, vaccine impact is more marked in settings of lower prior infection.

Figure 32: Infections and deaths for Scenario 15: younger population, high TP, 20% initial vaccine coverage, immune escape at 2 years, boosting from 2 years.
Figure 33: Infections and deaths for Scenario 16: younger population, low TP, 20% initial vaccine coverage, immune escape at 2 years, boosting from 2 years.
Cost effectiveness for Scenarios 15 and 16

No boosting strategy appears to be cost-effective, regardless of transmission potential in younger countries with very low (20%) initial vaccination coverage. High-risk boosting strategies only appear cost-effective when vaccine is donated, and base case home-based care cost assumptions are maintained. In particular, further primary pediatric vaccination is clearly not cost-effective.

![Cost-effectiveness plane for Scenarios 15 and 16.](image)

Figure 34: Cost-effectiveness plane for Scenarios 15 and 16.
How does vaccine induced protection change over time and after multiple rounds of vaccination?

Deborah Cromer, Gerry Ryan, Nick Golding

Background to Efficacy Modelling

Throughout our transmission modelling, we have assumed that vaccine induced protection against symptomatic COVID-19 disease varies according to the neutralising antibodies present in a population, and that it is determined according to the model proposed by Khoury et. al. in [1]. This relationship has been verified to hold over time, against new variants and for both symptomatic and severe disease [2, 3]. The parameters of the original model have been updated over time in line with emerging estimates of vaccine effectiveness over time and after different vaccination histories as data and studies have continued to be release, including for booster and fourth doses.

In essence, higher levels of neutralising antibodies in a population lead to higher levels of protection, however this relationship is not a linear relationship, and instead is governed by the model proposed in [1] (reproduced from [3] in Figure 1 below).

![Figure 1 Relationship between neutralising antibody titres (as fold of antibodies against ancestral virus in convalescent plasma) and protection from symptomatic (red) and severe (orange) COVID-19 disease. (Reproduced from [3])](image)

A key parameter of relevance to the model is the change in neutralising antibody titres that are observed against new variants. These were estimated in detail for the Alpha, Beta, Delta and Omicron variants in [2, 5], however the difference in neutralisation of emerging variants is not known in advance.

Neutralising Antibodies over time and after multiple rounds of vaccination

We have previously assumed that neutralising antibodies wane with a half life of 108 days based on calculations from [1, 6]. What has been unclear is how neutralising antibodies titres their rate of waning change after multiple vaccination rounds. This will have flow on effects onto calculations of vaccine effectiveness.
We analysed the data from the 8[7-14] reports used in [4] that included a comparison of immunogenicity before and after an ancestral based booster vaccine against multiple SARS-CoV-2 variants and after different numbers of previous vaccines. Although we cannot directly compare neutralising antibody titres from different studies (since different assays were used), we still observe a clear trend in increasing neutralising antibody titres against the ancestral variant (Figure 2) and other variants of concern.

Figure 3) after boosting and after an increased number of vaccination doses.

Figure 2 Neutralising Antibody titres to the ancestral variant plotted by number of vaccination doses. Lines join reported neutralising antibody titres from the same study. We note that although the neutralising antibody titres reported in the different studies are not directly comparable (since different assays were used) there is a trend towards increasing antibody levels after boosting, and after more previous vaccinations.

Figure 3 Neutralising Antibody titres to variants of concern plotted by number of vaccination doses. Lines join reported neutralising antibody titres from the same study. We note that although the neutralising antibody titres reported in the different studies are not directly comparable (since different assays were used) there is a trend towards increasing antibody levels after boosting, and after more previous vaccinations.
Impact of different types of booster vaccination

We have also considered how different booster vaccinations (ancestral based or variant modified) result in different neutralising antibody titres, and considered how these influence vaccine effectiveness. This is used to highlight the fact that:

(a) booster doses increase neutralising antibody levels
(b) the change in neutralising antibody levels is different for different types of vaccine boosters
(c) These changes in neutralising antibody levels have a flow on effect to vaccine effectiveness.

We have found that on average, an ancestral based booster increases neutralising antibody levels by 11 fold (A), and that a variant modified booster is likely to increase these titres against variants of concern by approximately 1.5 times as much as an ancestral based booster (B) [4].

Combining these estimates with our model of vaccine effectiveness, we find that for a population that has 50% protection against symptomatic COVID-19, boosting of the population with an ancestral based booster would result in an increase in vaccine effectiveness of 35.6 percentage points over a 6 month period. This could be increased by a further 4.6 percentage points if a variant modified booster were used instead.

Figure 4 Increase in neutralising antibody titres as a result of (A) boosting with an ancestral based booster (compared to pre-boost antibody levels) and (B) a variant modified booster (compared to an ancestral-based booster). Figure reproduced from [4].

How these findings are incorporated into the model

The model used in this work is a Bayesian implementation and extension of the model in [1], which refits the model and then is able to predict vaccine effectiveness continually over time, incorporating updates to data on the relationship between neutralising antibody levels and vaccine efficacy, and cohort observations of efficacy from the literature [15]. It also implements an infection-acquired immunity effect to calculate the protective effect of neutralising antibodies developed from infection, and a hybrid immunity effect from prior infection as well as vaccination. Previous versions of this model implemented an antibody ceiling at two doses for individuals with no previous infection, or two doses plus infection for those with previous infection. However based on the updated information above it is clear that further levels of vaccination do indeed raise antibody levels beyond this ceiling and the model has been adapted accordingly (figure 5).
The scenario modelled here shows a 33% increase in neutralising antibody levels over baseline following a booster mRNA vaccination dose, and a further increase of the same level following a 4th dose of an mRNA vaccine, both for vaccine-derived and hybrid immunity.

**Figure 5.** Vaccine efficacy over time from 0 to 200 days, shown here for AZ and Pfizer dose 2, mRNA booster, mRNA dose 4, Omicron infection only, or Omicron infection in combination with either Pfizer dose 2, mRNA booster or mRNA dose 4, showing efficacy against death, hospitalisation, symptomatic infection, acquisition, and onward transmission.

**References**


15. Golding N., et al., *Analyses to predict the efficacy and waning of vaccines and previous infection against transmission and clinical outcomes of SARS-CoV-2 variants*. https://github.com/goldingn/neuts2efficacy
Cost-effectiveness Analysis of COVID-19 Vaccination Strategies in the Western Pacific Region: Description of methods

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1. Introduction

Countries in the World Health Organization (WHO) Western Pacific Region (WPR) have experienced different timing of SARS-CoV-2 epidemics while also facing a wide range of COVID-19 vaccine coverage to date, as access and acceptability have been highly variable across populations and settings. The cost and benefits of additional COVID-19 vaccination programs will vary by population demographics, target population group(s) and delivery strategy selected, whether multiple booster doses are required and how often, and the nature of future COVID-19 epidemic waves, including attack rates and timing of emergence of variants. Furthermore, any vaccination program costs must be weighed against existing health priorities within already strained health and immunisation budgets.

In addition to epidemiological considerations, decision-making on further COVID-19 vaccination programs will require evidence of the incremental cost-effectiveness of additional vaccination strategies compared to a counterfactual strategy without further vaccination. Alongside cost-effectiveness, policymakers must also understand the total cost and resulting budget impact of different vaccination strategies.

In this context, we will estimate the cost-effectiveness of a range of vaccination strategies compared to no further vaccination, to mitigate future epidemic waves in populations with differing vaccine uptake and epidemics. We will use outputs from an infection transmission/dynamics model linked to a mechanical agent-based model (ABM) with an additional clinical pathway model which has been described elsewhere [1].

2. Health economic model overview

The cost-effectiveness analysis has been conducted from the healthcare system perspective, including direct medical costs only. All costs are reported in 2020 United States dollars (USD). Future costs and health outcomes are discounted by 3% in the base case.

The main categories of costs included in the cost-effectiveness analysis are (1) programmatic costs related to the vaccination intervention, including vaccine dose costs, wastage, and delivery costs; and (2) disease management costs in outpatient and inpatient settings for symptomatic COVID-19 related illness. COVID-19 testing costs were not included. While these costs have been estimated to be substantial [2], they remain highly uncertain. In any resurgence, we estimate much broader use of rapid antigen testing than polymerase chain reaction (PCR) for case ascertainment, thus historical use of testing strategies cannot inform future testing use. Furthermore, PCR capacity varies dramatically by country, and use of different types of tests will likely vary by case numbers. The main categories of costs included in the cost-effectiveness analysis are (1) programmatic costs related to the vaccination
intervention, including vaccine dose costs, wastage, and delivery costs; and (2) disease management costs in outpatient and inpatient settings for symptomatic COVID-19 related illness. COVID-19 testing costs were not included. While these costs have been estimated to be substantial [2], they remain highly uncertain. In any resurgence, we estimate much broader use of rapid antigen testing than polymerase chain reaction (PCR) for case ascertainment, thus historical use of testing strategies cannot inform future testing use. Furthermore, PCR capacity varies dramatically by country, and use of different types of tests will likely vary by case numbers.

Health outcomes are provided in terms of disability-adjusted life years (DALYs) using disability weights from the Global Burden of Disease study (GBD) [3-8], assumptions on the duration of illness from prior studies, and estimates of life years lost from WHO life tables. The cost-effectiveness model uses as inputs the outputs from a clinical pathways model linked to a mechanical agent-based model (ABM) that in turn is linked to an infection transmission/dynamics model as depicted in Fig 1, and described in more detail elsewhere [1]. These models provide scenario-specific mean estimates of vaccination doses delivered per 100,000 people, COVID-19 infections (all, symptomatic, hospital admissions, hospital occupancy, intensive care unit (ICU) admissions and ICU occupancy), and COVID-19 related deaths by 10-year age groups.

Figure 1: Diagram of cost-effectiveness model (in yellow/orange) as extension to overall simulation procedure.

2.1. Defining exemplar country contexts for cost-effectiveness analysis

All countries in the WPR started COVID-19 vaccination programs in 2021. While countries had different vaccination strategies, in general first doses were assigned to frontline workers, at risk adults and the elderly, followed by the remaining adult population. Programs were expanded to include children aged 12 and above starting in early 2022. The majority of
countries further expanded their vaccine policy to include children 5 years and older in mid-2022.

According to WHO data, 2-dose vaccine coverage varies significantly throughout the Western Pacific (Table A1 and A2 in Appendix). High income, ‘older’ demographic countries tend to have higher vaccination coverage, ranging from 64.5% in New Caledonia to 87.4% in Singapore with a median of 84.5% in New Zealand (as a proportion of total population as of 22/12/22) (Appendix Reference 1). Lower-middle and upper-middle income countries with younger demographics displayed a much wider range of vaccination coverage ranging from 3.6% in Papua New Guinea (PNG) to 101.9% in Brunei with a median coverage 67.4% in The Philippines. Booster coverage displayed a similar pattern.

In alignment with the two ABM populations, representing differing demographics within the WPR, we consider three key groupings of ‘exemplar’ countries in terms of: (1) demography (typical ‘older’ versus ‘younger’ population demographics); (2) health systems capacity and prior primary COVID-19 vaccine coverage rates (strong health systems and high prior primary vaccine coverage versus relatively weaker health systems and lower prior primary vaccine coverage); (3) income group level (high income, upper-middle income, or lower-middle income); and (4) vaccination delivery unit costs and disease management costs.

The representative 'exemplar' countries groupings are as follows, with full details provided in the appendix:

(1) **Group A**: High income, older population with strong health systems capacity and high (~80%) prior primary vaccine coverage. Highest unit costs for vaccine delivery and disease management. (*Examples: Japan, Australia*)

(2) **Group B**: Upper- and lower- middle income, younger population with middle-to-strong health systems capacity and high (~80%) or mid (~50%) prior primary vaccine coverage. Low-to-high unit costs for vaccine delivery (depending on geography and population size) and low-to-middle unit costs for disease management. (*Examples: Fiji, Philippines, Cambodia, Kiribati*)

(3) **Group C**: Lower-middle income, younger population with weak health systems capacity and low (~20%) prior primary vaccine coverage. Low unit costs for vaccine delivery and disease management. (*Examples: PNG, Solomon Islands*)

Some WPR countries are not included in these representative 'exemplar' country groupings (for example, those with demographics that classify as neither 'older' nor 'younger'). The implications for these countries would need to be considered in light of the findings for Groups A and B.

### 3. Resource use and costs
Inputs and data sources for estimating costs of COVID-19 vaccination and disease management are presented in Table 1.

3.1. COVID-19 vaccine dose cost

COVID-19 vaccine price data were retrieved from the WHO COVID-19 vaccine price report [9]. This report summarizes vaccine dose price data based on the WHO MI4A COVID-19 Vaccine Purchase Database [10], which includes vaccine purchase data from public sources and data reported by countries through the WHO/UNICEF Joint Reporting Form (eJRF). Countries' names are not available in the dataset; however, the WHO region and income level are provided. According to the latest version of the WHO database updated on 27 June 2022, few countries in the Western Pacific Region (WPRO) had available price data, so our study has used global pricing data, by income group.

The vaccine dose price used in the base case was the average price per dose (all vaccines, Pfizer BioNTech - Comirnaty, Moderna - mRNA-1273, Janssen - Ad26.COV 2-S, AstraZeneca – Vaxzevria (AZ)) from both public source and eJRF, segregated by income group and prior vaccine coverage level (Table 1). We explore sensitivity analyses using higher and lower vaccine dose prices. It is understood that AZ is no longer a preferred vaccine; however, we have included the AZ vaccine as a comparison in the economic model as it has been used widely in the Western Pacific region in the past and has the lowest price across all other vaccines. However the lower estimate came from the Janssen vaccine, assuming half the number of doses are required to achieve the same coverage.

![Figure 2: COVID-19 vaccine price by type of vaccine and income group from WHO vaccine price report](image)

1. C-19 Vaccine price data from public source and as reported by countries to WHO
### Table 1. Inputs for estimating COVID-19 vaccination and disease management costs.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source of data and rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost per dose of vaccine ($)</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A (older population, high coverage)</td>
<td>14.2 (3.9–25.2)</td>
<td>Data from WHO COVID-19 vaccine price report [9]. We use mean estimate across all vaccines, by income group as base case, and min and max by vaccine type.</td>
</tr>
<tr>
<td>Group B (younger population, high/middle coverage)</td>
<td>7.8 (3.8–10.0)</td>
<td>WHO COVID-19 vaccine price report [9]. We use mean estimate across all vaccines, by income group as base case, and min and max by vaccine type.</td>
</tr>
<tr>
<td>Group C (younger population, low coverage)</td>
<td>7.8 (3.8–10.0)</td>
<td>WHO COVID-19 vaccine price report [9]. We use mean estimate across all vaccines, by income group as base case, and min and max by vaccine type.</td>
</tr>
<tr>
<td><strong>Delivery cost per dose, 70% coverage ($)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A (older population, high coverage)</td>
<td>23.2 (11.1-33.6)</td>
<td>Base case is average across all countries with available estimates, range is minimum and maximum estimates. Data from: Australia and Japanese Government report [11, 12]; Local studies from Korea and Hong Kong [13, 14]</td>
</tr>
<tr>
<td>Group B (younger population, high coverage)</td>
<td>13.4 (0.7-29.3)</td>
<td>UNICEF 2022 report [15]</td>
</tr>
<tr>
<td><strong>Delivery cost per dose, 50% coverage ($)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B (younger population, middle coverage)</td>
<td>13.4 (0.7-29.3)</td>
<td>Estimated based on UNICEF reports [15]</td>
</tr>
<tr>
<td><strong>Delivery cost per dose, 20% coverage ($)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group C (younger population, low coverage)</td>
<td>7.7 (2.5-10.5)</td>
<td>Estimated based on UNICEF reports, assuming double the cost at 70% coverage [15, 16]</td>
</tr>
<tr>
<td><strong>Proportion of doses wasted</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A (older population, high coverage)</td>
<td>5% (0%-10%)</td>
<td>Estimated based on UNICEF 2022 report [15]</td>
</tr>
<tr>
<td>Group B (younger population, high/middle coverage)</td>
<td>10% (0%-20%)</td>
<td>UNICEF 2022 report [15]</td>
</tr>
<tr>
<td>Group C (younger population, low coverage)</td>
<td>10% (0%-20%)</td>
<td>UNICEF 2022 report [15]</td>
</tr>
<tr>
<td><strong>Cost for non-hospitalized per case ($)</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A (older population, high coverage)</td>
<td>54.0 (53.5-114.7)</td>
<td>Australia, Japanese and Hong Kong Medical Fee Schedule[17-19]; WHO choice for Korea [20]</td>
</tr>
</tbody>
</table>
### Cost for hospitalization without ICU, per day ($)

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Cost Range</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (older population, high coverage)</td>
<td>267.0 (208.7-657.2)</td>
<td>Australia, Japanese and Hong Kong Medical Fee Schedule [17-19]; Local study from Korea [14]</td>
<td></td>
</tr>
<tr>
<td>Group B (younger population, high/middle coverage)</td>
<td>44.8 (20.8-131.1)</td>
<td>Torres-Rueda, et al [2]</td>
<td></td>
</tr>
<tr>
<td>Group C (younger population, low coverage)</td>
<td>31.4 (28.0-34.8)</td>
<td>Torres-Rueda, et al [2]</td>
<td></td>
</tr>
</tbody>
</table>

### Cost for hospitalization with ICU, per day ($)

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Cost Range</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (older population, high coverage)</td>
<td>2120.5 (825.0-5294.9)</td>
<td>Australia, Japanese and Hong Kong Medical Fee Schedule [17-19]; Local study from Korea [14]</td>
<td></td>
</tr>
<tr>
<td>Group B (younger population, high/middle coverage)</td>
<td>399.5 (295.1-1272.7)</td>
<td>Torres-Rueda, et al [2]</td>
<td></td>
</tr>
<tr>
<td>Group C (younger population, low coverage)</td>
<td>347.2 (340.9-353.5)</td>
<td>Torres-Rueda, et al [2]</td>
<td></td>
</tr>
</tbody>
</table>

### Cost per COVID-related death ($)

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body bag</td>
<td>64.5</td>
<td>Torres-Rueda, et al [2]</td>
</tr>
</tbody>
</table>

Costs are reported in 2020 United States dollars.

1. Includes Janssen vaccine as lower-bound as single dose is considered as fully vaccinated.
2. Includes two visits to clinic.
3. Costs of hospitalized critical case from original report included both ICU and non-ICU bed days and thus have been inflated by 20% to represent the cost of an ICU bed day alone.

### 3.2. COVID-19 vaccine delivery cost

The cost of COVID-19 vaccine delivery remains uncertain. Delivery costs will vary by vaccine type (including cold chain requirements), country health systems capacity, delivery mechanism and target population and coverage level.

#### 3.2.1. Group A (‘Older’ population, high income countries)

There are no consistent estimates of delivery costs for high-income countries. We sought to estimate or find COVID-19 vaccination delivery costs for a select number of countries in Group A where these were available, to use as inputs for the modelling. Delivery costs per dose for Hong Kong and Korea were taken from previous publications with assumed COVID-19 vaccination coverage rates of 72% and 80%, respectively [13, 21]. Delivery costs per dose for Japan were taken from the Japanese Government's National Treasury's burden for the vaccination measures against the COVID-19 report, however the coverage rate was unspecified.
After comparing the cost with those of other HICs, we assumed that it was at 80% coverage [12]. Delivery costs for Australia were calculated by dividing the Australian government's reported funding for COVID-19 vaccine distribution and delivery in 2020-2022 by the total dose administrated up to mid-2022 (about 80% coverage) [11]. These unit delivery costs were used for the 80% and 50% coverage scenarios, and multiplied by two to estimate the delivery costs at 20% coverage. We use the average cost across all estimates obtained for the base case delivery cost, and the minimum and maximum delivery cost estimates as upper and lower-bound ranges.

3.2.2. Group B and C (‘Younger’ population, middle-income countries)

The COVID-19 vaccine delivery cost estimates used in modelling the ‘younger’ demographic populations were based on two recent UNICEF reports that provided estimates for low- and middle-income countries (LMICs). [15, 16] The delivery costs refer to the costs associated with delivering vaccines to target populations exclusive of vaccine purchase costs. The costs estimated in both reports are financial costs, including (1) variable costs (e.g., cold chain equipment, per diem for outreach, personal protective equipment, vaccine transport, and management, etc.) and (2) fixed costs (i.e., handwash station, training, planning and coordination, social mobilization, pharmacovigilance, behavioural and social data collection). We assume for the purposes of this study, that the economic costs required for a cost-effectiveness analysis, would be similar to the financial costs, and use these estimates in the base case.

In the latest UNICEF report, COVID-19 vaccine delivery costs were estimated for countries achieving a 70% of total population coverage (equivalent to 92% coverage rate in population ≥12 years of age) in four different scenarios (leveraging fixed delivery sites, balancing human resource protection, protecting human resources partially, protecting human resources fully) [15]. In the earlier report, which focussed on achieving 20% coverage, the estimation was based on the leveraging fixed delivery sites scenario only. For consistency, we have chosen the delivery costs under this scenario as the base case, which assumed 10% of the available workforce allocated to delivery, 85% fixed site delivery, and 15% outreach delivery. We explore a higher-cost scenario as a sensitivity analysis. The fixed-outreach proportion was close to the data for the Western Pacific region in 85 National Deployment and Vaccination Plans (86%-14%) [15]. In the leveraging scenario from the earlier UNICEF report, the average cost per dose delivery at 20% coverage was approximately double that of 70% coverage, as fewer people shared fixed costs. Due to the lack of country-specific estimates at 20% coverage, we also assumed that the delivery costs at 20% coverage were double those at 70% coverage. We also assumed that the 50% coverage scenario has the same unit delivery costs as the 70% coverage scenario. Delivery cost estimates used in the model are provided in Table 1.
3.3. COVID-19 treatment cost

3.3.1. Group A (‘Older’ population, high income countries)

Based on the previous costing methods [2], we used the Australian medical fee schedules and publically available government data to calculate the three types of case management costs [18, 22]. We used the same method to estimate the case management costs in Japan by applying the Japanese medical fee schedule [17]. Of note, in the home-based cases in HICs, we have excluded the home-based bed-day cost due to lack of detailed costing method in the reference article. Also, in hospital-based critical cases, we dropped the general ward bed-day input and changed the number of units per input for ICU bed-day from 0.66 to 1. Malaria testing was included in all LMICs hospital-based cases, but we removed it from the costs for HICs, given that HICs are low-prevalence malaria regions where this testing may not be a routine admission test. The costs of inpatient cases in Hong Kong were taken from a cost-effectiveness study of the COVID-19 vaccine in Hong Kong, with the source being the public charges for non-eligible persons [13, 19]. The costs of hospitalisation cases in Korea were obtained from a COVID-19 cost-effectiveness analysis in Korea, which employed the cost estimations by Korea Disease Control and Prevention Agency [14]. The outpatient costs for home-based care in Korea were based on WHO CHOICE unit costs (2011), which we adjusted for inflation and currency conversion [20].

3.3.2. Group B and C (‘Younger’ population, middle-income countries)

All disease costs for LMICs were available directly from a model-based cost estimations study [2]. The study used data from three LMICs (Ethiopia, Pakistan, and South Africa) as the model references to extrapolate the case management costs for home-based care, hospitalisation for severe care, and critical care across all LMICs. The original costs reported in the study were inflated to 2020 USD.

Home-based care costs are defined as the cost per mild-to-severe case requiring home-based care, including 1) the cost of home-based care bed-day; 2) the cost of community-based care via a clinician's visit. The number of bed-day and clinician visit was set at 5 and 2, respectively. Hospitalised severe care costs were calculated per case and per day, including 1) general ward bed-day; 2) diagnostics.

Hospitalised critical care costs were also presented per case and per day. Compared with severe cases, the additional costs per case per day were: 1) ICU bed-day; 2) additional resourcing per COVID-related complication. However, as the modelled epidemiological data is presented by ICU admission (rather than combining a patient who has received ICU and general ward care) the cost shown in this report likely underestimates the actual cost per day of a patient treated in an ICU. As general ward costs were considered representative of 1/3 of the bed day costs, we conservatively inflated the bed day cost by 20% when applying these costs in the economic model. Further clarification is presented in supplementary appendix Table A5 and Table A6.
4. Health Outcomes

Health outcomes were presented as disability-adjusted life-years (DALYs) for each modelled scenario. DALYs were calculated as the sum of years of life lost (YLLs) and years lived with disability (YLDs).

4.1. Years of life lost

YLLs following a premature death due to COVID-19 were calculated as the sum of the number of deaths (N) multiplied by life expectancy (L) for the age at death. We obtained the number of deaths and age at death (in ten-year age groups, up to 80 years plus) from the epidemiological model for each scenario. These were multiplied by a reference life expectancy for each exemplar country groupings from WHO lifetables for each 10-year age band. For Group A, we use the Japan life table given 'older' high-income countries in WPR have higher life expectancies than the global high-income country lifetable. For Groups B and C, we use the global lower-middle income lifetable, given 'younger' countries in WPR have a lower life expectancy than global upper-middle income and the WPR life table. In the base case, we discounted future YLLs at 3% annually according to the following formula:

$$YLL = \frac{N(1-e^{-0.03L})}{0.03}$$

4.2. Years lived with disability

The YLD component was calculated for the acute phase of the disease and post-acute consequences following severe disease. We do not include long-COVID due to a lack of available data to specify this condition. We classified cases into four following mutually exclusive categories–asymptomatic, symptomatic non-hospitalized, hospitalized without ICU stay, and hospitalized with ICU stay. We specified an illness severity pathway for each category consisting of four health states (mild/moderate, severe, critical, and post-acute). The post-acute phase refers to the recovery period following hospitalisaton, and has been expressed in other cost-effectiveness models [4]. Based on the illness severity pathway for these categories (
Table 2), we calculated YLDs by summing up the product of time spent in each health state, the disability weight for that state, and the number of incident cases. YLDs have been calculated using the following formula:

$$YLD = \sum_{i} I_i \times L_i \times DW_i$$

where $i$ is an index for health state, $I_i$ is the number of incident cases for each health state, $L_i$ is the duration of disability in years, and $DW_i$ is the disability weight. The duration of illness for each state was based on the average length of hospital and ICU stay from the literature (
Table 2).
Table 2. Health states, duration of illness, and disability weights for calculating years lived with disability

<table>
<thead>
<tr>
<th>COVID-19 patient category</th>
<th>Health state</th>
<th>Days in state Base case (range)</th>
<th>Disability weight Base case (range)</th>
<th>Notes and sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. asymptomatic cases</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Zero disability for asymptomatic cases.</td>
</tr>
<tr>
<td>B. symptomatic non-hospitalized</td>
<td>Mild or moderate</td>
<td>7.0 (2.0–9.5)</td>
<td>0.051 (0.032–0.074)</td>
<td>GBD 2019 disability weight for moderate lower respiratory infections [3]. Days in mild/moderate state from literature [4, 8]. Assume no post-acute phase.</td>
</tr>
<tr>
<td></td>
<td>Mild or moderate</td>
<td>7.0 (2.0–9.5)</td>
<td>0.051 (0.032–0.074)</td>
<td>Disability weights from GBD 2019 for moderate lower respiratory infections, severe lower respiratory infections and post-acute consequences (fatigue, emotional lability, insomnia) for infectious disease [3]. Using 7 days from symptom onset to hospital, same as category B patients and a Belgian study [5]. Using same number of hospital days (5 days) used in category D patients [6]. Assume 1-week post-acute phase +/- 50% [4].</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>5.0 (3.0–9.0)</td>
<td>0.133 (0.088–0.190)</td>
<td></td>
</tr>
<tr>
<td>C. hospitalized without ICU stay</td>
<td>Post-acute</td>
<td>7.0 (3.5–10.5)</td>
<td>0.219 (0.148–0.308)</td>
<td></td>
</tr>
<tr>
<td>D. hospitalized with ICU stay</td>
<td>Mild or moderate</td>
<td>7.0 (2.0–9.5)</td>
<td>0.051 (0.032–0.074)</td>
<td>Disability weights from Nomura 2019 [7] (critical) and GBD 2019 (others). Symptom onset to ICU discharge of 18 days [8]. Out of this number, assume 7 days from symptom to hospital [5], 5 days in hospital [6] and 7 days in ICU [6]. Assume 2 weeks post-acute phase +/- 50% [4].</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>5.0 (3.0–9.0)</td>
<td>0.133 (0.088–0.190)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Critical</td>
<td>7.0 (4.0–11.0)</td>
<td>0.675 (0.506–0.822)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-acute</td>
<td>14.0 (7.0–21.0)</td>
<td>0.219 (0.148–0.308)</td>
<td></td>
</tr>
</tbody>
</table>

5. Cost-effectiveness analysis

5.1. Cost-effectiveness thresholds
Willingness to pay (WTP) thresholds for the representative country groupings were based on updated estimates developed by Woods et al. (2016) and Ochalek et al. (2015) [23] and are presented in Table 3. The WTP threshold for older demographic countries with high vaccination coverage was estimated to range between $20,000 to $40,000. Younger demographic countries with mid to high vaccination coverage had an estimated WTP between $50 - $2,500, and younger demographic countries with low vaccination coverage had an estimated WTP between $50 - $1,000. (Full data on WTP thresholds for countries in the WPR can be found in supplementary appendix Table A3)

Table 3. Estimated willingness to pay thresholds

<table>
<thead>
<tr>
<th>Age demographics / Prior primary vaccine coverage</th>
<th>Key representative countries / Areas</th>
<th>Estimated WTP range (2020 USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A: Older population High vaccination coverage</strong></td>
<td>Australia, Japan, Rep. of Korea, Hong Kong, New Zealand, Singapore</td>
<td>$20,000 – $40,000</td>
</tr>
<tr>
<td><strong>Group B: Younger population Mid to high vaccination coverage</strong></td>
<td>Fiji, Samoa, Tonga, Mongolia, Cambodia, Lao PDR, Philippines, Vanuatu, Kiribati, Micronesia, Fed. Sts.</td>
<td>$50 - $2,500</td>
</tr>
<tr>
<td><strong>Group C: Younger population Low vaccine coverage</strong></td>
<td>Solomon Islands, Papua New Guinea</td>
<td>$50 - $1,000</td>
</tr>
</tbody>
</table>

5.2. Cost-effectiveness results and interpretation

We present the results as incremental cost-effectiveness ratios (ICERs) for the modelled vaccination options compared to a counterfactual of no further vaccination. These ICERs are presented on a cost-effectiveness plane, which shows the DALYs averted and additional costs for the vaccination scenarios (described above) compared to the cost-effectiveness thresholds for the three scenarios. Results that fall below these thresholds indicate a vaccination strategy that is likely to be cost-effective. We have expressed these costs and outcomes per 100,000 people.

We have also performed one-way sensitivity analyses to determine the impact of various cost and epidemiological variables on the ICER. We have presented the results of these analyses on
a tornado diagram, which indicates the change in ICER when varying parameters within a plausible range, thus accounting for parameter uncertainty.

Additionally, as we are already varying several key epidemiological and demographic parameters (for example, R0 through high/low transmission scenarios and young vs older populations), we can compare these parameters' influence on CE results to the costing parameters. This process has demonstrated apparent differences in CEA by allocation strategy across that broad variation, so it's unlikely that the conclusions of a more detailed uncertainty analysis would vary substantially.

6. Limitations

There are several limitations of this analysis that warrant mentioning.

1. We do not include testing costs, as previously explained. Testing costs can represent a substantial proportion of total costs related to COVID-19 in some countries, however these remain highly uncertain particularly across modelled future scenarios. It is unclear what impact the exclusion of testing costs would have on findings.
2. While indirect costs due to COVID-19, such as productivity losses, also make up a large proportion of total costs related to COVID-19, these costs have not been included in the current analysis. Accounting for indirect costs would make additional boosting vaccination programs appear more cost-effective than our findings indicate. In future work, a societal perspective may be considered.
3. We have not accounted for vaccine-related side effects, including both the costs and health impacts. These are unlikely to impact on cost-effectiveness findings.
4. We are currently not accounting for the costs or health impacts of long-COVID, due to data limitations.
5. We have not directly considered stochastic uncertainty within the economic model, although this has been considered within the various epidemiological models described elsewhere. Stochastic uncertainty is unlikely to significantly impact the cost-effectiveness results, particularly when compared to the parameter uncertainty considered within the one-way sensitivity analyses. We have also not conducted a full probabilistic sensitivity analysis capturing uncertainty across the economic, epidemiological and clinical parameters. In future iterations of this collaboration, we hope to capture more uncertainty in all models together; however this was not feasible in the current timeframe.
6. Finally, a full budget impact has not been conducted alongside this cost-effectiveness analysis. A budget impact should also consider a lower bound vaccine dose cost of $0 for donated vaccines with no financial costs to health systems.
7. References


# 8. Appendix

Table A1. All countries and areas included in WHO Western Pacific Region (WPR) and characteristics

<table>
<thead>
<tr>
<th>Country</th>
<th>Income Classification</th>
<th>Younger/Older</th>
<th>Population Size</th>
<th>2 dose Vaccination Coverage</th>
<th>Booster Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Samoa</td>
<td>Upper middle</td>
<td>-</td>
<td>45,035</td>
<td>75.05%</td>
<td>43.77%</td>
</tr>
<tr>
<td>Australia</td>
<td>High</td>
<td>Older</td>
<td>25,688,079</td>
<td>84.92%</td>
<td>56.06%</td>
</tr>
<tr>
<td>Brunei Darussalam</td>
<td>High</td>
<td>Younger</td>
<td>445,373</td>
<td>101.93%</td>
<td>77.49%</td>
</tr>
<tr>
<td>Cambodia</td>
<td>Lower middle</td>
<td>Younger</td>
<td>16,589,023</td>
<td>87.33%</td>
<td>62.21%</td>
</tr>
<tr>
<td>China</td>
<td>Upper middle</td>
<td>Older</td>
<td>1,412,360,000</td>
<td>86.82%</td>
<td>54.7%</td>
</tr>
<tr>
<td>Cook Islands</td>
<td>-</td>
<td>-</td>
<td>17,604*</td>
<td>83.56%</td>
<td>30.38%</td>
</tr>
<tr>
<td>Fiji</td>
<td>Upper middle</td>
<td>Younger</td>
<td>924,610</td>
<td>71.33%</td>
<td>18.78%</td>
</tr>
<tr>
<td>French Polynesia</td>
<td>High</td>
<td>Older</td>
<td>304,032</td>
<td>66.23%</td>
<td>39.95%</td>
</tr>
<tr>
<td>Guam (USA)</td>
<td>High</td>
<td>Older</td>
<td>170,534</td>
<td>83.55%</td>
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</tr>
<tr>
<td>Hong Kong</td>
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<td>Older</td>
<td>7,413,100</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Japan</td>
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<td>125,681,593</td>
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<td>66.67%</td>
</tr>
<tr>
<td>Kiribati</td>
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<td>128,874</td>
<td>61.86%</td>
<td>19.61%</td>
</tr>
<tr>
<td>Lao PDR</td>
<td>Lower middle</td>
<td>Younger</td>
<td>7,425,057</td>
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<td>27.86%</td>
</tr>
<tr>
<td>Macao SAR</td>
<td>High</td>
<td>Older</td>
<td>686,607</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Malaysia</td>
<td>Upper middle</td>
<td>-</td>
<td>33,573,874</td>
<td>85.06%</td>
<td>50.28%</td>
</tr>
<tr>
<td>Marshall Islands</td>
<td>Upper middle</td>
<td>-</td>
<td>42,050</td>
<td>61.89%</td>
<td>36.41%</td>
</tr>
<tr>
<td>Micronesia, Federates States of</td>
<td>Lower middle</td>
<td>Younger</td>
<td>113,131</td>
<td>57.53%</td>
<td>26.55%</td>
</tr>
<tr>
<td>Mongolia</td>
<td>Lower middle</td>
<td>Younger</td>
<td>3,347,782</td>
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<td>32.25%</td>
</tr>
<tr>
<td>Nauru</td>
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<td>-</td>
<td>12,511</td>
<td>79.24%</td>
<td>46.75%</td>
</tr>
<tr>
<td>New Caledonia</td>
<td>High</td>
<td>Older</td>
<td>271,030</td>
<td>64.49%</td>
<td>32.96%</td>
</tr>
<tr>
<td>New Zealand</td>
<td>High</td>
<td>Older</td>
<td>5,122,600</td>
<td>84.87%</td>
<td>56.33%</td>
</tr>
<tr>
<td>Niue</td>
<td>-</td>
<td>-</td>
<td>1,653*</td>
<td>100.99%</td>
<td>75.65%</td>
</tr>
<tr>
<td>Country</td>
<td>Income Classification</td>
<td>Age Group</td>
<td>Population</td>
<td>2-Dose Coverage</td>
<td>Booster Coverage</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Northern Mariana Islands</td>
<td>High</td>
<td>-</td>
<td>49,481</td>
<td>78.2%</td>
<td>42.11%</td>
</tr>
<tr>
<td>Commonwealth of the USA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palau</td>
<td>Upper middle</td>
<td>-</td>
<td>18,024</td>
<td>101.07%</td>
<td>71.11%</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>Lower middle</td>
<td>Younger</td>
<td>9,949,437</td>
<td>3.46%</td>
<td>0.36%</td>
</tr>
<tr>
<td>Philippines</td>
<td>Lower middle</td>
<td>Younger</td>
<td>113,880,328</td>
<td>67.42%</td>
<td>19.38%</td>
</tr>
<tr>
<td>Pitcairn Island</td>
<td></td>
<td></td>
<td>50*</td>
<td>74%</td>
<td>46%</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>High</td>
<td>Older</td>
<td>51,744,876</td>
<td>87.17%</td>
<td>65.63%</td>
</tr>
<tr>
<td>Samoa</td>
<td>Lower middle</td>
<td>Younger</td>
<td>218,764</td>
<td>89.54%</td>
<td>39.85%</td>
</tr>
<tr>
<td>Singapore</td>
<td>High</td>
<td>Older</td>
<td>5,453,566</td>
<td>87.4%</td>
<td>77.34%</td>
</tr>
<tr>
<td>Solomon Islands</td>
<td>Lower middle</td>
<td>Younger</td>
<td>707,851</td>
<td>31.68%</td>
<td>2.54%</td>
</tr>
<tr>
<td>Tokelau</td>
<td></td>
<td></td>
<td>1,399*</td>
<td>163.19%</td>
<td>71.7%</td>
</tr>
<tr>
<td>Tonga</td>
<td>Upper middle</td>
<td>Younger</td>
<td>106,017</td>
<td>72.72%</td>
<td>36.24%</td>
</tr>
<tr>
<td>Tuvalu</td>
<td>Upper middle</td>
<td>-</td>
<td>11,204</td>
<td>79.05%</td>
<td>46.88%</td>
</tr>
<tr>
<td>Vanuatu</td>
<td>Lower middle</td>
<td>Younger</td>
<td>319,137</td>
<td>42.75%</td>
<td>5.39%</td>
</tr>
<tr>
<td>Vietnam</td>
<td>Lower middle</td>
<td>-</td>
<td>97,468,029</td>
<td>87.89%</td>
<td>59%</td>
</tr>
<tr>
<td>Wallis and Futuna</td>
<td></td>
<td></td>
<td>10,749*</td>
<td>62.15%</td>
<td>28.46%</td>
</tr>
</tbody>
</table>

Abbreviations: PDR, people’s Democratic Republic; SAR, Special Administrative Region; USA, United States of America

*Income Classification data sourced from World Bank https://data.worldbank.org/ 22/12/22

*Population data from Our World in Data 22/12/22

*Data retrieved from WHO Coronavirus (COVID-19) Dashboard https://covid19.who.int/table 22/12/22. Data on 2-dose coverage and booster coverage are estimated based on number of doses administered and total population size

*Data not available from Our World in Data sourced from Worldometer

NOTE: Group A (green) High income, older population with strong health systems capacity and high prior primary coverage; Group B (yellow) Upper- and lower-middle income, younger population with middle-to-strong health systems capacity and middle-to-high prior primary vaccine coverage; Group C (blue) lower middle income, younger population with weak health systems capacity and lower prior primary vaccine coverage; countries that are not highlighted are not included in these representative ‘exemplar’ country groupings. The implications for these countries would need to be considered in light of the findings for Groups A and B, as they would likely sit somewhere in between these groupings.
Table A2: Median vaccination coverage by age demographic in WPR

<table>
<thead>
<tr>
<th>Age Demographic</th>
<th>Median coverage*</th>
<th>2-dose IQR</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger</td>
<td>67.42%</td>
<td>57.53% - 74.54%</td>
<td>3.46% - 101.93%</td>
</tr>
<tr>
<td>Older</td>
<td>84.87%</td>
<td>81.43% - 86.82%</td>
<td>64.49% - 87.4%</td>
</tr>
</tbody>
</table>

*as % of total population, as of 22/12/22
<table>
<thead>
<tr>
<th>Country</th>
<th>Income Classification</th>
<th>(^a)Woods (2016) (2013 USD)</th>
<th>(^b)Ochalek Section 2 (Year 2000 International dollars)</th>
<th>(^c)Ochalek Section 3 (Year 2000 International dollars)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>DALY 1</td>
<td>DALY 2</td>
</tr>
<tr>
<td>American Samoa</td>
<td>Upper middle</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Australia</td>
<td>High</td>
<td>32,771-41,732</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Brunei Darussalam</td>
<td>High</td>
<td>16,065-39,294</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cambodia</td>
<td>Lower middle</td>
<td>44 - 518</td>
<td>112</td>
<td>58</td>
</tr>
<tr>
<td>China</td>
<td>Upper middle</td>
<td>1,151 – 4,550</td>
<td>584</td>
<td>369</td>
</tr>
<tr>
<td>Cook Islands</td>
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<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fiji</td>
<td>Upper middle</td>
<td>507 – 2,307</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>French Polynesia</td>
<td>High</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Guam (USA)</td>
<td>High</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------</td>
<td>--------------</td>
<td>----------------</td>
<td>------</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>High</td>
<td>17,409 – 28,801</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Japan</td>
<td>High</td>
<td>19,769 - 19,854</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kiribati</td>
<td>Lower middle</td>
<td>43-848</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lao PDR</td>
<td>Lower middle</td>
<td>113 - 852</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Macao SAR</td>
<td>High</td>
<td>30,832 – 184,977</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Malaysia</td>
<td>Upper middle</td>
<td>3,481 – 6,192</td>
<td>1691</td>
<td>918</td>
</tr>
<tr>
<td>Marshall Islands</td>
<td>Upper middle</td>
<td>182 – 1,774</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Micronesia, Federates</td>
<td>Lower middle</td>
<td>162 – 1,646</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>States of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mongolia</td>
<td>Lower middle</td>
<td>543 - 2,085</td>
<td>165</td>
<td>122</td>
</tr>
<tr>
<td>Nauru</td>
<td>High</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>New Caledonia</td>
<td>High</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>New Zealand</td>
<td>High</td>
<td>20,555 – 21,619</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Niue</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Country</td>
<td>Level of Development</td>
<td>Population</td>
<td></td>
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</tr>
<tr>
<td>-------------------------------------</td>
<td>----------------------</td>
<td>------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern Mariana Islands Commonwealth of the USA</td>
<td>High</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palau</td>
<td>Upper middle</td>
<td>2,513 – 7,940</td>
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<td></td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>Lower middle</td>
<td>75 – 1,073</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Philippines</td>
<td>Lower middle</td>
<td>256 – 1,421</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pitcairn Island</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>High</td>
<td>12,227 – 13,722</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Samoa</td>
<td>Lower middle</td>
<td>265 – 1,897</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singapore</td>
<td>High</td>
<td>22,342 – 61,701</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solomon Islands</td>
<td>Lower middle</td>
<td>57 – 1,004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tokelau</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonga</td>
<td>Upper middle</td>
<td>333 – 2,275</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Income Group</td>
<td>200 – 1,991</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------</td>
<td>-------------</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Tuvalu</td>
<td>Upper middle</td>
<td>200 – 1,991</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vanuatu</td>
<td>Lower middle</td>
<td>139 – 1,685</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vietnam</td>
<td>Lower middle</td>
<td>144 - 982</td>
<td>172</td>
<td>110</td>
</tr>
<tr>
<td>Wallis and Futuna</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: DALY, Disability-adjusted life year; PDR, People's Democratic Republic; SAR, Special Administrative Region; USA, United States of America, USD, United States Dollars;

*CETs were estimated based empirical estimates collected using marginal costs invested and marginal health outcomes across different NHS jurisdictions (k) assumed vsl = value of a life year = income elasticity for QALY. If similar elasticity for v and k exists than estimates were created based on differing GDP income elasticities*

*Health care expenditure from Bohari which was initially modelled against U5 and Maternal mortality was used on cross sectional data from GBD. Morbidity is estimated with population health estimates. DALY 1-4 information in Table 2 p16*

*Based on panel data modelled against U5 mortality and adult male and adult female mortality. DALY 1-4 information in table 6 p29*
Table A4. Vaccination delivery Costs (2020 USD) by country

<table>
<thead>
<tr>
<th>Country</th>
<th>Group</th>
<th>20% Coverage</th>
<th>50% Coverage</th>
<th>70% Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>A</td>
<td>-</td>
<td>-</td>
<td>$22.9</td>
</tr>
<tr>
<td>Japan</td>
<td>A</td>
<td>-</td>
<td>-</td>
<td>$33.6</td>
</tr>
<tr>
<td>Korea, Rep.</td>
<td>A</td>
<td>-</td>
<td>-</td>
<td>$11.1</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>A</td>
<td>-</td>
<td>-</td>
<td>$25.3</td>
</tr>
<tr>
<td>Fiji</td>
<td>B</td>
<td>-</td>
<td>$10.5</td>
<td>$10.5</td>
</tr>
<tr>
<td>Samoa</td>
<td>B</td>
<td>-</td>
<td>$17.8</td>
<td>$17.8</td>
</tr>
<tr>
<td>Tonga</td>
<td>B</td>
<td>-</td>
<td>$19.1</td>
<td>$19.1</td>
</tr>
<tr>
<td>Mongolia</td>
<td>B</td>
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<td>$13.4</td>
<td>$13.4</td>
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<tr>
<td>Cambodia</td>
<td>B</td>
<td>-</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Lao PDR</td>
<td>B</td>
<td>-</td>
<td>$1.3</td>
<td>$1.3</td>
</tr>
<tr>
<td>Philippines</td>
<td>B</td>
<td>-</td>
<td>$0.7</td>
<td>$0.7</td>
</tr>
<tr>
<td>Vanuatu</td>
<td>B</td>
<td>-</td>
<td>$5.7</td>
<td>$5.7</td>
</tr>
<tr>
<td>Kiribati</td>
<td>B</td>
<td>-</td>
<td>$29.3</td>
<td>$29.3</td>
</tr>
<tr>
<td>Micronesia, Fed. Sts.</td>
<td>B</td>
<td>-</td>
<td>$23.1</td>
<td>$23.1</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>C</td>
<td>$5.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Solomon Islands</td>
<td>C</td>
<td>$10.5</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

1Cambodia delivery costs were not available in UNICEF report.
### Table A5. Disease management unit costs (2020 USD) by country

<table>
<thead>
<tr>
<th>Country</th>
<th>Group</th>
<th>Non-hospitalised, per case</th>
<th>Hospitalised without ICU, per day</th>
<th>Hospitalised with ICU, per day</th>
<th>Death, per case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>A</td>
<td>$53.5</td>
<td>$271.6</td>
<td>$5,294.9</td>
<td>$64.5</td>
</tr>
<tr>
<td>Japan</td>
<td>A</td>
<td>$54.0</td>
<td>$208.7</td>
<td>$2,120.5</td>
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Table A6. Units input and unit costs (2020 USD) for Japan and Australia

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<thead>
<tr>
<th>Input Description</th>
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<th>Australia</th>
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<tr>
<td><strong>a. Home-based care</strong></td>
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<tr>
<td>community-based care via clinical visit</td>
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<tr>
<td><strong>Total</strong>.a</td>
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<tr>
<td><strong>b. Hospital-based (severe)</strong></td>
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<td></td>
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<tr>
<td>Inpatient ward bed-day (severe)</td>
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<td>Chest X-ray</td>
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<td>$19.70</td>
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<tr>
<td>Full blood count (including haemoglobin test)</td>
<td>0.125</td>
<td>$27.70</td>
</tr>
<tr>
<td>Blood urea and electrolyte test (including C-reactive protein test)</td>
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<td>$22.20</td>
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<tr>
<td>HIV test</td>
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<td>$26.20</td>
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<tr>
<td><strong>Total</strong>.b</td>
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<td>$208.70</td>
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<tr>
<td><strong>c. Hospital-based (critical)</strong></td>
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<td></td>
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<tr>
<td>Full blood count (including haemoglobin test)</td>
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<td>Bacteraemia days</td>
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<td>Urinary tract infection days</td>
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<td>Septic shock days</td>
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<td><strong>Total</strong>.c</td>
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References


Technical presentation 2
Warwick-Lancaster
global COVID-19 model

Ioana Bouros, Matt Keeling, Ed Hill,
Sam Moore, Robin Thompson
Outline

- The Warwick-Lancaster transmission model
- Model parameterisation
- Results: Faced with a wave of a novel variant, who should be targeted for booster vaccination?
- Future plans
Model Structure

- Extended age-stratified SEIR model
- 6 vaccination statuses:
  - Unvaccinated (S)
  - Fully vaccinated – 1 or 2 doses (S_F)
  - Boosted (S_B)
  - Partially waned – at 3 months (S_w1)
  - Waned – at further 3 months (S_w2)
  - Immunity due to an older/different variant (S_w3)

- Disease outcomes (hospitalisations and deaths) derived from numbers of symptomatic infections
Model fitting

- Infection parameters – global, fitted to hospitalisations and deaths from second Omicron wave in the UK.
- Disease outcomes – country specific, fitted to excess mortality estimates.
- Population demographics and mixing patterns – country specific.
- Vaccination effectiveness – global, assumed to have similar efficacy characteristics to those observed against Omicron.
Starting state estimates

- Full protection: from recent infection/vaccination
- Partially waned: from vaccination/infection 3-6 months ago
- Waned: from vaccination/infection >6 months ago
Boosting Scenarios

Testing 7 different booster vaccination scenarios:

- Decreasing order of age groups (75+, 70-74, 65-69, ...)
- 60-74 first, followed by 75+, and then in decreasing order of age groups
- 60-74 first, followed by 50-59, then 75+, and then in decreasing order of age groups
- 50-59 first, followed by 60-74, then 75+, and then in decreasing order of age groups
- 20-49 first, followed by 50-74, then 75+
- 20-49 first, followed by 75+, then by 50-74
- No booster

We assume:

i) Booster availability = 10% of country population size
ii) Maximum vaccine uptake = 90% within each age group
United Kingdom

Sierra Leone

Prioritise 75+
10.0% boosted

Total population
Existing high protection (recently vaccinated)
Newly boosted
Identical booster vaccination strategies have different implications in different countries.
Daily number of new deaths for different scenarios (10% boosted)

No boosters

Prioritise 60-74, then 75+

Prioritise 75+

Prioritise 20-49, 50-74, then 75+
Daily number of new deaths for different countries (10% boosted)

United Kingdom

Brazil

Philippines

Syria

Deaths per 100,000 for Philippines

Deaths per 100,000 for Brazil

Deaths per 100k

Daily number of new deaths for different countries (10% boosted)
Scenario-specific total number of deaths in each country

Deaths per 100,000 for different countries and scenarios

- Prioritise 75+, 10.0% boosted
- Prioritise 60-74 then 75+, 10.0% boosted
- Prioritise those 60-74 then 50-59, then 75+, 10.0% boosted
- Prioritise those 50-59 then 60-74, then 75+, 10.0% boosted
- Prioritise those 20-49, then 50-74 then 75+, 10.0% boosted
- Prioritise those 20-49, then 75+, then 50-74, 10.0% boosted
- No boosters, 0% boosted

Prioritising the older age groups for boosters first leads to fewest deaths
Scenario-specific total number of years of life lost in each country

Years of Life Lost per 100,000 for different countries and scenarios

- Prioritise 75+
- Prioritise 60-74 then 75+
- Prioritise those 60-74 then 50-59, then 75+
- Prioritise those 50-59 then 60-74, then 75+
- Prioritise those 20-49, then 50-74 then 75+
- Prioritise those 20-49, then 75+, then 50-74
- No boosters

Prioritising the older age groups for boosters first leads to fewest YLL
Summary

Given a wave of a novel variant, assuming similar vaccination effectiveness as for original COVID-19 vaccines against Omicron, our model suggests that:

- Targeting booster vaccination at the *oldest first* achieves the *largest reduction in deaths*

- Targeting booster vaccination at the *oldest first* achieves *fewest Years of Life Lost*
**Future plans**

- Explore the robustness of our results to different model assumptions (e.g. availability of booster vaccines; sensitivity to assumed immunity levels in different countries)

- Consider different frequencies of booster vaccination (by varying initial conditions of the model)

- Consider effect of booster vaccination on other model outputs (e.g. infections, hospitalisations)

- Consider different assumptions surrounding the effectiveness of vaccination (variant-specific boosters) and the characteristics of the variant

- How to prioritise different vaccines (general vaccine vs variant-adapted vaccine with production/distribution delay)
Questions?

Ioana Bouros, Matt Keeling, Ed Hill, Sam Moore, Robin Thompson
Retrospectively modeling the effects of increased global vaccine sharing on the COVID-19 pandemic

Sam Moore, Edward M. Hill, Louise Dyson, Michael J. Tildesley and Matt J. Keeling

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has caused considerable morbidity and mortality worldwide. The protection provided by vaccines and booster doses offered a method of mitigating severe clinical outcomes and mortality. However, by the end of 2021, the global distribution of vaccines was highly heterogeneous, with some countries gaining over 90% coverage in adults, whereas others reached less than 2%. In this study, we used an age-structured model of SARS-CoV-2 dynamics, matched to national data from 152 countries in 2021, to investigate the global impact of different potential vaccine sharing protocols that attempted to address this inequity. We quantified the effects of implemented vaccine rollout strategies on the spread of SARS-CoV-2, the subsequent global burden of disease and the emergence of novel variants. We found that greater vaccine sharing would have lowered the total global burden of disease, and any associated increases in infections in previously vaccine-rich countries could have been mitigated by reduced relaxation of non-pharmaceutical interventions. Our results reinforce the health message, pertinent to future pandemics, that vaccine distribution proportional to wealth, rather than to need, may be detrimental to all.

Since its emergence in Wuhan, China, at the end of 2019, SARS-CoV-2 has rapidly spread around the world, causing epidemics in nearly every country. As the causative agent of Coronavirus Disease 2019 (COVID-19) disease, the virus has caused considerable morbidity and mortality globally. During 2020, the containment of the pandemic relied predominantly on non-pharmaceutical interventions (NPIs) to limit the spread of infection, thereby reducing severe disease and preventing health services from being overwhelmed. Although this approach was broadly effective, it was also economically and socially damaging. During late 2020 and early 2021, numerous vaccines were approved for public use, representing unparalleled development speeds, which has enabled many countries to implement mass vaccination campaigns as a means of mitigation.

By January 2022, approximately 49% of the global population had received a full two doses of a COVID-19 vaccine, although delivery varied greatly between (and within) countries. Many high-income countries enjoyed very successful vaccination campaigns, with several exceeding 90% coverage of adults (aged 16 years and older). However, among many low-income and lower-middle-income countries, vaccine availability continues to be considerably more limited, with low-income countries counting for as little as 0.9% of the overall total vaccine deployed.

Low-income and lower-middle-income countries have been mostly dependent on donations from wealthier countries and vaccine sharing schemes, such as the World Health Organization (WHO)-directed COVAX initiative. As an increasing number of countries begin to...
The SARS-CoV-2 pandemic has caused considerable morbidity and mortality worldwide. Although the protection offered by vaccines (and booster doses) offers a method of mitigating the worst effects, by the end of 2021 the distribution of vaccine was highly heterogeneous, with some countries achieving over 90% coverage in adults, whereas others reached less than 2%. In part, this is due to the availability of a sufficient vaccine, although vaccine hesitancy also plays a role. We combined estimates of historic SARS-CoV-2 infections and vaccine uptake with an age-structured model for 152 countries to consider the implications of different vaccine sharing policies that go some way to addressing this imbalance.

Table 1 | Policy summary

| Background | The SARS-CoV-2 pandemic has caused considerable morbidity and mortality worldwide. Although the protection offered by vaccines (and booster doses) offers a method of mitigating the worst effects, by the end of 2021 the distribution of vaccine was highly heterogeneous, with some countries achieving over 90% coverage in adults, whereas others reached less than 2%. In part, this is due to the availability of a sufficient vaccine, although vaccine hesitancy also plays a role. We combined estimates of historic SARS-CoV-2 infections and vaccine uptake with an age-structured model for 152 countries to consider the implications of different vaccine sharing policies that go some way to addressing this imbalance. |
| Main findings and limitations | We calculated that increased vaccine sharing, without any changes to NPIs, would have substantially reduced COVID-19 infection mortality in lower-income countries, although some high-income countries would have had increased mortality unless additional measures were taken. Overall, we estimate that this vaccine sharing scenario would have prevented 1.3 million deaths worldwide (as a direct result of COVID-19) by the end of 2021, although this figure could be substantially increased if increased vaccine sharing from high-income countries had been compensated for with slower easing of NPIs. This global decrease in mortality is due to a combination of greater protection of the most vulnerable and the lower level of global infection, leading to fewer opportunities for new variants to arise. This study is limited to considering vaccine supply constraints, although additional pressures induced by uptake hesitancy and delivery limitations are becoming increasingly relevant. |
| Policy implications | Although the focus of this work is a retrospective study of the COVID-19 pandemic, there are naturally conclusions to be drawn about national and international policies going forward. Our simulations provide strong analytical evidence to support the message that distributing vaccines across the globe proportional to need, rather than to wealth, can have beneficial effects for all. |

In high-income countries that have achieved high levels of vaccine coverage, they face the decision of whether to continue with a nationalistic approach to vaccination—by extending rollout to the young, providing booster jabs to protect against waning immunity and stockpiling surplus resources for future use—or whether to begin donating more vaccines to places where there may be markedly higher payoffs per dose in reducing infection and mortality. Although high-income countries typically have larger elderly populations and, consequently, more individuals who are directly vulnerable to the effects of COVID-19, low-income countries are typically well equipped to deal with high levels of morbidity. The effects of increased pressure on already limited healthcare resources in low-income countries has had critical impacts on a range of endemic diseases, and, without surplus welfare resources available in such countries, NPIs are unsustainable.

In high-income countries that have achieved high levels of vaccination, campaigns have proven highly effective in limiting disease impacts while allowing the relaxation of restrictions and a return to pre-pandemic-like behavior. However, the estimated waning of vaccine efficacy has meant that many countries are now investing in booster campaigns, with third and fourth doses becoming widely implemented. The huge numbers of global infections (estimated at more than 14 billion infections to date) have generated considerable opportunities for viral mutation and the emergence of variants that have notable transmission and/or immune escape advantages over ancestral strains. Such variants of concern have raised the reproductive number and, hence, prolonged the pandemic by causing new waves of infection. The continued threat of further mutation equates to a large level of uncertainty in future infection patterns. Consequently, although national vaccination campaigns have proven effective in limiting disease impact nationally, epidemic containment may be fully achieved only if high levels of new global infections are avoided, minimizing the threat of generating further variants of concern.
Through the use of a detailed global model, matched to country-level COVID-19 disease and incorporating SARS-CoV-2 vaccination data to the end of 2021 in 152 different countries, we explored the effects that increased historic levels of global vaccine sharing would have had on the likely state of the pandemic, projected from early 2020 to the end of 2021. The model simulates five levels of vaccine sharing: from the observed scenario, through sharing, once vaccine-rich countries have offered two doses to all individuals, those over 40 years of age or those over 65 years of age, to full sharing based on protecting either equal proportions of each country or the oldest individuals first across the globe. The model also captures two forms of NPIs: either following the observed controls irrespective of infection levels or with adaptive behavior in which countries that share more vaccine than observed may relax controls more slowly to compensate. We show that increased vaccine sharing may substantially decrease mortality in lower-income countries with only limited increases in some high-income donor nations, provided that the most vulnerable are still vaccinated in a timely manner. We also show the broader potential of more equally distributed vaccination. In return for an increased duration of control measures in the currently vaccine-rich countries, vaccine sharing can substantially decrease the number of overall infections in 2021, reducing the potential for the evolution and spread of increasingly severe variants and, subsequently, substantially improving the outlook of the pandemic both nationally and globally. The main findings and policy implications of this work are provided in Table 1.

Results

By the end of 2021, nearly 50% of the global population had been fully vaccinated (two doses), although large disparities in coverage across the globe mean that this figure is closer to 75% across high-income countries but less than 2% in many low-income countries (Fig. 1a). Any increased degree of vaccine sharing will at least partially address this balance, potentially generating substantial gains in sparsely vaccinated nations, although inevitably leading to some increase of infection in the most highly vaccinated countries (Fig. 2 and Extended Data Fig. 1). In total, we estimate that a full vaccine sharing scenario would have prevented 295.8 million infections and 1.3 million deaths worldwide (as a direct result of COVID-19) by the end of 2021 without any associated changes in behavior (Fig. 2b, Extended Data Fig. 1k and Supplementary Table 1). Any increased degree of vaccine sharing will at least partially address this balance, potentially generating substantial gains in sparsely vaccinated nations, although inevitably leading to some increase of infection in the most highly vaccinated countries (Fig. 2 and Extended Data Fig. 1). In total, we estimate that a full vaccine sharing scenario would have prevented 295.8 million infections and 1.3 million deaths worldwide (as a direct result of COVID-19) by the end of 2021 without any associated changes in behavior (Fig. 2b, Extended Data Fig. 1k and Supplementary Table 1). We found that increased vaccine sharing would likely have reduced infections in low-income, lower-middle-income and even higher-middle-income countries across early to mid 2021, with an estimated 25.9%, 12.6% and 15% reductions in these regions, respectively, in the full sharing scenario (Extended Data Fig. 1k and Supplementary Table 2). However, these benefits might have been partially offset by substantial increases in infections experienced in high-income countries later in 2021 as other control measures were relaxed (Fig. 3a–d), with approximately 42.7% more infections in these countries for the full sharing scenario (Supplementary Table 2). Australia and New Zealand appear as notable exceptions to this, as having relatively late starting vaccination programs means few doses are given to default adaptation.
away in any scenario, and very low infection levels throughout 2021 mean that even small advantages from delayed variant emergence translate into large percentage gains (Extended Data Fig. 1b,e,h,k; results for individual countries are provided in Supplementary Table 3). With later increases in infection, the corresponding mortality is markedly less pronounced (Fig. 3e,f). This is due to most vulnerable people having been offered vaccination in high-income countries by this time in all scenarios, because we assume oldest-first vaccination. Hence, the bulk of this increased infection would be felt by the younger and less vulnerable or in vaccinated individuals. Conversely, the earlier infection prevention in lower-income countries by increased vaccine sharing is likely to have had included many of the elderly and vulnerable and, as such, translated into a substantial saving of lives. As a result, we estimate that there would have been 17.7 fewer deaths per 100,000. This is driven further by prioritizing initial vaccine doses worldwide over booster doses and stockpiling in the wealthiest countries. Consequently, the higher impact per dose of initial vaccine doses above booster doses results in some evidence of potential further benefits in the late stages of 2021 in all sharing scenarios, particularly as new emerging variants drive further transmission increases (Fig. 3a,e,i,j).

If the increased infection seen in high-income countries due to increased vaccine sharing resulted in extended behavioral caution (adapted behavior or longer use of NPIs), we estimate a much greater reduction in global infections than in scenarios where behavior remains unchanged (Fig. 3i,j). We estimate that the global population infected and mortality rates by the end of 2021 would have been substantially reduced for the full vaccine sharing strategy scenario (29.1% infected, 84 deaths per 100,000); Fig. 2i, Extended Data Fig. II and Supplementary Table 2) compared to the default scenario (48.4% infected, 133.1 deaths per 100,000). This is driven by the benefits of early vaccine sharing for lower-income countries persisting throughout 2021 (Extended Data Fig. 2), reducing infection and, hence, the potential for the emergence and spread of variants. This would create a positive feedback loop with less infection causing fewer variants and less increase in the basic reproduction number ($R_0$), itself leading to less infection; while infection levels are kept below -35%, there is not the opportunity for

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**Fig. 3** Relative changes over time and total infections and mortality in each economic region under the central vaccine sharing scenarios. a–h. Time series plots showing the reduction (positive values) or increase (negative values) in the global number of daily infections and daily deaths compared to the default scenario, each assuming unchanged behavior (equivalent figures for adapted behavior are provided in Extended Data Fig. 2). i,j. Estimated total proportion of infected and deaths from COVID-19 per 100,000, respectively, until the start of 2022 (so, over all of 2020 and 2021) in each of the economic regions. All results represent medians of 100 simulations, with model fitting spanning the range of uncertainty in infection and mortality estimates for each country. These are presented as caricatures to compare scenario impact with detailed data and associated prediction intervals provided in Supplementary Table 2.
...with wealthier countries reserving vaccines for their own populations. This age-biased vaccine sharing strategy typically benefits those countries with older populations. If countries are limited by vaccine availability, a more equitable share of vaccines would have less of an impact on mortality, particularly in low-income countries. However, in scenarios with a moderate increase in vaccine adverse events, the shared mortality risks are also reduced. Proportionally, vaccination strategies are better able to allocate vaccines in times of need, and they enable countries to promptly adjust their responses based on the unfolding epidemic. Overall, the model shows that, with the Delta variant on the rise, age-biased vaccine sharing may benefit countries with older populations, such as Lithuania, China, and Romania, where the majority of the population is aged 60 years or older. In contrast, countries with a younger population, such as the United Kingdom and Israel, may experience a higher transmission rate and consequently a greater number of infections. Therefore, the distribution of vaccines should be adjusted to account for the age demographics of each country. In summary, the model suggests that age-biased vaccine sharing may have limited benefit in reducing mortality rates, but it could be more effective in controlling the spread of SARS-CoV-2 in countries with older populations. Despite the limitations of the model, these findings may inform future vaccine distribution strategies.
and reduced global burden of infection is of benefit to all, it may necessitate the short-term re-imposition of some non-pharmaceutical mitigation measures (with their associated economic consequences and social disruption) instead of additional booster vaccines in some countries.

We show that a more equitable approach to global vaccine distribution over the course of 2021 would have reduced the level of global mortality associated with COVID-19 disease. Our conclusions are based on simulations fitted to historical infection and mortality estimates and from varying the distribution of vaccination between countries while maintaining total vaccine supply. Similar studies have previously been run by Wagner et al.\textsuperscript{21}, who used a simple two-country conceptual model, and Watson et al.\textsuperscript{29}, who followed a similar approach to estimate the impact on global mortality had overall vaccine supply varied. Any historical deviation in vaccine distribution would likely precipitate a range of consequences, including changes in other policy areas, social behavior, overall vaccine uptake, patterns of viral spread and variant evolution. Although such compounding factors are difficult to predict, the simulation results presented here include potential changes to policy (or behavior) and account for the consequences for variant accrretion, increasing the robustness of our findings.

We estimate that the greatest reductions in infection and mortality are associated with vaccine sharing earlier in the pandemic, with less extensive or delayed strategies presenting more modest benefits. In our model, given the high transmissibility of SARS-COV-2 infection, countries without high and early vaccine coverage are likely to rapidly incur high infection levels and, hence, substantial population immunity; as such, the effects of late vaccine sharing to these countries are much reduced. In addition, due to limited delivery capacities and increasing public distrust of vaccination\textsuperscript{23}, starting vaccination earlier may have led to more successful vaccination campaigns in general. However, with increasing transmission and possible immune escape from new variants\textsuperscript{28} and the risk of waning efficacy, vaccine sharing remains important: our model suggests that even late vaccine sharing, once wealthy countries had delivered all second doses, would have been sizeable benefits in late 2021 and into 2022.

We estimate that increased vaccine sharing would have provided large benefits in low-income and lower-middle-income countries; this benefit comes at a cost to some high-income countries where increased or prolonged use of NPI measures would have been required to suppress disease in the short term. This substantial reduction in disease burden could have reduced the unmanageable waves of disease experienced by many of the poorest countries that are least well equipped to manage the pandemic. In addition, as high sharing scenarios delay infections until later in the year, these infections would have occurred once knowledge and treatments had improved and so may have been better managed.

This study is subject to several limitations. First, we concentrated on supply constraints. Assuming that a fixed amount of vaccine was available throughout 2021, the key issue addressed is where this should have been deployed. Supply has historically been a major factor causing heterogeneity in worldwide coverage\textsuperscript{27}—when vaccines first became available, the limited quantities produced were purchased primarily by wealthier nations. A confounding factor in this calculation is that, because the countries producing and financing the vaccines have typically already had access to large amounts of vaccine, there has been little incentive to substantially increase production\textsuperscript{19}. One might hypothesize that increased sharing might have encouraged additional resources to be put into production, increasing the overall volume of vaccines available.

In this analysis, we also assumed that vaccine efficacy profiles used are uniform across nations; however, many lower-income countries rely on substantially less effective vaccines than the more desirable counterparts employed by high-income countries\textsuperscript{29}. During the course of simulation, we tested sensitivity to vaccine efficacy, and, as expected, if redistributed vaccines were of lower or higher efficacy, the benefits of sharing would be reduced or increased, respectively. Imbalances in vaccine efficacy may then mean that the heterogeneity in effective vaccine coverage would be even greater than assumed, and increasing vaccine sharing to address this imbalance would be even more critical.

With numerous different vaccines now being produced and the success of the COVAX scheme increasing vaccine availability\textsuperscript{7}, limitations surrounding delivery and uptake are becoming increasingly important\textsuperscript{19}. In our model, it is unsurprising that, if the level of vaccine uptake resulting from increased supplies was lower than presented, the benefits of sharing would be comparatively reduced. Many lower-income countries lack the infrastructure needed to rapidly deliver vaccines on the scale required, especially where there are large, hard-to-reach population sectors. Similarly, although vaccine hesitancy has been a recognized problem in all nations, in countries where public health messaging and education is limited, hesitancy is becoming a severe limiting factor for increased vaccine coverage\textsuperscript{30,31,32}.

Future support may, therefore, need to include assistance with vaccine delivery and logistical support in addition to the provision of vaccine doses.

Finally, we have not explored the major threat of variants that escape vaccine and/or naturally induced immunity, owing to their lack of substantial impact during 2021 (ref. \textsuperscript{1}). The emergence of Omicron in November 2021 has posed just such a threat\textsuperscript{33-36}, with the potential for large waves of infection and the need to re-vaccinate some vulnerable populations. This emergence strengthens the arguments for vaccine sharing as a means of reducing the global levels of infection and, hence, retarding the accumulation of new variants.

Vaccines generally offer greater protection against severe disease than infection\textsuperscript{14,17}, and the effects against severe disease are likely to be more robust against both waning immunity and vaccine escape\textsuperscript{37,38}. Hence, deploying vaccines to regions where there remains a high proportion of unprotected vulnerable individuals would have a much greater impact per dose than extending vaccination in countries that have already protected most of their vulnerable population. A complication to this vaccine equity picture is that the number of elderly and vulnerable individuals is larger in high-income countries, although reduced welfare resources and limited access to effective treatments, as often seen in low-income countries, make a true determination of vaccine need challenging. However, our model-based results reinforce the global public health message that vaccine nationalism (protecting one’s own country to the detriment of others) not only leads to greater levels of infection and mortality worldwide but also adversely impacts all countries in the long term\textsuperscript{39-41}.

Online content
Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-022-02064-y.

References
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Methods
This study was based on simulations using a mathematical model of SARS-CoV-2 transmission and COVID-19 outcomes, using data pre-existing in the public domain. As such, there were no relevant ethical regulations to consider. Simulations included 152 different countries, each with its own parameters reflecting demographics and social structure. The countries were simulated in parallel, using independent, age-structured, deterministic, compartmental infection models but coupled by the global evolution of new variants and the sharing of vaccines when national conditions are met. Given the strong correlation between per capita income and the level of COVID-19 vaccination\(^1\), we partitioned the 152 countries simulated into the four income group classifications given by the World Bank\(^2\) (Fig. 1a). Exclusions (gray regions in Fig. 1, listed with Supplementary Table 3), made only for countries where data are missing from sources used, are assumed average for each income group.

Individuals within each country were classified as susceptible (S), exposed (E), infectious and symptomatic (I), infectious and asymptomatic (A) or recovered (R). We used a set of ordinary differential equations to describe the flow of individuals between these compartments. Susceptible individuals were subjected to a force of infection proportional to \(\beta\) for each country, where \(\beta\) is an age-dependent discounting factor used to represent reduced transmission from asymptomatic individuals compared to symptomatic individuals; superscripts here denote 5-year age bands. The exposed class was further subdivided into three separate states, \(E_1\), \(E_2\), and \(E_3\), meaning that, in a stochastic formulation, the distribution of the latent period would become an Erlang distribution, creating more realistic infection time scales.

Age is recognized to play an important role in the dynamics of the SARS-CoV-2 epidemic, strongly influencing both the outcome after infection and the characteristic social mixing behavior\(^3\) that facilitates transmission. These age-based heterogeneities were captured by stratifying the modeled populations into 5-year age groups using country-level data on age demographics\(^4\), each with their own parameters for susceptibility, the occurrence of symptoms and the risk of severe disease.

Throughout the pandemic, most countries have responded to rising levels of disease with mitigation measures, including social distancing, quarantining, mandatory mask wearing and contact tracing\(^5\), and increased caution among residents may act to substantially slow viral spread. To account for these effects, epidemiologically relevant contacts within each country are varied in a time-varying manner by a country-specific control factor \(\phi\) that modulates transmission. These age-based heterogeneities were captured by stratifying the modeled populations into 5-year age groups using country-level data on age demographics\(^4\), each with their own parameters for susceptibility, the occurrence of symptoms and the risk of severe disease.

The core infection parameters used were assumed to be the same across all countries. These include age-dependent variables for transmission, \(\beta\); the probability of exhibiting symptoms, \(d\); the progression rate between exposure and infection, \(\alpha\); the recovery rate, \(\gamma\); and the reduction in asymptomatic transmission, \(r\). Estimates for these values were fitted from early age-stratified United Kingdom case data to match growth rate, reproductive number and age profiles of infection between the start of the pandemic and the emergence of the Alpha variant in early 2021. Country models vary in demographics, informed by WHO estimates\(^6\) and mixing patterns, based on contact matrices, \(M\), described by Prem et al.\(^7\), vaccination levels, mitigating control factors, \(\phi\), as well as disease outcomes.

Statistical analysis
Parameters for national control measures and death rates were determined as maximum likelihood estimates, using data estimates for the total number of all new infections and deaths (together with levels of uncertainty) as proposed by the Institute for Health Metrics and Evaluation (IHME)\(^8\). Due to inconsistencies and under-reporting of COVID-19 metrics in many countries, rather than relying on official reports, their estimates are made based on excess mortality statistics, comparing death rates in each country during the pandemic to historical data, tracking past trends and seasonality. Other similar excess mortality estimates have been made elsewhere with reasonable consistency; for instance, Karlinsky et al.\(^9\) estimated 160,000 deaths in South Africa by 27 June 2021 (60,000 reported) compared to the IHME estimate of 156,373 deaths (with a high and low estimate range of 90,221 to 258,352).

Uncertainty in these values is accounted for by taking 100 independent random samples informed by the high and low IHME estimates and propagating these samples through the fitting and simulation to generate means and 95% prediction intervals. Sample size was chosen to cover the range of parameter estimates while remaining sufficiently computationally inexpensive, and no statistical method was used to predetermine this sample size. No data were excluded from the analyses, and the experiments were not otherwise randomized. The investigators were not blinded to allocation during experiments and outcome assessment.

Variants
Across the course of the pandemic, there has been a substantial rise in the level of transmissibility of the dominant SARS-CoV-2 variant. Initially, when COVID-19 was first detected in China, the basic reproductive number, \(R_0\), was estimated between 2 and 2.4 (ref.\(^1\)). Transmissibility has seen three major step changes due to the Alpha variant (\(R_0 = 4 - 5\)) at the end of 2020; the Delta variant (\(R_0 = 5 - 7\))\(^{10}\) becoming dominant in many countries by early summer 2021; and the emergence of the Omicron variant (\(R_0 = 10 - 16\)) at the end of 2021.

By considering the global proportion of each variant (as averaged across countries for which such data are available from the GISAID database\(^6\), assuming wild-type has \(R_0 = 2.2\), Alpha variant has \(R_0 = 4\), Delta has \(R_0 = 6\) and Omicron has \(R_0 = 12\)), we may visualize the trend of increasing \(R_0\) (Fig. 4b) and the associated level of infection up to that time. The relationship between total historic infections (blue) and the average basic reproductive number (red) is then used to realize the impact of varying infection levels on variant emergence in the simulations—relating a given level of historic infection to an average basic reproductive ratio due to the emergence of new variants (Fig. 4c).

Vaccination and sharing scenarios
We make the assumption that all countries aim to eventually achieve vaccine coverage in all individuals from the age of 12 and older, with a 90% uptake for those older than 60 years and 80% for those younger (although vaccine hesitancy may present substantial difficulty in achieving this in some nations). We also assume that an oldest-first approach to vaccine distribution is used in all nations, delivering vaccines to the most vulnerable first\(^6\). Although deviation from this
approach has been seen in some countries that have chosen to prioritize essential workers or key disease spreaders (including those, such as taxi drivers, in high-contact professions), the strategy of oldest-first is the most widely employed⁴⁸.

Vaccination is assumed to provide individual protection against four measures: susceptibility, onward transmission, symptom probability and hospitalization/death. These are based on efficacy characteristics similar to one or two doses of ChAdOx1-S/nCoV-19 (AstraZeneca) vaccine⁴⁴—the being one of the most widely distributed and well-studied COVID-19 vaccines to date. This is an approximation of the heterogeneous global picture⁵⁵, with some vaccines (such as Sinopharm) considered to provide lower protection⁴⁹ and the widely deployed Johnson & Johnson vaccine requiring only a single dose⁵⁰. Specifically, before waning, we take vaccine efficacy against:

- Infection: 60% one dose, 75% two doses
- Transmission: 45% one dose, 45% two doses
- Symptoms: 60% one dose, 83% two doses
- Severe disease: 80% one dose, 98% two doses

In addition, efficacy can also vary with age, dose interval and between variants. All four forms of vaccine protection are assumed to wane over time, from a maximum shortly after the second dose to minimum levels after 6 months of age (48 months) later (Fig. 4a). Countries completing two-dose vaccination coverage (subject to assumptions made for eligibility and uptake), and with sufficient vaccine supply, are assumed to commence delivery of booster vaccinations to all individuals at 6-month dose intervals, again in oldest to youngest priority order. Booster doses when delivered are taken to reset waning back to the maximum efficacy level. Alongside a default, low sharing scenario reflecting actual historical vaccine delivery, several more collaborative strategies that consider alternative distribution scenarios over the course of 2021 are investigated:

- Current scenario, low sharing: Past reports for daily vaccines administered are followed in each country.
- Two-dose threshold: The simulation progresses in each country, with daily vaccination numbers equal to the current scenario until the two-dose vaccination program is completed (subject to uptake assumptions). Subsequent daily vaccine deliveries from that country are then divided between all countries proportional to the remaining number of individuals pending vaccination (again, within the assumptions made for eligibility and uptake).
- 40+ threshold: Similar to the two-dose threshold scenario except that vaccine sharing begins in each country after a two-dose vaccination is completed for all individuals 40 years of age and older.
- 65+ threshold: Similar to the two-dose threshold scenario except that vaccine sharing begins in each country after a two-dose vaccination is completed for all individuals 65 years of age and older.

Full sharing: Vaccine sharing begins at the start of 2021 with all vaccination pooled and divided between all countries proportional to the number of unvaccinated individuals remaining in each.

In the central scenarios presented, vaccination is redistributed proportionally to the number of eligible individuals in each country who remain unvaccinated, although we additionally present strategies (Extended Data Figs. 5 and 6) where vaccine redistribution is proportional to the number of eligible individuals in each country. In scenarios where some countries have reduced vaccine supply due to increased demand, it is likely that, without a change to behavior or controls, infections would increase compared to the current scenario. We, therefore, perform two projections, one where the behavior follows inferred levels irrespective of infections and one where behavior adapts. We implement this behavioral response by increasing/decreasing the control parameter, ϕ, for each country that is sharing vaccines, dependent on whether the number of active infections is increasing or decreasing (subject to a 5-day time lag to reflect delays in detection and reaction). An example showing behavior adaptation is given in Fig. 4f.

Adapted behavior

In scenarios where some countries have reduced vaccine supply due to increased demand, it is likely that, without a change to behavior or controls, infections would increase compared to the current scenario. We, therefore, perform two projections, one where the behavior follows inferred levels irrespective of infections and one where behavior adapts. We implement this behavioral response by increasing/decreasing the control parameter, ϕ, for each country that is sharing vaccines, dependent on whether the number of active infections is increasing or decreasing (subject to a 5-day time lag to reflect delays in detection and reaction). An example showing behavior adaptation is given in Fig. 4f.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The study was based on data from a variety of publicly available sources: population demographic data provided by the WHO;¹² income group classifications provided by the World Bank;¹³ COVID-19 vaccine deployment provided by Our World in Data;¹⁴ COVID-19 mortality and infection estimates to date made by the Institute for Health Metrics and Evaluation;¹⁵ and data on COVID-19 variants collated by GISAID.¹⁶

Code availability

Model code was written in MATLAB R2020a and is available in the following repository: https://github.com/sammoore25/The-impacts-of-increased-global-vaccine-sharing-in-the-COVID-19-pandemic/.

References

45. Global Population Demographics (World Health Organization, 2021); https://apps.who.int/gho/data/node

Acknowledgements
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Author contributions
S.M. and M.J.K. conceived the study and devised the methodology. S.M. undertook the formal analysis, software and visualization and wrote the original draft. S.M., M.J.K., E.M.H., L.D. and M.J.T. validated, reviewed and edited the study.

Competing interests
The authors declare no competing interests.

Additional information
Extended data is available for this paper at https://doi.org/10.1038/s41591-022-02064-y.

Supplementary information
The online version contains supplementary material available at https://doi.org/10.1038/s41591-022-02064-y.

Correspondence and requests for materials should be addressed to Sam Moore.

Peer review information Nature Medicine thanks Mitsuru Mukaigawara and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary handling editor: Jennifer Sargent, in collaboration with the Nature Medicine team.

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Extended Data Fig. 1 | Relative changes in infection per country under central sharing scenarios. Country level estimates of vaccination coverage at the start of 2022 (a,d,g,j), total number of infections over 2021 relative to the current scenario with unchanged behaviour but increased vaccine sharing (b,e,h,k), and total number of infections over 2021 relative to the current scenario with adaptive behaviour and increased vaccine sharing (c,f,i,l). All results represent medians of 100 simulations with model fitting spanning the range of uncertainty in infection and mortality estimates for each country. These are presented as caricatures to compare scenario impact with detailed data and associated prediction intervals provided in Supplementary Table 3. Analogous figures for mortality estimates are given in Fig. 2.
Extended Data Fig. 2 | Relative changes in infection and mortality over time in each economic region for scenarios with adapted behaviour. Time series plots showing the reduction (positive values) or increase (negative values) in the global number of daily infections (a–d) and daily deaths (e–h) compared to the default scenario, each with adapted behaviour (equivalent figures for unchanged behaviour are given in Fig. 3). All results represent medians of 100 simulations with model fitting spanning the range of uncertainty in infection and mortality estimates for each country. These are presented as caricatures to compare scenario impact with detailed data and associated prediction intervals provided in Supplementary Table 2.
Extended Data Fig. 3 | Total infections and mortality per economic region under scenarios with lower level behaviour adaptation. Plots comparing estimates based on unchanged behaviour and lower level adapted behaviour. Estimated total proportion infected (a) and deaths from COVID-19 per 100,000 (b) until the start of 2022 (so over all of 2020 and 2021) in each of the economic regions. All results represent medians of 100 simulations with model fitting spanning the range of uncertainty in infection and mortality estimates for each country. These are presented as caricatures to compare scenario impact with detailed data and associated prediction intervals provided in Supplementary Tables 5 and 6.
Extended Data Fig. 4 | Relative changes in mortality per country under scenarios with lower level behaviour adaptation. Plots comparing estimates based on unchanged behaviour and lower level adapted behaviour. Country level estimates of vaccination coverage at the start of 2022 (a,d,g,j), total number of deaths over 2021 relative to the current scenario with unchanged behaviour but increased vaccine sharing (b,e,h,k), and total number of deaths over 2021 relative to the current scenario with lower level adaptive behaviour and increased vaccine sharing (c,f,i,l). All results represent medians of 100 simulations with model fitting spanning the range of uncertainty in infection and mortality estimates for each country. These are presented as caricatures to compare scenario impact with detailed data and associated prediction intervals provided at an income group level in Tables S5 and S6.
Extended Data Fig. 5 | Relative changes over time and total infections and mortality in each economic region for scenarios with age biased vaccine distribution. Plots presenting estimates based on scenarios with age biased vaccine redistribution. Panels a-h show time series plots showing the reduction (positive values) or increase (negative values) in the global number of daily infections and daily deaths compared to the default scenario, each assuming un-adapted behaviour. Panels i and j show estimated total proportion infected and deaths from COVID-19 per 100,000 respectively until the start of 2022 (so over all of 2020 and 2021) in each of the economic regions. All results represent medians of 100 simulations with model fitting spanning the range of uncertainty in infection and mortality estimates for each country. These are presented as caricatures to compare scenario impact with detailed data and associated prediction intervals provided in Supplementary Tables 7 and 8.
Extended Data Fig. 6 | Relative changes in mortality per country under scenarios with age biased vaccine distribution. Plots presenting estimates based on scenarios with age biased vaccine redistribution. Country level estimates of vaccination coverage at the start of 2022 (a,d,g,j), total number of deaths over 2021 relative to the current scenario with unchanged behaviour but increased vaccine sharing (b,e,h,k), and total number of deaths over 2021 relative to the current scenario with adaptive behaviour and increased vaccine sharing (c,f,i,l). All results represent medians of 100 simulations with model fitting spanning the range of uncertainty in infection and mortality estimates for each country. These are presented as caricatures to compare scenario impact with detailed data and associated prediction intervals provided at an income group level in Supplementary Table 7.
Reporting Summary

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- The statistical test(s) used AND whether they are one- or two-sided
- Only common tests should be described solely by name; describe more complex techniques in the Methods section.
- A description of all covariates tested
- A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
- A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) and variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
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- For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
- For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
- Estimates of effect sizes (e.g. Cohen's d, Pearson's r), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection
No software was used for data collection.

Data analysis
Analysis was made using a model coded in MATLAB R2020a. Model code is available in the repository https://github.com/sammoore25/The impacts of increased global vaccine sharing in the COVID-19 pandemic. A statement of this is included in the manuscript.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

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The study was based on data from a variety of publicly available sources: population demographic data provided by the WHO [45]; income group classifications given by the World Bank [44]; COVID vaccine deployment provided by Our World in Data [5]; COVID mortality and infection estimates to date made by the Institute for Health Metrics and Evaluation [18]; data on COVID variants collated by GISAID [20]. [References provided in the manuscript.]
Human research participants

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size

100 independent simulations were performed. This number was chosen to cover the range of parameter estimates while remaining sufficiently computationally inexpensive and no statistical method was used to predetermine this sample size.

Data exclusions

Countries were excluded from the study only where an incomplete dataset was available, due to omission from one or more data source.

Replication

Model code is made available alongside a fully public dataset, allowing replication of all presented results.

Randomization

Uncertainty was accounted for by taking 100 independent random samples informed by the high and low HME estimates, and propagating these samples through the fitting and simulation to generate means and 95% prediction intervals, the simulations were not otherwise randomized.

Blinding

The study was based on simulations using freely available and anonymous data. As such no blinding was relevant to the study.

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We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

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Methods

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<td>MRI-based neuroimaging</td>
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Technical presentation 3
Disentangling the impact of natural infections and vaccination in a rapidly evolving pandemic: prioritizing limited vaccine supplies in low- and middle-income countries

PIs: Alicia N.M. Kraay and Pamela P. Martinez
Student researchers: Iffat Noor (Aim 1) and Sophie Larsen (Aim 2)
Objectives

• **Aim 1:** Assess how immunological history (prior infection and/or vaccination) and ongoing evolution influences optimal vaccine policy based on severity of infection and mortality

• **Aim 2:** Assess how immune imprinting and specific cross reactions between COVID-19 serotypes influences optimal vaccine policy
Aim 1 Model Structure

Stratified model by:
- Age
- SES

Account for social contact structure by country
Outcomes

• Deaths averted through:
  • Child primary series
  • Boosters

• Impact on deaths/health burden
Baseline vaccine coverage

<table>
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<th>Scenario</th>
<th>India</th>
<th>Ecuador</th>
<th>Malaysia</th>
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<td>High Baseline immunity</td>
<td>63.4%</td>
<td>29.9%</td>
<td>81.1%</td>
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<tr>
<td>Low Baseline Immunity</td>
<td>15.3%</td>
<td>14.7%</td>
<td>42.9%</td>
</tr>
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</table>

All three countries had high baseline vaccine coverage among adults and child vaccine coverage was also high among children in Ecuador and Malaysia.
# Results

## Interventions Cumulative deaths per mill Percent deaths averted

<table>
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<th>Cumulative deaths per mill</th>
<th>Percent deaths averted</th>
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<td>India</td>
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<tr>
<td><strong>Duration of immunity=10 months, high immunity</strong></td>
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<tr>
<td>No booster benefit</td>
<td>419.3</td>
<td>670.3</td>
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<tr>
<td>AZ-like booster</td>
<td>323.2</td>
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<tr>
<td>mRNA-like booster</td>
<td>179.7</td>
<td>502.9</td>
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</tbody>
</table>

## Duration of immunity=3 months, high immunity

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<th>Cumulative deaths per mill</th>
<th>Percent deaths averted</th>
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</thead>
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<td>India</td>
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<tr>
<td>No booster benefit</td>
<td>1045.6</td>
<td>1199.5</td>
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<tr>
<td>AZ-like booster</td>
<td>724.7</td>
<td>844.0</td>
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<tr>
<td>mRNA-like booster</td>
<td>253.7</td>
<td>541.6</td>
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</table>
ooster VE against hospitalization
Implications

• Booster vaccination can make a substantial contribution to ongoing control efforts.
• Infection blocking vaccines should be prioritized.
• Child vaccination is not expected to be substantially beneficial.
• Booster doses are expected to avert the greatest number and proportions of deaths in countries with lower natural immunity.
Limitations: Underreporting

• Baseline immunity
  Possibly underestimated, particularly among children:
  - As few as 1-2% of cases have been reported even in HIC (Lau et al, 2021)

• Current incidence underreported
Limitations: Underreporting

- Baseline immunity
  Possibly underestimated, particularly among children:
  - As few as 1-2% of cases have been reported even in HIC (Lau et al, 2021)

- Current incidence underreported
Aim 2 Model Structure

Vaccination trends by SES

SEIR diagram

Examples of immune history

<table>
<thead>
<tr>
<th></th>
<th>Wild-type</th>
<th>Omicron</th>
<th>Vaccine</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Booster</td>
</tr>
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</table>

|                      |           |         |         |
|                      |           |         |         |
Aim 2 Model Structure

- Stratified by:
  - Age
  - SES

- Different vaccination trajectories
- Different immune histories

<table>
<thead>
<tr>
<th>Immune History</th>
<th>wild-type</th>
<th>delta</th>
<th>omicron</th>
<th>omicron*</th>
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</tr>
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<tr>
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<tr>
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<tr>
<td>Infection followed by vaccination</td>
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<td>0.16</td>
<td>0.37</td>
<td>0.4</td>
</tr>
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<td>Remaining history generalization</td>
<td>0.27</td>
<td>0.3</td>
<td>0.58</td>
<td>0.61</td>
</tr>
</tbody>
</table>
Outcomes

• Infection prevalence over time
• Deaths averted under 3 boosters:
  - Astra-Zeneca booster “AZ-like” (reference): VE₁ = 0.5, VEₛ=0.7
  - mRNA bivalent booster “mRNA-like”: VE₁ = 0.9, VEₛ=0.9
  - “Immune-escape”: VE₁ = 0, VEₛ=0.5
• Two scenarios of booster immunity duration:
  • 3 months
  • 10 months
<table>
<thead>
<tr>
<th>Country</th>
<th>Scenario</th>
<th>waning: 10 months</th>
<th>waning: 3 months</th>
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<tr>
<td>Ecuador</td>
<td>AZ-like</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Ecuador</td>
<td>Immune escape</td>
<td>-28.7 %</td>
<td>-31.3 %</td>
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<tr>
<td>Ecuador</td>
<td>mRNA-like</td>
<td>17.9 %</td>
<td>5.8 %</td>
</tr>
<tr>
<td>India</td>
<td>AZ-like</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>India</td>
<td>Immune escape</td>
<td>-30.0 %</td>
<td>-26.9 %</td>
</tr>
<tr>
<td>India</td>
<td>mRNA-like</td>
<td>21.7 %</td>
<td>13.5 %</td>
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<td>Immune escape</td>
<td>-47.6 %</td>
<td>-33.1 %</td>
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<td>Malaysia</td>
<td>mRNA-like</td>
<td>18.3 %</td>
<td>8.6 %</td>
</tr>
</tbody>
</table>

Table 4: Deaths averted in the omicron* period under an mRNA-like or immune-escape booster compared to an AZ-like booster. The duration of booster immunity is assumed to be 10 months or 3 months.
Key Findings

- Ecuador, which has the highest prevalence of all countries during the delta wave in our model, also experiences the smallest impact of an mRNA-like booster.
- Malaysia, which has the lowest omicron prevalence of the three countries, is highly sensitive to an immune escape scenario.
- Across countries, the deaths during omicron* are more sensitive to immune-escape than moving to an mRNA-like booster.
Implications

• Implementing an updated booster is more important than whether that booster is highly or moderately effective.

• The impact of a booster intervention is highly dependent on the immune history and structure of the population.

• Countries that experienced higher delta waves may have a lower impact of the mRNA booster.

• Countries that experienced lower levels of omicron may be more sensitive to immune escape.
Limitations: Social Distancing

Intensity Highly Time Variable

COVID-19: Stringency Index

The stringency index is a composite measure based on nine response indicators including school closures, workplace closures, and travel bans, rescaled to a value from 0 to 100 (100 = strictest).
Conclusions

• Potentially immunity stronger than we thought, less need for boosters (maybe need *predictive boosters* like for flu)

• **Relative impacts are** likely to be more stable even though **absolute impacts** are off.
The role of booster vaccination and ongoing viral evolution in seasonal circulation of SARS-CoV-2

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Periodic resurgences of COVID-19 in the coming years can be expected, while public health interventions may be able to reduce their intensity. We used a transmission model to assess how the use of booster doses and non-pharmaceutical interventions (NPIs) amid ongoing pathogen evolution might influence future transmission waves. We find that incidence is likely to increase as NPIs relax, with a second seasonally driven surge expected in autumn 2022. However, booster doses can greatly reduce the intensity of both waves and reduce cumulative deaths by 20\% between 7 January 2022 and 7 January 2023. Reintroducing NPIs during the autumn as incidence begins to increase again could also be impactful. Combining boosters and NPIs results in a 30\% decrease in cumulative deaths, with potential for greater impacts if variant-adapted boosters are used. Reintroducing these NPIs in autumn 2022 as transmission rates increase provides similar benefits to sustaining NPIs indefinitely (307,000 deaths with indefinite NPIs and boosters compared with 304,000 deaths with transient NPIs and boosters). If novel variants with increased transmissibility or immune escape emerge, deaths will be higher, but vaccination and NPIs are expected to remain effective tools to decrease both cumulative and peak health system burden, providing proportionally similar relative impacts.

1. Introduction

COVID-19 has caused catastrophic loss of life and health system strain in the United States [1]. Since the US epidemic first began in early 2020, multiple transmission waves have occurred, triggered by changes in social distancing and circulating variants. In response, the US government enacted widespread non-pharmaceutical interventions (NPIs) to slow epidemic spread. Over time, these measures relaxed in favour of more targeted approaches, particularly as vaccination became more available.

As of June 2022, three types of highly effective COVID-19 vaccines are available in the USA [2], two of which have been authorized for emergency use in children six months and above [3]. However, vaccine effectiveness has decreased over time, partly due to waning efficacy and partly due to the emergence of novel variants against which vaccines are less effective [4]. As a result, booster doses have been recommended to maintain efficacy [2].

The US epidemic beginning in early 2020 was triggered by the Wuhan variant, with the winter 2020 surge driven by the Delta variant, which was...
more infectious and severe than prior dominant variants [5,6]. In late 2021, the Omicron variant began to predominate. The Omicron variant seems to be more transmissible but less severe than prior variants [6,7]. Moreover, vaccine efficacy against both infection and severe disease appears to be lower against the Omicron variant [8]. However, booster doses may at least temporarily increase vaccine efficacy against circulating variants [9].

As circulation continues, ongoing SARS-CoV-2 evolution might allow immune escape to occur, influencing the intensity of follow-up waves [10]. Additional NPIs might be rolled out in response to subsequent surges in cases, influencing the severity of future transmission waves. We used a transmission model to evaluate how booster doses and resuming NPIs amid ongoing pathogen evolution might influence the severity of SARS-CoV-2 transmission.

2. Methods

Our transmission model extends classic compartmental susceptible–exposed–infected–recovered (SEIR) epidemiological models to incorporate additional features relevant to the transmission dynamics of SARS-CoV-2. Our SEIR-like model includes seven compartments (figure 1). Initially, many individuals are susceptible to infection (S). Upon exposure, they enter a latent period (E), during which they cannot transmit. They can then develop asymptomatic infection (entering the A class) or symptomatic infection (entering the I class). We assume that all asymptomatic individuals will recover (R). Those with symptomatic infections can either recover (entering the R class) or require hospitalization (entering the H class). Some of those hospitalized will die (entering the deceased class D), and the rest will recover (entering the R class). After immunity wanes, individuals in the R class return to their S class, depending on vaccine status. The model was also stratified by age (less than 20 years, 20–64 years and greater than or equal to 65 years) and risk of acquiring infection (high versus low).

Vaccination was implemented by adding a daily rate of vaccination and additional compartments for vaccinated individuals, which mirror the compartments in the base model: S_V, E_V, A_V, I_V, H_V, R_V, D_V. For simplicity, we assume that individuals in the S or R classes can be vaccinated but individuals in the other compartments will not be. Following vaccination, susceptible individuals S move into the susceptible vaccinated compartment S_V, and all recovered individuals move into the recovered vaccinated compartment R_V. We used coverage estimates from 6 January 2022 to estimate the baseline prevalence of vaccination [1]. We assume that all adults who intend to be vaccinated have already done so and that future vaccines will be allocated to children or will be booster doses, with peak child vaccine coverage being reached by late October 2022, consistent with current vaccine rates [1]. Baseline immunity and initial age distribution of infections were estimated using seroprevalence data [11]. Primary series vaccination was modelled as reducing the risk of severe disease by 70% (50% reduction in infection and 40% reduction in hospitalization given infection) [12] and 90% if booster doses are used (50% reduction in infection and 80% reduction in severe disease given infection) [9]. In the absence of any new vaccine products, we assume that all boosted individuals remain current on their boosted status and that any further vaccinations do not increase efficacy further such that only one boosted class is sufficient.

We also consider potential impacts if a variant-specific booster becomes available in autumn 2022 (electronic supplementary material, figure S2). For this analysis, we added a third vaccine
class to the model, with vaccine efficacy against infection being increased to 90% for individuals with the variant-adapted booster, consistent with initial efficacy data for both mRNA vaccines [13]. Vaccine efficacy against severe disease was assumed to be similar with first and second boosters, such that the combined effectiveness against hospitalization with an adapted booster was 98%. All booster doses administered after 1 September, 2022 were assumed to be with the variant-adapted booster.

To parametrize this model, we set parameter values where known. For uncertain parameters, we selected model parameters based on both reasonable values from the literature and the ability of the model to reproduce Omicron dynamics. Model parameters are shown in the electronic supplementary material, table S1. As the duration of immunity is uncertain, we also conducted a sensitivity analysis with a shorter duration of immunity (90 days).

We assume that relaxation of NPIs began in March 2022, reaching baseline [14] (i.e. pre-pandemic) levels by 7 July 2022. This timeline is consistent with announced policy decisions in multiple US states [15]. We consider a scenario where these NPIs remained at their relaxed level as the seasonal transmission rate increases. We then explore whether a temporary increase in social distancing to levels observed during Omicron might impact risk if implemented in autumn 2022.

To explore impacts in the context of ongoing pathogen evolution, we first use model parameters consistent with the circulating Omicron variant (electronic supplementary material, table S1) for 1 year, beginning 7 January 2022. Our seasonal transmission model implies that transmission will increase in the autumn, even if no novel variants emerge. We then consider how increasing transmissibility might impact model dynamics. For this scenario, we assume that the novel variant begins to emerge in the autumn, coincident with increases in the seasonal transmission rate and that the maximum seasonal beta term is increased by 20–50% at the start of the autumn. The circulation of this variant thus has the potential to drive a surge in infections beyond the effect that increases in the seasonal transmission rate can have on driving an autumn wave. We also consider how changes in the new variant’s ability to escape immunity might impact dynamics by increasing the rate of waning immunity by 50%, consistent with immune escape.

3. Results

Our model closely matches peak daily deaths and hospitalization rates observed for the Omicron wave in January and February 2022, with peak daily deaths around 2200 day\(^{-1}\). In our model, incidence is predicted to rebound in June 2022 as NPIs relax and natural immunity wanes (figure 2). This rebound is expected to be largely driven by relaxing NPIs, with waning immunity playing a secondary role. Specifically, deaths were predicted to increase from a low of 520 to 1064 day\(^{-1}\) after 180 days (a 104% increase). Twenty-five per cent of this increase was attributable to waning immunity.
immunity alone, with the remainder being due to relaxing NPIs and the interaction between NPI relaxation and waning immunity (electronic supplementary material, figure S1 and text). Booster doses can influence the intensity of this spring/summer resurgence. Daily deaths at the end of the summer wave (on 21 July 2022) were 18% lower if boosters were used.

Additionally, seasonal changes in transmission are expected to produce a new transmission wave in autumn 2022. The severity of this autumn transmission wave will depend on the implementation and uptake of public health interventions over the coming months as well as ongoing variant evolution. In the absence of a new immune variant emerging that has increased transmissibility, high uptake of booster doses could reduce cumulative deaths between March 2022 and January 2023 by 20% while also reducing the intensity of the autumn surge. Reintroducing NPIs as the seasonal transmission rate begins to increase can also further reduce risk and could effectively halt an autumn resurgence if immune escape does not occur or if its level is low (figure 2). Combining booster doses with NPIs could reduce cumulative deaths by up to 30% compared with a scenario without booster doses or NPIs. Increased transmissibility could increase peak deaths, but the per cent reduction in deaths achievable through booster vaccination is similar (the fraction of preventable deaths is 20% with 50% immune escape and increases to 27% with combined boosters and NPIs). Similarly, immune escape could lead to increased deaths (electronic supplementary material, figure S4), but booster vaccination remains beneficial. Roll-out of variant-specific boosters that have increased effectiveness against infection could be beneficial, but predicted impacts are small due to the expected constant roll-out rates of these variant-specific boosters (e.g. we do not model an aggressive vaccine campaign in autumn 2022). Specifically, if variant-adapted booster vaccination continues at the roll-out rates observed in January 2022, combined boosting and NPIs could reduce deaths by 34% without any increases in transmissibility or 30% with increased transmissibility (electronic supplementary material, table S3).

In addition to reducing deaths, NPIs also reduced overall infections (figure 2). Without immune escape, NPIs alone could reduce infections by 16% between 21 July 2022 and 6 January 2023. If immune escape occurs, the overall impact of NPIs is reduced, with similar NPIs reducing infections by 11% during the autumn. By contrast, standard booster doses do not impact overall infection rates. Adapted booster doses could reduce infection rates in future waves, but are unlikely to do so substantially during the autumn 2022 wave. We also found that the benefit of NPIs is specific to high transmission periods—when booster vaccines are used, allowing NPIs to relax during the summer and reintroducing in the autumn provides similar benefits to indefinite NPIs (307 000 deaths with indefinite NPIs compared with 317 000 with targeted NPIs).

While reintroducing NPIs during the autumn was beneficial, our model also revealed that relaxing NPIs during the summer was beneficial for follow-up transmission waves because it allowed for population immunity to accrue, reducing the number of people who were simultaneously susceptible to infection. When NPIs are sustained, the overall number of susceptible individuals is about 30% higher at the start of the autumn surge compared with the scenario where NPIs are allowed to relax. For this reason, daily deaths are higher if a novel variant with increased transmissibility emerges and NPIs are sustained indefinitely (electronic supplementary material, figure S1).

As a sensitivity analysis, we considered implications if natural infection provides additional immunity equivalent to receiving either (i) a two-dose series of vaccine or (ii) a booster dose (electronic supplementary material, figure S3). In this sensitivity analysis, the patterns seen in the overall results were similar, but deaths and infections were lower. For example, combining NPIs and booster doses reduced deaths by 25% without immune escape for the hybrid immunity extension compared with 30% in the base model. However, overall deaths between January 2022 and January 2023 were 237 000 with hybrid immunity, boosters and NPIs compared with 317 000 for the same scenario without hybrid immunity (electronic supplementary material, table S3 and figure S3).

We also considered implications if the duration of immunity to COVID-19 lasted three months rather than the seven months we used for our main model simulations. While peak deaths and were higher in this model and the autumn surge was more intense, the impact of boosting and reintroducing NPIs was similar (electronic supplementary material, figure S6).

4. Discussion

Our model predicts both a mid-year peak (driven by relaxing NPIs) and an autumn resurgence (driven by seasonal increases in the transmission rate). However, public health interventions can substantially impact these dynamics; combining boosters and NPIs could reduce deaths by up to 34%. If a novel variant emerges that escapes immunity, deaths could increase, but both interventions remain beneficial. While combining booster doses and NPIs reduce morbidity and mortality, we find that targeting NPI use to high transmission periods has similar benefits to indefinite NPIs. Thus, widespread use of booster doses can allow NPIs to remain more relaxed with relative safety.

While vaccines may not be as effective against infection with novel variants, evidence to date suggests that existing vaccines are likely to provide good protection against more severe disease, even for genetically distant variants like Omicron [16], particularly if booster doses are used [17]. New vaccine formulations targeted to circulating variants have the potential to improve efficacy. However, in our model, the impact of adapted boosting was modest. This pattern probably occurred because booster doses were not administered quickly enough to curtail an autumn transmission surge. We predicted that 30% of older adults, 27% of adults and 17% of children would be vaccinated with a variant-adapted booster by January 2023. Faster roll-out rates might enhance impacts beyond what we have modelled.

These findings are meant to be understood qualitatively in terms of the overall pattern of risk rather than predicting a precise level of future burden; real disease risk is likely to be lower than we have modelled for a few reasons. For example, while we predict a relatively high level of ongoing deaths, fatality from COVID-19 may be lower due to both incomplete waning of immunity and improved treatment. We have used simple assumptions in this model, with an average immunity level of seven months followed by complete waning to baseline risk by vaccine group. However, immunity may accrue...
more gradually over repeated infections and reach a higher level, as has been shown for other pathogens [18] and preliminary data show might also be true for SARS-CoV-2 [19]. Our sensitivity analysis suggests that this tendency would probably decrease deaths, but would not impact the overall utility of booster doses and NPIs.

In conclusion, our simulations suggest that resurgences in COVID-19 cases are likely both in the summer, as NPIs continue to relax, and in the autumn, as seasonal factors push the transmission rate higher. However, widespread use of booster doses can make a substantial impact on the ongoing public health burden, even as novel variants continue to emerge. Re-establishing NPIs can also reduce the impact of future transmission waves. While ongoing viral evolution that results in increased transmissibility may increase cases and deaths, both vaccines and NPIs remain beneficial to reduce the public health burden of future surges of COVID-19.

Data accessibility. All relevant data have been previously published and are cited appropriately or are contained within the article and its electronic supplementary material [20].

References

1 Introduction

The overall goals of this work are to estimate the impact of different vaccine strategies in Low and Middle Income countries. We will focus on India, Ecuador, and Malaysia. All three of these countries have had substantial COVID-19 incidence, so naturally derived immunity to COVID-19 is expected to be high, which may influence the optimal vaccine policy.

In this work, we consider whether and how child vaccination or variant-specific boosters might reduce deaths from COVID-19. Variant-specific boosters have recently become available in the United States, but their impact remains uncertain, particularly as novel sub-strains of omicron continue to emerge. Our approach extends a recently published vaccine model calibrated to the United States population [1].

2 Methods

2.1 Model structure

Our transmission model extends classic compartmental susceptible-exposed-infected-recovered (SEIR) epidemiological models to incorporate additional features relevant to the transmission dynamics of SARS-CoV-2. Our SEIR-like model includes six compartments (Figure 1). This model was generally adapted from [1]. Initially, many individuals are susceptible to infection (S). Upon exposure, they enter a latent period (E), during which they cannot transmit. They can then develop asymptomatic infection (entering the A class) or symptomatic infection (entering the I class). We assume that all asymptomatic individuals will recover (R). Those with symptomatic infections can either recover (entering the R class) or die (entering the deceased class D), and the rest will recover (entering the R class). The model was also stratified by age (<20 years, 20-64 years, and ≥ 65 years), socioeconomic status (high vs. low), and vaccine status (unvaccinated, primary series, and boosted). To reflect the fact that coverage of vaccine boosters is low in LMICs, only one boosted class was used and its efficacy was varied to reflect the potential benefit of variant specific boosters as well as the consequences of immune escape.

Vaccination Vaccination was implemented by adding a daily rate of vaccination and additional compartments for vaccinated/vaccinated and boosted individuals, which mirror the compartments in the base model: \(S_V\), \(E_V\), \(A_V\), \(I_V\), \(R_V\), and \(D_V\) for vaccination. To capture the potential for booster vaccination, we added additional compartments (\(S_{V2}\), \(E_{V2}\), \(A_{V2}\), \(I_{V2}\), \(R_{V2}\), and \(D_{V2}\)). For simplicity, we assume that individuals in the \(S\) or \(R\) classes can be vaccinated but individuals in the other compartments will not be. Individuals were
Figure 1: Model diagram for the base model (panel A) and the hybrid immunity model (panel B). Child vaccination is shown in dashed blue arrows and booster vaccination is shown in thicker green arrows. In the base model (panel A) individuals wane into their own vaccine class after recovering from natural infection. In the hybrid immunity model (panel B) individuals wane into one higher vaccine class after recovering from natural infection. Thus, in the hybrid immunity model, vaccinated individuals who are naturally infected wane into the booster class even if there are no booster vaccines being administered.
vaccinated at a daily rate until peak vaccination coverage was reached, after which no further vaccination was modeled. We used a combination of publicly available coverage estimates from October 17, 2022 and unpublished data from Larsen et al. to estimate the baseline prevalence of vaccination by age group and SES class \[2, 3\]. The booster vaccine rate was modeled as occurring at the peak vaccine rate for each SES class, to account for the fact that infrastructure needed to vaccinate is already well in place.

We assumed that all adults who were planning to receive their primary vaccine series had already done so as of October 2022, so that any remaining primary series vaccinations would be to children, and that up to 90% of children would be vaccinated. We also assumed that children would not receive vaccine boosters, even if they were vaccinated. We assumed that up to 99% of the vaccinated population of adults would receive a booster if rolled out at a country level.

Following vaccination, susceptible individuals \( S \) move into the susceptible vaccinated compartment \( S_V \), and all recovered individuals move into the recovered vaccinated compartment \( R_V \). Because uptake of booster doses is low, the formulation is changing, and coverage data is not readily available by age group/vaccine product, our models assumed that no individuals were vaccinated and boosted at the start of the simulation but that they might become boosted depending on vaccine policy. This assumption could be revised in future sensitivity analyses.

Vaccine efficacy for the primary series was assumed to reduce the risk of severe disease by 70%, consistent with data on Astra-Zeneca protection after 6 months \[4, 5, 6, 7\]. While primary series vaccination for Astra-Zeneca can reduce risk of infection by about 50% reduction, these benefits are only present shortly after vaccination \[4, 5, 6, 7\]. Given that the populations included in our model completed their vaccine campaigns earlier and current rollout rates are low, we do not model any protection against infection for the primary vaccination class.

Booster vaccination can enhance protection against both infection and severe disease. We varied the booster vaccine protection against both hospitalization (50-100%) and infection (0-100%) to reflect different possible vaccine products and immune escape scenarios. For benchmarking purposes, we chose discrete scenarios corresponding to predicted vaccine efficacy for the mRNA bivalent booster (\( V_{E_i} = 0.9, V_{E_h} = 0.9 \)), an Astra-Zeneca booster (\( V_{E_i} = 0.5, V_{E_h} = 0.7 \)), no additional booster protection (\( V_{E_i} = 0, V_{E_h} = 0.7 \)), and a hypothetical immune escape scenario (\( V_{E_i} = 0, V_{E_h} = 0.5 \)) \[4, 5, 6, 7\]. We note that for the immune escape scenario in the current model, booster vaccine efficacy is lower than primary series efficacy in these simulations, but is unlikely to dramatically affect the results due to the fast rate of booster rollout. This may be addressed in follow up analyses.

Immunity structures We consider two main structures for immunity: complete waning and hybrid immunity. For the complete waning model, after immunity wanes, individuals in the \( R \) class return to their \( S \) class, depending on vaccine status. For the hybrid immunity model, natural after immunity wanes, individuals wane into a higher vaccine class. We do not explicitly model waning of vaccine derived immunity. For the purposes of this report, we focus on the hybrid immunity model, as it is thought to be most consistent with empirical data/trends.

Initial conditions Baseline immunity and initial age distribution of infections and deaths were estimated using seroprevalence data and incidence data from Our World In Data (OWID) \[18\]. Specifically, we compared seroprevalence data reported from the individual countries with reported cases from Our World In Data as of 12 days before the estimated seroprevalence was conducted to allow time for seroconversion \[19, 21, 20\].
<table>
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<th>Parameter</th>
<th>symbol</th>
<th>value</th>
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<td>[3, 9, 10]</td>
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<td>$\rho_{cl}$</td>
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<tr>
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<td>$\rho_{al}$</td>
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<td>$\rho_{el}$</td>
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<td>Social distancing reduction</td>
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<td>[18]</td>
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<tr>
<td>Two doses, no booster</td>
<td></td>
<td></td>
<td>[4, 5, 7]</td>
</tr>
<tr>
<td>Infection effectiveness</td>
<td>$VE_I$</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Severe disease effectiveness</td>
<td>$VE_P$</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Two doses, with booster</td>
<td></td>
<td></td>
<td>[4, 5, 6, 7]</td>
</tr>
<tr>
<td>Infection effectiveness</td>
<td>$VE_I$</td>
<td>(0-0.95)</td>
<td></td>
</tr>
<tr>
<td>Severe disease effectiveness</td>
<td>$VE_P$</td>
<td>(0.5-0.95)</td>
<td></td>
</tr>
<tr>
<td>Vaccination rates</td>
<td></td>
<td></td>
<td>Larsen et al, unpublished</td>
</tr>
<tr>
<td>India</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High SES</td>
<td>$\lambda_h$</td>
<td>0.00429</td>
<td></td>
</tr>
<tr>
<td>Low SES</td>
<td>$\lambda_l$</td>
<td>0.00230</td>
<td></td>
</tr>
<tr>
<td>Ecuador</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High SES</td>
<td>$\lambda_h$</td>
<td>0.00496</td>
<td></td>
</tr>
<tr>
<td>Low SES</td>
<td>$\lambda_l$</td>
<td>0.0038</td>
<td></td>
</tr>
<tr>
<td>Malaysia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High SES</td>
<td>$\lambda_h$</td>
<td>0.0098</td>
<td></td>
</tr>
<tr>
<td>Low SES</td>
<td>$\lambda_l$</td>
<td>0.0062</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Parameter values used in model simulations. Note that the beta terms vary by country because they were scaled such that the product of $\beta$ and the maximum number of social contacts for the highest contact age group was the same across all models, roughly corresponding to an $\mathcal{R}_0$ of 10.
We assumed that each individual had been infected with symptomatic COVID-19 no more than once. The ratio of these two quantities produced a reporting rate. We then applied the inverse of this reporting rate to cumulative cases reported to OWID as of early October 2022, assuming that the estimated reporting rate had been constant on average throughout the pandemic.

We considered two possibilities for baseline immunity. First, we assumed that all individuals with prior infection, as estimated by the inverse reporting rate, were currently in the \( R \) compartment (high immunity scenario). Second, we assumed that only individuals estimated to be infected in the past year were currently in the recovered compartment (low immunity scenario). The difference between these two immunity levels was estimated to be the fraction of individuals who were previously infected but had waned, such that they could be reinfected. For the low immunity scenario and the hybrid immunity model, we moved this fraction of individuals from their corresponding recovered compartment to the next susceptible compartment. For example, for India, 48.1% of the population was estimated as being previously infected but having waned by October 2022. Thus, 48.1% of the unvaccinated population was moved to the vaccinated and susceptible class (\( S_V \)).

We did not explicitly include an additional protected class for individuals who had been naturally infected prior to vaccination. However, individuals who became infected during the simulation after having received their primary vaccine series waned into the booster class, thus receiving a boost in protection.

For both scenarios, as a simplifying assumption (and due to insufficient data to consider other possibilities), we assumed that prior infection history was independent of vaccine status, age, and SES, so that the fraction of individuals in the recovered class was the same for each age, vaccine, and SES class.

<table>
<thead>
<tr>
<th>Country</th>
<th>Child</th>
<th>Adult</th>
<th>Older adult</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>Baseline prevalence of vaccination</td>
<td>16%</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td></td>
<td>Age distribution of infections</td>
<td>35.4%</td>
<td>58.6%</td>
<td>5.9%</td>
</tr>
<tr>
<td></td>
<td>Population age distribution</td>
<td>40.1%</td>
<td>54.1%</td>
<td>5.7%</td>
</tr>
<tr>
<td></td>
<td>Initial fraction recovered</td>
<td>63.4% (15.3%)</td>
<td>63.4% (15.3%)</td>
<td>63.4% (15.3%)</td>
</tr>
<tr>
<td>Ecuador</td>
<td>Baseline prevalence of vaccination</td>
<td>79-99%</td>
<td>79-99%</td>
<td>79-99%</td>
</tr>
<tr>
<td></td>
<td>Age distribution of infections</td>
<td>70.2%</td>
<td>26.9%</td>
<td>2.9%</td>
</tr>
<tr>
<td></td>
<td>Population age distribution</td>
<td>41.0%</td>
<td>52.6%</td>
<td>6.4%</td>
</tr>
<tr>
<td></td>
<td>Initial fraction recovered</td>
<td>29.9% (14.7%)</td>
<td>29.9% (14.7%)</td>
<td>29.9% (14.7%)</td>
</tr>
<tr>
<td>Malaysia</td>
<td>Baseline prevalence of vaccination</td>
<td>65-88%</td>
<td>72-97%</td>
<td>72-97%</td>
</tr>
<tr>
<td></td>
<td>Age distribution of infections</td>
<td>36.7%</td>
<td>57.8%</td>
<td>5.5%</td>
</tr>
<tr>
<td></td>
<td>Population age distribution</td>
<td>36.2%</td>
<td>59.0%</td>
<td>4.8%</td>
</tr>
<tr>
<td></td>
<td>Initial fraction recovered</td>
<td>81.1% (42.9%)</td>
<td>81.1% (42.9%)</td>
<td>81.1% (42.9%)</td>
</tr>
</tbody>
</table>

Table 2: Age specific population parameters. For the initial fraction infected, the value in parentheses indicates a lower bound on proportion infected, used in sensitivity analysis. For the ranges in baseline vaccine coverage, the lower bound corresponds to the estimated vaccine coverage among the low SES population and the upper bound corresponds to the estimated vaccine coverage among the high SES population.
<table>
<thead>
<tr>
<th>Age</th>
<th>Child</th>
<th>Adult</th>
<th>Older adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child</td>
<td>15.78</td>
<td>10.17</td>
<td>0.191</td>
</tr>
<tr>
<td>Adult</td>
<td>7.54</td>
<td>24.73</td>
<td>0.339</td>
</tr>
<tr>
<td>Older adult</td>
<td>1.61</td>
<td>3.87</td>
<td>0.254</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Child</th>
<th>Adult</th>
<th>Older adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child</td>
<td>14.5</td>
<td>5.53</td>
<td>0.201</td>
</tr>
<tr>
<td>Adult</td>
<td>4.31</td>
<td>10.12</td>
<td>0.193</td>
</tr>
<tr>
<td>Older adult</td>
<td>1.58</td>
<td>1.94</td>
<td>0.456</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Child</th>
<th>Adult</th>
<th>Older adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child</td>
<td>11.98</td>
<td>6.14</td>
<td>0.146</td>
</tr>
<tr>
<td>Adult</td>
<td>3.77</td>
<td>11.36</td>
<td>0.141</td>
</tr>
<tr>
<td>Older adult</td>
<td>1.30</td>
<td>2.03</td>
<td>0.396</td>
</tr>
</tbody>
</table>

Table 3: Social contact matrices from [22]

In addition to baseline immunity, we also considered two different rates of waning for naturally infected individuals in forward simulations: 10 months and 3 months (see Table [1]).

**Age** Age structure was used to capture differential risk of severe disease by age (higher case fatality rates for older groups) as well as age-stratified mixing patterns. Social contact patterns were taken from Prem et al. [22] for each country and the corresponding matrix is shown in Table 3.

**Socioeconomic status (SES)** For each age class, we modeled a high SES and low SES class, with each class constituting 50% of the population of each age group. Low SES individuals had a higher transmission rate (reflecting more social contacts and/or increased propensity of those contact to cause infection due to limited social distancing) and also had a higher case fatality rate (estimated using data from Mena et al. [8]). We also assumed that rollout of child vaccination and variant-specific boosters was patterned by SES such that high SES individuals received child vaccinations and/or variant specific boosters at a higher rate than low SES individuals. Given that the infrastructure needed for vaccine rollout and, at least for child vaccination, supply already exists, we assumed that rollout rates were similar to what was observed in each country for peak rollout of a standard series for each SES class.

**Social distancing** While we use social contacts from Prem et al. to quantify baseline social contacts, we also incorporate a social distancing parameter that reduces the likelihood of transmission given reductions in both the number and type of social contacts. For our model simulations, we assumed that this reduction was proportional to the COVID stringency index reported in each country in early October 2022 (37% for India, 14% for Ecuador, 30% for Malaysia). This value for Malaysia was mistaken and is more consistent with stringency in spring 2022; a reduction of 11% is more consistent with patterns in fall 2022. In future iterations, we will re-run the Malaysia model runs with a lower stringency to better reflect expected patterns.

### 2.2 Model simulation

We ran our transmission model for 365 days to explore medium term dynamics. However, for all cumulative deaths, we focus on deaths after 180 days, which was used to reflect a single transmission wave.
conditions were estimated to be consistent with current case and infection data as of early October 2022. We aimed to produce estimates of vaccine impact in terms of cumulative burden and potential deaths averted for different potential policy decisions given specific scenarios for vaccine efficacy, duration of immunity, and interactions between vaccine and natural immunity. We considered the potential impact of primary vaccination + boosters, primary vaccinations + boosters with child vaccination, including how these combinations varied by vaccine efficacy.

Our default vaccine efficacy condition for normal boosters was based on current best estimates for protection against omicron with the Astra-Zeneca vaccine after 6 months, when protection against infection has waned. For boosters, we assumed that an excellent variant booster might, at most, achieve effectiveness similar to initial mRNA vaccine effectiveness against the wild-type strain of COVID-19. At worst, immune escape could occur so that protection against severe disease is also reduced. We therefore simulated for a range of booster efficacy values within these bounds.

We note that, because no child booster vaccine with any type of booster is modeled, child vaccine efficacy against infection is zero for all simulations. Additionally, for the hybrid immunity model, naturally infected individuals are assumed to enter a boosted class even without rollout of variant-specific boosters. The protection experienced by this boosted and infected class upon waning was modeled as being similar to the parallel scenarios in the variant booster model (i.e., $VE_I=90\%$ for the full efficacy scenario or $VE_I=50\%$ for the reduced efficacy scenario).

In aim 1, we consider impacts for a future transmission wave given an average level of population protection. In aim 2, we consider how these impacts vary based on country-specific immunologic history throughout the entire pandemic.

3 Results and Discussion

Overall, our results suggest that booster vaccination can make a substantial contribution to ongoing control efforts. To achieve maximal protection, infection blocking vaccines should be prioritized. In contrast, child vaccination is not expected to be substantially beneficial. Booster doses are expected to avert the greatest number and proportions of deaths in countries with lower natural immunity.

We found that boosting with COVID-19 vaccines could avert 11-93\% of all deaths over the next 6 months compared with not boosting, with the ultimate impact varying by country, booster type, and immune scenario (Table 4, Figures 2 3 4 5 6 7). For all heat maps, the dashed line shows predicted booster VE against hospitalization without boosting and the red point in each panel shows expected deaths without booster vaccination. While deaths were higher in more pessimistic immune scenarios, booster doses had the greatest proportional benefit in scenarios with the lowest levels of baseline immunity and fastest waning (up to 93\%), whereas relative impacts were much smaller when baseline immunity was higher and waning immunity was lower (up to 36\% reduction). While the exact percentages of deaths averted varied by country, these general patterns were consistent across countries.

In our model, additional child vaccination had almost no impact (Figure 8 9. This pattern is likely due to two main reasons. First, we assumed that child boosters would not be used (as no child boosters have yet been approved), so child vaccines could only protect against severe disease, not infection. Second, Ecuador and Malaysia have already implemented strong child vaccination campaigns. Thus, additional child primary
Table 4: Overall impacts of vaccination on cumulative deaths and deaths averted by modeled scenario and country

series vaccination had a minimal impact for these countries. If child boosters are also used, the impact of child vaccination would be expected to be far greater.

In general, cumulative expected deaths per million were highest in Ecuador, intermediate in India, and lowest in Malaysia. These country-specific differences appeared to be predominantly driven by the country-specific level of baseline immunity, which followed this same pattern. The much higher proportional impacts of vaccination in Malaysia stemmed from the fact that vaccination was predicted to prevent a new wave of COVID-19 for both the low and high baseline immunity conditions (Figure ??, ??).

While we focused on the first 180 days for quantifying impacts on deaths, we also examined predicted dynamics over the next year to determine how waning immunity might impact future resurgences. These longer term analyses suggest that, unless a strong infection-blocking booster becomes available, resurgences of COVID-19 are likely to occur (Figure ??, ??). This pattern is even more likely if seasonality interacts with waning immunity, increasing the likelihood of follow up transmission waves [1]. The rate of waning immunity did not dramatically impact the initial transmission wave strength, but had a greater impact on the level of endemic incidence expected.

For strong infection blocking vaccines (70% or greater) additional protection against hospitalization has a minimal impact on the expected number of deaths. In contrast, for a vaccine that does not block infection, protection against more severe disease is important to achieve similar reductions in deaths (Figures 3, 5, 7).
Figure 2: Cumulative deaths in India after 1 year by booster vaccine efficacy and immunity scenario. Row 1 shows expected results for a low immunity scenario (1-year maximum protection) and row 2 shows expected results for a high immunity scenario (protection for the entirety of the pandemic).
Figure 3: Percent of deaths averted in India after 1 year by booster vaccine efficacy and immunity scenario. Row 1 shows expected results for a low immunity scenario (1-year maximum protection) and row 2 shows expected results for a high immunity scenario (protection for the entirety of the pandemic)
Figure 4: Cumulative deaths in Ecuador after 1 year by booster vaccine efficacy and immunity scenario. Row 1 shows expected results for a low immunity scenario (1-year maximum protection) and row 2 shows expected results for a high immunity scenario (protection for the entirety of the pandemic).
Figure 5: Percent of deaths averted in Ecuador after 1 year by booster vaccine efficacy and immunity scenario. Row 1 shows expected results for a low immunity scenario (1-year maximum protection) and row 2 shows expected results for a high immunity scenario (protection for the entirety of the pandemic).
Figure 6: Cumulative deaths in Malaysia after 1 year by booster vaccine efficacy and immunity scenario. Row 1 shows expected results for a low immunity scenario (1-year maximum protection) and row 2 shows expected results for a high immunity scenario (protection for the entirety of the pandemic).
Figure 7: Percent of deaths averted in Malaysia after 1 year by booster vaccine efficacy and immunity scenario. Row 1 shows expected results for a low immunity scenario (1-year maximum protection) and row 2 shows expected results for a high immunity scenario (protection for the entirety of the pandemic).
Figure 8: Cumulative deaths per million population after 180 days by country for different hypothetical vaccine boosters for the higher baseline immunity and the slower (10 month) waning immunity scenario for all three countries.
Figure 9: Cumulative deaths per million population after 180 days by country for different hypothetical vaccine boosters for the lower baseline immunity and the faster (3 month) waning immunity scenario
Figure 10: Daily death count after booster vaccination since Oct 5, 2022 for the high baseline immunity scenario
Figure 11: Daily deaths per million population after booster vaccination since Oct 5, 2022 for the low baseline immunity scenario
References


[6] Zeneca A. Boosting with AstraZeneca’s vaccine provides high protection against Omicron, equivalent to mRNA COVID-19 vaccines.;


[22] Prem K, Cook AR, Jit M. Projecting social contact matrices in 152 countries using contact surveys and demographic data. PLOS Computational Biology. 2017;13:e1005697.
WHO Aim 2 Final Report
Sophie Larsen, Eliana Chandra, Haylee West, Iffat Noor, Alicia Kraay, Pamela P. Martinez
University of Illinois at Urbana Champaign
December 15, 2022

1 Introduction

Host heterogeneity is key to understanding the potential efficacy of vaccine intervention and particularly of an updated booster. Previous work has established substantial differences in immune response to SARS-CoV-2 variants and vaccination by immune history (e.g. [1, 2]). Vaccination followed by omicron infection has been shown to confer greater protection if the individual is naive prior to vaccination than if they had a prior wild-type infection [2]. These findings suggest the presence of an immune imprinting effect, where an individual's prior exposure can impact the adaptive immune response to new infections [1, 2].

In addition to questions about immune imprinting, demographic characteristics of the host can also influence transmission and severity of disease. A previous work showed stark socioeconomic disparities in COVID-19 testing, infection fatality rates, and ability to reduce mobility during lockdowns [3]. Unpublished work by our group has also identified significant disparities in vaccine uptake across socioeconomic groups over time in dozens of countries, including Ecuador, India, and Malaysia. For example, we found that after 17 months of vaccination in India, the average vaccination rate was 89.8% in high SES groups, compared to 68.5% in low SES groups (figure 1 top, Larsen et al.). Understanding country-specific vaccination temporal trends can provide insights into the pool of people eligible to receive a booster vaccination across low- and middle-income countries.

The overall goal of this project is to estimate the impact of different vaccine strategies in low- and middle-income countries, taking into consideration host heterogeneity across multiple levels. We implemented an individual-based model, stratified by age, socioeconomic status, and immune history, to track 4 waves of COVID-19 variants: wild-type, delta, omicron, and new emergent variants denoted as omicron*. By tracking the immune history of individual hosts, we can better characterize how immune imprinting may impact a variant-specific booster vaccination campaign at the population level. In this report, we provide estimates of the impact of a booster vaccine under different scenarios for efficacy against infection ($V_{E_I}$), efficacy against severe disease ($V_{E_S}$), and duration of immunity for three countries: Ecuador, India, and Malaysia.

2 Methods

2.1 Transmission model

We implemented an individual-based model in python to simulate SARS-CoV-2 infections. In this model, individuals move through susceptible, exposed, infected, and recovered (but possibly susceptible) classes during waves of transmission characterized by 4 variants: wild-type (0-420 days), delta (421-630 days), omicron (631-840 days), and more recent variants of concern, omicron* (841-990 days). For each country, we divided the population into age groups of 0-20, 21-65, and 65+ relative to their true country-specific distributions [4], and scaled it to have a population size of approx. 100,000 individuals (table 1), with 50% of each population assigned to be high and low socioeconomic status (SES). Parameter values used in the model and their references are shown in table 2.
We implemented the Gillespie algorithm [5] to choose which event will occur and when. If a contact event is triggered, two individuals are selected from the population. Susceptible individuals who encounter an infected individual can become infected with a base probability $\mu$. We use wave-specific probabilities of infection given contact for each variant [6]. Starting with an equal number of contacts for each SES group, we assumed that 60% of an individual's contact is within the same SES group and 40% is outside SES group. Additionally, we assume that low SES people have a 30% reduction in contact from social distancing and high SES have a 60% reduction [3]. Based on a household contact previous finding [6], we further scaled down all contacts by 0.2. Contact assumptions are the same across countries.

Once an individual is infected, they are considered exposed and then infectious. Once infectious, an individual can recover or die due to infection, with probabilities that are pulled from [3], stratified by age, SES, and immune history. Upon recovery from infection, the variant an individual was infected with is appended to their immune history.

<table>
<thead>
<tr>
<th>Country</th>
<th>Starting population</th>
<th>Children</th>
<th>Adults</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecuador</td>
<td>105,150</td>
<td>23.62%</td>
<td>63.26%</td>
<td>13.11%</td>
</tr>
<tr>
<td>Malaysia</td>
<td>104,650</td>
<td>21.44%</td>
<td>64.72%</td>
<td>11.22%</td>
</tr>
<tr>
<td>India</td>
<td>106,200</td>
<td>24.05%</td>
<td>64.73%</td>
<td>11.22%</td>
</tr>
</tbody>
</table>

Table 1: Population size by country and age.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>symbol</th>
<th>value</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact rate per day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low SES contacts Low SES</td>
<td>$c_{LL}$</td>
<td>0.3528</td>
<td>assumption</td>
</tr>
<tr>
<td>Low SES contacts High SES</td>
<td>$c_{LH}$</td>
<td>0.2352</td>
<td>assumption</td>
</tr>
<tr>
<td>High SES contacts High SES</td>
<td>$c_{LH}$</td>
<td>0.2016</td>
<td>assumption</td>
</tr>
<tr>
<td>High SES contacts Low SES</td>
<td>$c_{LH}$</td>
<td>0.1344</td>
<td>assumption</td>
</tr>
<tr>
<td>Base probability of infection given contact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>$\mu$</td>
<td>18.9%</td>
<td>[6]</td>
</tr>
<tr>
<td>Delta</td>
<td>$\mu$</td>
<td>29.7%</td>
<td>[6]</td>
</tr>
<tr>
<td>Omicron</td>
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<td>42.7%</td>
<td>[6]</td>
</tr>
<tr>
<td>Omicron*</td>
<td>$\mu$</td>
<td>42.7%</td>
<td>assumption</td>
</tr>
<tr>
<td>Incubation period</td>
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<td>[7]</td>
</tr>
<tr>
<td>Infectious Period</td>
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<td>[8]</td>
</tr>
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<td>Waning of immunity</td>
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<td>[9, 10]</td>
</tr>
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<td>Boosted-derived immunity</td>
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<tr>
<td>Case fatality rate</td>
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</tr>
<tr>
<td>High SES</td>
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<td>Children</td>
<td>$\alpha_{ch}$</td>
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<td>[3, 12]</td>
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<td>Adults</td>
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<td>[3, 12]</td>
</tr>
<tr>
<td>Older adults</td>
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<td>0.173</td>
<td>[3, 12]</td>
</tr>
<tr>
<td>Low SES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
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<td>[3, 12]</td>
</tr>
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<td>Adults</td>
<td>$\alpha_{al}$</td>
<td>0.0426</td>
<td>[3, 12]</td>
</tr>
<tr>
<td>Older adults</td>
<td>$\alpha_{el}$</td>
<td>0.173</td>
<td>[3, 12]</td>
</tr>
<tr>
<td>Proportion of infected that could die (symptomatic)</td>
<td>$\nu$</td>
<td>0.4</td>
<td>[13, 12, 14]</td>
</tr>
<tr>
<td>Booster effectiveness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRNA-like</td>
<td>$VE_I = 90%$</td>
<td>$VE_S = 90%$</td>
<td></td>
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<td>AZ-like</td>
<td>$VE_I = 50%$</td>
<td>$VE_S = 70%$</td>
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<tr>
<td>Immune escape</td>
<td>$VE_I = 0%$</td>
<td>$VE_S = 50%$</td>
<td></td>
</tr>
<tr>
<td>Scale infectiousness for secondary infections</td>
<td>$s_i$</td>
<td>0.27</td>
<td>[19]</td>
</tr>
</tbody>
</table>

Table 2: Transmission parameters

### 2.2 First vaccine intervention

We implement a vaccine intervention during the end of the wild-type wave and throughout the delta wave (321-630 days), which is stratified by socioeconomic status using data on first-dose roll-out in the three countries (figure 1 top). Anyone who is not currently infectious can be vaccinated, moving them to the recovered class. Vaccination is similarly appended to the immune history of the host and confer protection against infection and severity of the disease based on the parameters shown in table 3.

### 2.3 Immune histories

The base probabilities of being infected after contact and death due to infections are multiplied by a dampening parameter depending on immune history. We projected previously reported data on immune response by immune history [20] onto a scale from 0.05-1, with 0.05 being the highest and 1 being the lowest protection against
<table>
<thead>
<tr>
<th>Immune History</th>
<th>wild-type</th>
<th>delta</th>
<th>omicron</th>
<th>omicron*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type</td>
<td>0.38</td>
<td>0.45</td>
<td>0.77</td>
<td>0.8</td>
</tr>
<tr>
<td>Delta</td>
<td>0.41</td>
<td>0.35</td>
<td>0.71</td>
<td>0.74</td>
</tr>
<tr>
<td>Vaccine only</td>
<td>0.36</td>
<td>0.42</td>
<td>0.69</td>
<td>0.72</td>
</tr>
<tr>
<td>Breakthrough - omicron</td>
<td>0.32</td>
<td>0.35</td>
<td>0.53</td>
<td>0.56</td>
</tr>
<tr>
<td>Breakthrough - delta</td>
<td>0.05</td>
<td>0.09</td>
<td>0.4</td>
<td>0.43</td>
</tr>
<tr>
<td>Infection followed by vaccination</td>
<td>0.1</td>
<td>0.16</td>
<td>0.37</td>
<td>0.4</td>
</tr>
<tr>
<td>Remaining history generalization</td>
<td>0.27</td>
<td>0.3</td>
<td>0.58</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Table 3: Immune history-specific parameter scaling for probability of infection and death

SARS-CoV-2 (see table 3 for details). We then multiplied the base transmissibility and infection fatality rate by this history-specific parameter for each wave. For those who have not been infected but are vaccinated, we used antibody titers corresponding to 2 doses of Sinovac and 1 dose of Astra Zeneca (i.e. a fully vaccinated individual)[20]. The base immune histories we considered were:

- Naive individuals (no vaccination or infection history)
- Only wild-type infections
- Only delta infections
- Vaccine only
- Prior infections followed by vaccination
- Breakthrough delta infection
- Breakthrough omicron infection
- A remaining immune history of multiple infections where the parameter was taken from an average of the other serotype parameters

### 2.4 Booster vaccination

We implemented booster vaccination at the beginning of the fourth wave when omicron* is seeded in the model (t = 841 days). During first-dose vaccination, we fit parameters to the data by country and SES that dictated the shape of the curve, the maximum proportion of the population vaccinated, and the week at which half of the maximum is vaccinated. We assume that the booster vaccination trends follow the same shape and halfway-week as first-dose vaccination. However, we assume that 100% of the eligible population will eventually receive a booster. This is different from our initial report, in which we assumed that the maximum proportion of vaccinated individuals who receive a booster would match the maximum proportion observed in first-dose rollout. In this report, we assumed that anyone who has previously been vaccinated and is not infectious is eligible to receive a booster, and when boosted they recover, with the booster added to their immune history.

We modeled three discrete scenarios corresponding to predicted vaccine efficacy against infection (VE_I) and against severe disease (VE_S) for the mRNA bivalent booster or ‘mRNA-like’ (VE_I = 0.9, VE_S = 0.9), an Astra-Zeneca booster or ‘AZ-like’ (VE_I = 0.5, VE_S = 0.7), and a hypothetical immune escape scenario ‘Immune escape’ (VE_I = 0, VE_S = 0.5) [15, 16, 17, 18], where (1 − vaccine efficacy) acts as a multiplier on the base immune-history parameters.

### 2.5 Waning Immunity

While recently recovered or vaccinated individuals have strong influence from their immune history, waning immunity can dampen this response. In our model, the protection from immune history is scaled down to 40% of the
original protection after waning, based on antibody titers following vaccination [11]. We also explored 2 scenarios for the duration of immunity from vaccination: waning after 3 months and after 10 months.

2.6 Key Model Assumptions

- The immune history influences the susceptibility and risk of death due to infection.
- After recovery from infection or being vaccinated, individuals have protective immunity but they can still get infected with a probability that is a function of their immune history.
- Immunity wanes over time, but immune history has a lasting influence on susceptibility to future infections.
- Rates of contact are dependent on socioeconomic status.
- The infection fatality rate varies by age and socioeconomic status.
- Vaccination and boosting rates vary over time by country and socioeconomic status.
- Population size is on the same order across countries but age structure is country-specific.

3 Results and Discussion

The model captures wild-type, delta, and omicron* waves of infections over a period of 33 months (figure 2). Regardless of immunity duration, infections from omicron* peak in months 28-29 and then decline. If there is immune-escape ($V_E_I = 0\%$, $V_E_S = 50\%$), the omicron* wave is prolonged, with a daily prevalence at month 33 above 0.5% of the population (figure 3). Under the AZ-like ($V_E_I = 50\%$, $V_E_S = 70\%$) and mRNA-like ($V_E_I = 90\%$, $V_E_S = 90\%$) boosting scenarios, the daily prevalence declines below 0.25% of the population.

When we looked at the distribution of cumulative deaths under these different scenarios (figure 4), we find some similarities among the three countries analyzed, with the highest mortality observed under immune-escape scenario and lowest under an mRNA-like booster. We also note that the difference between an AZ-like booster and mRNA-like booster is relatively small.

Figure 2: Country-specific trends in infections over time. Shaded areas colored by country illustrate 5-95% confidence intervals from 100 replicates. A booster intervention - mRNA-like ($V_E_I = 90\%$, $V_E_S = 90\%$), AZ-like ($V_E_I = 50\%$, $V_E_S = 70\%$), or immune escape ($V_E_I = 90\%$, $V_E_S = 90\%$) - is implemented 28 months into the pandemic, at the beginning of the omicron* wave (shaded in grey).
We analyzed the percent of deaths averted (based on the average values of 100 replicates) by boosting in the omicron* period using the AZ-like scenario as a reference (table 4). These findings show a larger effect than in our initial report, likely due to the change in the assumption that everyone who was vaccinated during the initial rollout will eventually get boosted.

Deaths averted by moving to an mRNA-like booster are modest, ranging from 5.8% (Ecuador, 3 month immunity) to 21.7% (India, 10 month immunity). Ecuador, which has the highest peak during the delta wave in our model, reports the smallest gains from this intervention overall, with 17.9% deaths averted under 10 month immunity compared to 18.3% (Malaysia) and 21.7% (India), and 5.8% averted under 3 month immunity compared to 8.6% (Malaysia) and 13.5% (India).

Excess deaths from immune escape are more substantial, ranging from 26.9% (India, 3 month immunity) to 47.6% (Malaysia, 10 month immunity). Under both scenarios of waning immunity, Malaysia, which has the lowest peaks during omicron in our model, is the country most impacted by immune escape during omicron*, over 17 percentage points away from the next highest country under a 10 month scenario, and 1.8 percentage points difference from the next highest country under a 3 month scenario. Across duration of immunity, Ecuador has the lowest cases during omicron* under an immune-escape scenario, possibly owing to the higher delta wave, but these values are still comparable to the excess deaths shown for India.

In summary, we show that it is more important that an effective booster is implemented than whether that booster is moderately or highly effective. In optimizing a booster intervention in low- and middle-income countries, it may be highly impactful to implement an AZ-like booster compared to immune-escape, but less impactful to upgrade to an mRNA-like booster. However, we acknowledge that the degree of these effects is highly population-specific, depending on age, SES, and immune history.

![Figure 3: Country-specific trends in infection prevalence during the omicron* wave. This plot is a zoom of the grey shaded region in figure 2.](image-url)
Figure 4: Country-specific cumulative deaths during omicron* when boosting is implemented - mRNA-like ($VE_I = 90\%, VE_S = 90\%$), AZ-like ($VE_I = 50\%, VE_S = 70\%$), or immune escape ($VE_I = 90\%, VE_S = 90\%$) - under 2 scenarios of booster immunity duration. The distribution of 100 replicates for each combination of parameters are shown in the violin plots. Booster scenarios are indicated by different color.

<table>
<thead>
<tr>
<th>Country</th>
<th>Scenario</th>
<th>waning: 10 months</th>
<th>waning: 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecuador</td>
<td>AZ-like</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Ecuador</td>
<td>Immune escape</td>
<td>-28.7 %</td>
<td>-31.3 %</td>
</tr>
<tr>
<td>Ecuador</td>
<td>mRNA-like</td>
<td>17.9 %</td>
<td>5.8 %</td>
</tr>
<tr>
<td>India</td>
<td>AZ-like</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>India</td>
<td>Immune escape</td>
<td>-30.0 %</td>
<td>-26.9 %</td>
</tr>
<tr>
<td>India</td>
<td>mRNA-like</td>
<td>21.7 %</td>
<td>13.5 %</td>
</tr>
<tr>
<td>Malaysia</td>
<td>AZ-like</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Malaysia</td>
<td>Immune escape</td>
<td>-47.6 %</td>
<td>-33.1 %</td>
</tr>
<tr>
<td>Malaysia</td>
<td>mRNA-like</td>
<td>18.3 %</td>
<td>8.6 %</td>
</tr>
</tbody>
</table>

Table 4: Deaths averted in the omicron* period under an mRNA-like or immune-escape booster compared to an AZ-like booster. The duration of booster immunity is assumed to be 10 months or 3 months.
References


Session 2

Dengue disease impact and cost-effectiveness: Optimizing public health impact
No public information available for this session.
Session 3

Dengue disease impact and cost-effectiveness: Benefit-risk assessments
Policy questions for modellers

1. What are the estimates of population-level and individual-level benefit/risk over 10 and 20 years, stratified by age of recipient, serostatus of recipient and by average transmission intensity in a setting?

Note: Transmission intensity is best quantified by average force of infection, though average seroprevalence in a specific age group (e.g. 11-year-olds) can be used as a proxy. A range of year-by-year serotype dominance scenarios should be examined, informed by surveillance data from a range of settings, as well as a range of vaccine efficacy (or lack of) by serotype and serostatus and serotype specific infectivity and disease severity.

2. What is the cost-benefit of vaccination programmes without pre-vaccination screening, or by pre-vaccination screening dependent upon seroprevalence in a specific age group (e.g. pre-vaccination screening in low seroprevalence settings, and no pre-vaccination screening in high seroprevalence settings).

3. What is the threshold seroprevalence for pre-vaccination screening by when such an effort becomes either cost-effective or has the most favorable benefit-risk ratio.
Session 4
MNTE validation methods for assessments in conflict areas
Maternal and neonatal tetanus elimination (MNTE) assessment in conflict settings – Proposed alternative options

Background

Meeting of the Advisory Committee on Immunization and Vaccines-related Implementation Research (IVIR-AC)

Geneva, Switzerland
13 to 17 February 2023
Background

47 / 59 Countries eliminated MNT between 2000 & 2022
(as of Nov 2022)
*(Partial elimination in Mali, Nigeria and Pakistan)

- The validation of the elimination of maternal and neonatal tetanus is done using the lot quality assurance-cluster sampling (LQA-CS) survey methods.
- The surveys target the poorest performing district(s) for MNT.
- The survey teams face extensive and conspicuous community-level exposure that may put their safety at higher risk in insecure circumstances.
- In the 12 countries (Angola, Afghanistan, Central African Republic, Guinea, Mali, Nigeria, Pakistan, Papua New Guinea, Somalia, South Sudan, Sudan and Yemen) that are yet to eliminate MNT, the poorest performing districts are most likely to be those with conflicts and other access constraining factors.
- The existing LQA-CS survey method and tools do not take into consideration the constrained access in conflict areas.
- A WHO-led MNT Expert Group proposes to the IVIR-AC for decision, two alternative options for validating MNT in conflict affected areas.
- These options will help to overcome current obstacles to assessing MNT in conflict areas and accelerate the global goal of eliminating MNT by 2025.
Options for validating Maternal and Neonatal Tetanus Elimination (MNTE) in the 12 countries where it has not yet been validated

IVIR-AC meeting
February 14, 2023

Michael Deming, MD, MPH
François Gasse, MD, MPH
Definition of Maternal & Neonatal Tetanus Elimination (MNTE) as a Public health Problem

<1 case of neonatal tetanus (NT) per 1,000 live births in every district every year

WHO screening requirements

Countries wishing to validate MNTE must first request WHO’s approval. Before giving it, WHO requires evidence that all districts are at low risk, meaning that the following screening requirements are met in every district based on a desk review of administrative estimates:

- <1 reported NT case/1,000 live births AND
- Skilled birth attendance (SBA) coverage ≥70% OR
- Administrative coverage of two or more doses of Tetanus Toxoid-Containing Vaccines (TTCV2+) ≥80% OR
- At least 80% of women of reproductive age (WRA) have received two or more doses of TTCV over the course of 3 supplementary immunization activities (SIAs). SIAs are district-level mass campaigns in which WRA are vaccinated with TTCV without regard to their vaccination history.
Validation options considered

1) The established method: a neonatal tetanus (NT) mortality survey

2) The established method without an NT mortality survey

3) An audit of TT SIAs

4) Use of large, multiple-indicator surveys like DHS and MICS

5) NT Surveillance
The established option. Used since 2000.

LQAS-CS is the acronym for “Lot Quality Assurance Sampling-Cluster Survey” or LQAS-CS. It determines if the NT mortality rate is <1 NT death per 1,000 live births using verbal autopsy.

NT mortality rate rather than the incidence rate for greater diagnostic specificity

**Pre-validation: The first step**

- Its purpose is to confirm the low-risk status of districts as reported to WHO and identify the 3-4 districts most at risk of *not* having achieved MNTE (even though WHO requirements are met)
- Rationale: If MNTE is validated in the most at-risk districts, it is considered validated nationally.
- Pre-validation starts with a structured review using 16 indicators and local expert knowledge to identify the 3-4 districts most at risk
- In each of them, the pre-validation team
  - Visits the district headquarters and 2 health facilities to review reported performance
  - Completes rapid assessments, including TTCV coverage, of two large communities relying on outreach services
  - Cross checks reported data.
- The team then decides if findings in these districts are compatible with MNTE despite their being the districts most at risk

**Option 1: Pre-validation followed by an LQAS-CS NT mortality survey**
Option 1: Pre-validation followed by an LQAS-CS mortality survey (cont’d)

- If the decision is “yes, the most at-risk districts are nonetheless compatible with MNTE,” then an LQAS-CS survey is conducted in the most at-risk district (and sometimes, for sample-size reasons, in the next one or two districts most at risk)

- MNTE is considered validated nationally if the survey passes

- If it fails, corrective measures are taken and pre-validation starts again
Option 1  Pre-validation followed by an LQAS-CS survey (cont’d)

Pros
- Well established. Used in all but two of the 49 countries where MNTE has been validated
- High specificity but variable sensitivity of verbal autopsy for NT in hospital-based studies
  - 83% sensitive and 89% specific (Bangladesh).  
  - 66.7% sensitive and 99.5% specific (Pakistan)
- Measures NTMR directly and provides an answer based on statistical probability
- Results well documented and widely recognized since most have been published in the WER.

Cons
- The survey teams face extensive and conspicuous community-level exposure that may put their safety at higher risk in insecure circumstances. This is why other options are needed.
  - They typically work in 100-150 cluster sites, many in remote locations
  - They ask questions at enough households to identify 1,200-2,500 live births

Recommendations of the MNTE Expert Group
- Continued use of this option in the remaining 12 countries whenever circumstances permit

Validation of maternal and neonatal tetanus elimination in the Democratic Republic of the Congo

Introduction
As of March 2019, 46/59 (78%) countries with a high burden of maternal and neonatal tetanus (MNT) had been validated as having eliminated this major cause of neonatal deaths; 13 countries remain to be validated, of which 11 are in the African and Eastern Mediterranean regions. Elimination of MNT is defined as

Validation de l’élimination du tétanos maternel et néonatal en République démocratique du Congo

Introduction
En mars 2019, l’élimination de cette cause majeure de mortalité néonatale a été validée dans 46/59 (78%) pays présentant une charge élevée de tétanos maternel et néonatal (TMN); l’élimination doit encore être validée dans 13 pays, dont 11 situés dans la Région africaine et dans la Région de la Méditerranée orientale. L’élimination du TMN est définie par la
Option 2 Pre-validation without an LQAS-CS survey

Same as Option 1 except the mortality survey is dropped. Validation based solely on whether the pre-validation findings for the 3 to 4 districts most at risk are considered compatible with MNTE.

Example of country where it might be used: Pakistan.

Pros

- Community exposure far less than with Option 1. The district, 2 health facilities and 2 community sites per health facility in the most at-risk 3-4 districts are visited compared to 100-150 cluster sites in the LQAS-CS survey.

- Therefore, Option 2 may be possible in countries where Option 1 cannot be used because of insecurity.
  - Especially if the local staff known to the community are used with remote support.

- Already used in the Autonomous Region, Mindanao, Philippines and the Somali Region of Ethiopia.

- High predictive value positive (next slide).

Cons

- Does not measure the NT mortality rate directly.

- Only useful if the pre-validation team’s assessment is a good predictor of the LQAS-CS result.
In all, 76 pre-validations concluded findings were consistent with MNTE. Each was followed by an LQAS-CS survey.

71 of the the LQAS-CS surveys passed, for a positive predictive value of $71/76=93.4\%$. This is the probability that an LQAS-CS survey passes when the pre-validation concludes that findings are consistent with MNTE.

Other indicators of the accuracy of the pre-validation MNTE conclusion, such as sensitivity, specificity and predictive value negative, cannot be calculated because only positive pre-validations have been followed by an LQAS-CS survey.

Little public-health harm in a false-negative pre-validation conclusion. All interventions to protect NT continue as the process repeats itself.

---

<table>
<thead>
<tr>
<th>Pre-validation findings considered consistent with MNTE?</th>
<th>LQAS-CS mortality survey</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Passed</td>
</tr>
<tr>
<td>Yes</td>
<td>71</td>
</tr>
<tr>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>

“NA” = not available
Option 2 Pre-validation assessment without an LQA-CS survey

Recommendations of the MNTE Expert Group

- Use Option 2 ONLY in areas adequately secure for a pre-validation but not for an LQAS-CS survey
- Use international-level coordination and remote support to provide additional quality control
- In situations where insecurity is due to conflicts that have the potential to end within a short, foreseeable period, consideration should be given to postponing MNTE validation so that Option 1 can be used
- The option should be piloted in other countries to gather additional evidence on how effectively it reduces the risk survey teams face when insecurity is a concern
Option 3  Audit of TTCV SIA coverage without an LQAS-CS survey

- For districts where insecurity prevents both the LQAS-CS survey in Option 1 and pre-validation in Option 2
- In such districts, SIAs are usually the main means by which WRA are vaccinated with TTCV
- The initial desk review for WHO is used to identify the 3-4 districts most at risk
- In these districts, an audit, assessing planning, execution and monitoring of performance done from a safe location, is conducted of the last 3 SIAs with the help of local staff and NGOs
- MNTE is validated if the audit is consistent with reaching the WHO TTCV coverage target of at least 80% of WRA in each of these district having received at least 2 doses of TTCV during the three SIA rounds

Example of where this method might be used: northern Mali.

Rationale

- An audit, using all available means, may be sufficiently accurate for MNTE validation while adequately reducing risk from insecurity. For example:
  - The audit could be planned in advance so that auditing mechanisms are in place throughout the SIAs
  - If wireless communication available, cell phones can be used to contact village chiefs and others to determine if SIA vaccination and mobilization events including vaccine acceptance took place when and where scheduled
Option 3 Audit of TTCV SIA TTCV coverage without an LQAS-CS survey

Outcome of the audit:

- Using standard, structured guidelines, the audit is expected to reach one of the following three conclusions:
  - Audit results do not support the conclusion that SIAs achieved TTCV coverage of ≥80%:
    MNTE not validated
  - Audit results are generally complete and consistent, but some questions remain:
    Coverage survey is needed, if possible. Validation decision based on results of survey
  - Audit results are complete and consistent with SIA TTCV of ≥80%:
    MNTE validated

Pros

- Potential to provide credible information for the validation decision with reduced exposure to risk compared to both Options 1 and 2
- Conservative, since TTCV doses received through routine services are not taken into account

Cons

- Since non-SIA doses are not taken into account, it may be too conservative, with frequent false negative conclusions
- If a coverage survey is required but not possible because of insecurity, then Option 3 would be inconclusive
Option 3  Audit of TT CV SIA planning, execution and performance followed by a coverage survey if indicated

Recommendations of the MNTE Expert Group

- Option not fully endorsed. Should **only** be used if
  - Options 1 and 2 not possible
  - Structured guidelines for the audit are developed and field-tested
  - Audit results are reviewed and accepted by a consultant who did not participate in the audit
  - Other MNTE-indicators are used to put Option 3 results in context
Option 4 Use of large, national, multiple-indicator household surveys (DHS, MICS, EPI-CES) to validate MNTE

MNTE would be considered validated nationally if TTCV coverage ≥80% or SBA≥70% in every region of a country (region, province, state – the first subnational level)

Pros

- Sustainable. Probability sampling. Standardization. Serology can be added.
- TTCV coverage (protection-at-birth) questions already a part of the surveys
- No need for the "most at risk approach" since results are available for every region
- Provide a good platform for measuring tetanus seroprevalence
- Might show MNTE achieved before insecurity began
Option 4 Use standardized national household surveys (DHS, MICS, EPI-CES) to validate MNTE

Cons
- Not designed to provide adequately precise results at the district level
- The same insecurity preventing other options may also prevent these surveys from being conducted
- The large number of variables measured make it difficult to ensure interviewer skill in asking the protected-at-birth questions

Recommendations of the MNTE Expert Group
- This option should not be used for validation because conclusions based on results at the regional rather than the district level are too great a difference from the definition of MNTE and previous validation methods
- In contrast, the option may have an important role in monitoring if MNTE is sustained.
- Further documentation of the relationship between protection-at-birth (PAB), TTCV coverage and seroprevalence would be useful
Option 5  Use neonatal tetanus (NT) surveillance for MNTE validation

The decision to validate would be made when the NT incidence rate, based on the surveillance system, according to WHO quality criteria is <1 NT case per 1,000 live births in all districts

Pros
• Of potential use in the future and potentially a cost-efficient and sustainable option but usable now only in a few urban settings

Cons
• Low sensitivity: <11% of cases are estimated currently to be reported worldwide*
• Uncertain specificity
• The populations most at risk for NT have the least developed surveillance capability
• In most settings, will require vital event registration followed by case investigation as well as zero-case reporting, site visits and record review. While this capacity has benefits beyond NT surveillance it will take time to acquire.

Option 5  Use neonatal tetanus (NT) surveillance for MNTE validation

Recommendations of the MNTE Expert Group

- Surveillance not a viable option at present for validating MNTE except in the uncommon circumstance of districts with a well-developed infrastructure where case investigation is done for all suspected reported NT deaths.

- MNTE initiative stakeholders should continue investing in efforts to strengthen NT surveillance in particular for the role it may play in monitoring how well MNTE is sustained.
<table>
<thead>
<tr>
<th>Option #</th>
<th>Method</th>
<th>MNTE Expert Group recommendation</th>
</tr>
</thead>
</table>
| 1        | Option 1 Pre-validation + LQAS-CS survey | ▪ Use wherever possible.  
▪ Accept delay if security expected to improve in short, foreseeable period. |
| 2        | Pre-validation only | ▪ Use in circumstances where a pre-validation can be conducted but not an LQAS-CS survey |
| 3        | TT CV SIA audit | ▪ Use when insecurity prevents an LQAS-CS survey and a pre-validation |
| 4        | Large, recurrent household surveys (DHS, MICS, EPI-CES) | ▪ Not for validation but consider as method to monitor if MNTE sustained |
| 5        | NT Surveillance | ▪ Not yet good enough for validation except in some urban settings where WHO criteria for reliability are met |
Questions to IVIRAC

- Does IVIRAC consider the two options recommended by the MNTE Expert Group appropriate to address the challenges to MNTE assessment in conflict affected areas?

- Does IVIRAC consider one of the recommended options more appropriate than the other for the purpose?

- What additional recommendations by IVIRAC to improve MNTE assessments in conflict affected areas?
Thank you!
Extra slides
Verbal autopsy for NT: sensitivity and specificity

• Collaborative study (WHO, Johns Hopkins, London School of Hygiene and Tropical Medicine, Oxford University and the Kenya Medical Research Institute,) 1999*

• Mothers in Bangladesh interviewed at home after their neonates were hospitalized, 18 with and 95 without hospital diagnosis of NT

• Verbal autopsy criteria for NT diagnosis:
  • Age 3-27 days
  • convulsions or spasms
  • able to suckle or cry normally after birth and stopped suckling or crying.

• Sensitivity 83%
• Specificity 89%

Selection bias a concern since accuracy of verbal diagnosis among mothers whose neonate with NT was hospitalized may be different from that of mothers whose neonate with NT was not hospitalized.

## Option 3. Recent tetanus seroprevalence surveys among women who have given birth in the last 5 years and protected-at-birth coverage their last-born child

<table>
<thead>
<tr>
<th>Area of survey</th>
<th>Year</th>
<th>Seroprevalence (%)</th>
<th>Protection-at-birth coverage (%)</th>
<th>TTCV2+ coverage (%)</th>
<th>Administrative TTCV2+ coverage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia, national(^1)</td>
<td>2012</td>
<td>93</td>
<td>83</td>
<td>70</td>
<td>73(^6)</td>
</tr>
<tr>
<td>Nigeria, national(^2)</td>
<td>2018</td>
<td>81.5</td>
<td>61.7</td>
<td>52.9</td>
<td>50.4(^6)</td>
</tr>
<tr>
<td>Nigeria, SE(^2)</td>
<td>2018</td>
<td>95.6</td>
<td>92.0</td>
<td>84.1</td>
<td>-</td>
</tr>
<tr>
<td>Nigeria, SW(^2)</td>
<td>2018</td>
<td>86.4</td>
<td>83.2</td>
<td>66.4</td>
<td>-</td>
</tr>
</tbody>
</table>


2) Need reference.

3) Among last-born children in the last 5 years, the proportion protected at birth according to the vaccination history of the mother, taking all doses into account if necessary and as remembered.

4) Among last-born children in the last 5 years, the proportion whose mothers received TT2+ during their pregnancy.

5) Total doses of TTCV given to pregnant women in a year reported as being dose 2, 3, 4, or 5/ divided by the estimated number of live births.

6) https://immunizationdata.who.int/pages/coverage/tt2plus.html
TTCV coverage

- Definition: proportion of newborns within the period of presumed protection conferred by their mother’s TTCV history
- Minimum intervals between doses and duration of presumed protection in TTCV’s 5-dose schedule. There is no maximum interval. The minimum intervals are often not taken into account.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Minimal interval from previous dose</th>
<th>Presumed duration of protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>Not protective</td>
</tr>
<tr>
<td>2</td>
<td>1 month</td>
<td>3 years</td>
</tr>
<tr>
<td>3</td>
<td>6 months</td>
<td>5 years</td>
</tr>
<tr>
<td>4</td>
<td>1 year</td>
<td>10 years</td>
</tr>
<tr>
<td>5</td>
<td>1 year</td>
<td>Rest of reproductive life</td>
</tr>
</tbody>
</table>
Calculating TTCV coverage can be more complex than for other EPI antigens

Example, other epi antigen: “Did this child receive measles-containing vaccine by her 1\textsuperscript{st} birthday?”

• TTCV: Was this child protected at birth by any one of the following scenarios? Before his birth, his mother received:
  • 2 doses, the last within 3 years of his birth OR
  • 3 doses, the last within 5 years of his birth OR
  • 4 doses, the last within 10 years of his birth OR
  • 5 doses, the last at anytime in the past

TTCV compared to other EPI antigens
• Recall period can be much longer (decades)
• Document with TTCV history kept at home less common
TTCV coverage: numerators and denominators

Protected-at-birth (PAB) coverage by survey. For sample of parous WRA:

\[
\# \text{ protected at time of birth by their mother's TTCV history} \frac{\text{most recent live births in the last 5 years}}{\text{estimated number of live births}}
\]

TTCV2+ or “administrative” coverage

women given a TTCV dose during antenatal visits reported as dose 2, 3, 4, or 5

**Protected-at-birth (PAB) questions, Gambia DHS, 2019: first 3 questions**

<table>
<thead>
<tr>
<th>Question</th>
<th>Description</th>
<th>Options</th>
</tr>
</thead>
</table>
| 414      | During this pregnancy, were you given an injection in the arm to prevent the baby from getting tetanus, that is, convulsions after birth? | YES .......................... 1  
NO .......................... 2  
(SKIP TO 417)  
DON'T KNOW  ................. 8 |
| 415      | During this pregnancy, how many times did you get a tetanus injection? | TIMES  .................  
DON'T KNOW  ................. 8 |
| 416      | CHECK 415: | 2 OR MORE TIMES  
(TIMES  
(SKIP TO 420)  
OTHER) |
<table>
<thead>
<tr>
<th>NO.</th>
<th>QUESTIONS AND FILTERS</th>
<th>LAST BIRTH</th>
<th>NEXT-TO-LAST BIRTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>417</td>
<td>At any time before this pregnancy, did you receive any tetanus injections?</td>
<td>YES 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO 2</td>
<td>(SKIP TO 420)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DON'T KNOW 8</td>
<td></td>
</tr>
<tr>
<td>418</td>
<td>Before this pregnancy, how many times did you receive a tetanus injection?</td>
<td>TIMES</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IF 7 OR MORE TIMES, RECORD '7'.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>419</td>
<td>CHECK 418: ONLY ONE ☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a) How many years ago did you receive that tetanus injection?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) How many years ago did you receive the last tetanus injection prior to this pregnancy?</td>
<td>YEARS AGO . . .</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MORE THAN ONE ☐</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Summary of the characteristics and key findings from LQA-CS surveys conducted from 2000 to 2019

*compiled as of 02 June 2021*

(Data sources: WER and mission reports)

<table>
<thead>
<tr>
<th>S/N</th>
<th>Country</th>
<th>Survey Year</th>
<th>Number of Districts</th>
<th>Sample Size</th>
<th>Set-up as single or double sampling</th>
<th>NT deaths</th>
<th>Pass / Fail</th>
<th>TTCV2+ PW (card &amp; history)</th>
<th>Deliveries with qualified assistance (in &amp; out HF)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zimbabwe</td>
<td>2000</td>
<td>3</td>
<td>3000</td>
<td>Double</td>
<td>1</td>
<td>Pass</td>
<td>83%</td>
<td></td>
<td>WER 06/04/2001</td>
</tr>
<tr>
<td>2</td>
<td>Namibia</td>
<td>2001</td>
<td>3</td>
<td>800</td>
<td>Double</td>
<td>0</td>
<td>Pass</td>
<td>86%</td>
<td></td>
<td>WER 12/04/2002</td>
</tr>
<tr>
<td>3</td>
<td>Morocco</td>
<td>2002</td>
<td>3</td>
<td>1000</td>
<td>Double</td>
<td>0</td>
<td>Pass</td>
<td>82%</td>
<td>30%</td>
<td>WER 27/09/2002</td>
</tr>
<tr>
<td>4</td>
<td>Malawi</td>
<td>2002</td>
<td>3</td>
<td>3015</td>
<td>Double</td>
<td>1</td>
<td>Pass</td>
<td>84%</td>
<td>45%</td>
<td>WER 09/01/2004</td>
</tr>
<tr>
<td>5</td>
<td>Eritrea</td>
<td>2003</td>
<td>4</td>
<td>1258</td>
<td>Single</td>
<td>0</td>
<td>Pass</td>
<td>80%</td>
<td>33%</td>
<td>WER 11/06/2004</td>
</tr>
<tr>
<td>6</td>
<td>Rwanda</td>
<td>2004</td>
<td>4</td>
<td>1007</td>
<td>Double</td>
<td>0</td>
<td>Pass</td>
<td>75%</td>
<td>32% (HF)</td>
<td>WER 12/11/2004</td>
</tr>
<tr>
<td>7</td>
<td>Togo</td>
<td>2005</td>
<td>5</td>
<td>996</td>
<td>Double</td>
<td>0</td>
<td>Pass</td>
<td>64%</td>
<td>48% (HF)</td>
<td>WER 27/01/2006</td>
</tr>
<tr>
<td>8</td>
<td>Nepal</td>
<td>2005</td>
<td>3</td>
<td>1898</td>
<td>Single</td>
<td>1</td>
<td>Pass</td>
<td>75%</td>
<td>27%</td>
<td>WER 31/03/2006</td>
</tr>
<tr>
<td>9</td>
<td>Vietnam</td>
<td>2005</td>
<td>3</td>
<td>937</td>
<td>Double</td>
<td>0</td>
<td>Pass</td>
<td>90%</td>
<td>83%</td>
<td>WER 07/07/2006</td>
</tr>
<tr>
<td>10</td>
<td>Egypt</td>
<td>2007</td>
<td>1</td>
<td>1314</td>
<td>Single</td>
<td>0</td>
<td>Pass</td>
<td>77%</td>
<td>68%</td>
<td>WER 29/06/2007</td>
</tr>
<tr>
<td>11</td>
<td>Mali</td>
<td>2007</td>
<td>1</td>
<td>1352</td>
<td>Single</td>
<td>4</td>
<td>Fail</td>
<td>51%</td>
<td>45%</td>
<td>WER 31/08/2007</td>
</tr>
<tr>
<td>12</td>
<td>Tanzania</td>
<td>2007</td>
<td>1</td>
<td>2752</td>
<td>Double</td>
<td>5</td>
<td>Fail</td>
<td>87%</td>
<td>37%</td>
<td>WER 17/07/2009</td>
</tr>
<tr>
<td>13</td>
<td>Zambia</td>
<td>2007</td>
<td>2</td>
<td>1386</td>
<td>Single</td>
<td>1</td>
<td>Pass</td>
<td>77%</td>
<td>59%</td>
<td>WER 04/04/2008</td>
</tr>
<tr>
<td>14</td>
<td>Bangladesh</td>
<td>2008</td>
<td>2</td>
<td>1985</td>
<td>Double</td>
<td>0</td>
<td>Pass</td>
<td>82%</td>
<td>41%</td>
<td>WER 22/08/2008</td>
</tr>
</tbody>
</table>
Option 5. Frequency of these surveys in the 12 countries where MNTE has not yet been validated, as of 2021

<table>
<thead>
<tr>
<th>Country</th>
<th>DHS¹</th>
<th>MICS²</th>
<th>EPI-CES³</th>
<th>Scheduled next 2 yrs</th>
<th>Country</th>
<th>DHS</th>
<th>MICS</th>
<th>EPI-CES</th>
<th>Scheduled next 2 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghanistan</td>
<td>2015</td>
<td>2011</td>
<td>2012</td>
<td>DHS</td>
<td>Pakistan</td>
<td>2018</td>
<td>2021⁵</td>
<td>2021</td>
<td>none</td>
</tr>
<tr>
<td>Guinea</td>
<td>2018</td>
<td>2016</td>
<td>2014</td>
<td>MICS</td>
<td>South Sudan</td>
<td>none</td>
<td>2010</td>
<td>2012</td>
<td>none</td>
</tr>
</tbody>
</table>

¹ If survey took place during two consecutive years, only the second year is shown.
² DHS countries and dates from [https://dhsprogram.com/countries/Country-List.cfm 9/7/2021](https://dhsprogram.com/countries/Country-List.cfm 9/7/2021)
³ MICS countries and dates from [https://mics.unicef.org/surveys](https://mics.unicef.org/surveys)
⁴ Personal communication, Dr. Nasir Yusuf
⁵ 5 Six MICS from 2017-21, one in each of Pakistan’s four provinces and two autonomous territories.

Summary: DHS, MICS or EPI-CES in the last 5 years: 8/12 (66.7%)
Planned in next 2 years: 9/12 (75.0%)
A neonate who feeds and cries normally for at least the first 2 days of life, and, between 3 and 28 days of life
Stops sucking normally
and
Develops stiffness/rigidity and/or spasms
Making Every Baby Count
Audit and review of stillbirths and neonatal deaths
Making Every Baby Count

Audit and review of stillbirths and neonatal deaths
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<td>19</td>
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<td>4.2 Setting up the system</td>
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<tr>
<td>Identifier-reporters</td>
<td>43</td>
</tr>
<tr>
<td>Reviewers</td>
<td>44</td>
</tr>
<tr>
<td>Transmission of information</td>
<td>45</td>
</tr>
</tbody>
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4.3 The six-step mortality audit cycle from the community perspective

Step 1: Identifying cases for review
Step 2: Collecting information
Step 3: Analysing information
Step 4: Recommending solutions
Steps 5 and 6: Implementing changes, evaluating and refining

Chapter 5. Creating an enabling environment for change

5.1 Creating an enabling environment to effect change
5.2 Legal and ethical issues
   Legal protection
   Access to information
   Use of the results
   Ethical considerations
5.3 Developing and disseminating policy and guidelines
5.4 Staff training, ongoing supervision and leadership

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6.2 Collating data and linking to existing information infrastructure
6.3 Ensuring appropriate resources and logistical support

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Annex 2: Births and Deaths Summary Form (and guidance for completion)
Annex 3: Minimum set of perinatal indicators to collect for all births and perinatal deaths (and guidance for completion)
Annex 4: Approaches for classifying modifiable factors
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Annex 7: Sample calculations for reporting
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Annex 10: Verbal and social autopsy tool for stillbirth and neonatal death audits in the community
## Acronyms and abbreviations

<table>
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<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHW</td>
<td>community health worker</td>
</tr>
<tr>
<td>CRVS</td>
<td>civil registration and vital statistics</td>
</tr>
<tr>
<td>ENAP</td>
<td>Every Newborn Action Plan</td>
</tr>
<tr>
<td>HMIS</td>
<td>health management information system</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Statistical Classification of Disease and Related Health Problems, 10th revision</td>
</tr>
<tr>
<td>ICD-MM</td>
<td>The WHO application of ICD-10 to deaths during pregnancy, childbirth and puerperium (ICD-Maternal Mortality) (WHO publication)</td>
</tr>
<tr>
<td>ICD-PM</td>
<td>The WHO application of ICD-10 to deaths during the perinatal period (ICD-Perinatal Mortality) (WHO publication)</td>
</tr>
<tr>
<td>MDSR</td>
<td>maternal death surveillance and response</td>
</tr>
<tr>
<td>PPIP</td>
<td>Perinatal Problem Identification Programme</td>
</tr>
<tr>
<td>SDG</td>
<td>Sustainable Development Goals</td>
</tr>
<tr>
<td>SMGL</td>
<td>Saving Mothers, Giving Life</td>
</tr>
<tr>
<td>VA</td>
<td>verbal autopsy</td>
</tr>
<tr>
<td>WHA</td>
<td>World Health Assembly</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Acknowledgements

The World Health Organization (WHO) acknowledges with thanks the contributions of technical experts and agency representatives.

Kate Kerber prepared the first draft of this guide for audit and review of stillbirths and neonatal deaths, and provided support during the process of reviews, revisions and finalization. Evelyn Twentyman, Florina Serbanescu and Diane Morof from the United States Centers for Disease Control and Prevention (CDC) drafted Chapter 4 on auditing stillbirths and neonatal deaths that occur in the community, and the verbal and social autopsy tool (Annex 10).


WHO is also grateful to the following experts who provided input to subsequent drafts of the guide and tools: Hannah Blencowe, Eckhart Buchmann, Alexandre Dumont, Vicky Flenady, Joy Lawn, Gwyneth Lewis, Diane Morof, Natasha Rhoda and Özge Tuncalp Mingard.

The draft guide was tested in four countries to evaluate its efficacy, effectiveness and user-friendliness. WHO acknowledges the helpful feedback received from participants at the pilot-testing sites:

- **Bhutan**: National Referral Hospital, Thimphu; Phuentsholing General Hospital, Chukha; and Paro Hospital, Paro;
- **Nigeria**: Federal Medical Centre, Lokoja, Ebonyi State; Federal Teaching Hospital, Abakaliki, Ebonyi State; ECWA Hospital, Egbe; Maitama District Hospital, Abuja; and University of Abuja Teaching Hospital, Gwagwalada;
- **Moldova**: Municipality of Chisinau perinatal care centre and three regional perinatal care centres in Balti, Cahul and Orhei;
- **Uganda**: Fort Portal Regional Referral Hospital; Kabarole Hospital; Virika Hospital; Kyenjojo Hospital; Kakumiro Health Centre IV (Kibaale Region); Kakindo Health Centre IV (Kibaale Region); Kagadi Hospital (Kibaale Region); and Kibaale Health Centre IV (Kibaale Region).
In addition, valuable inputs were received from participants at the 35th Annual Priorities in Perinatal Care Conference in Bela Bela, Limpopo, South Africa, in March 2016.

WHO also acknowledges the inputs received from the CDC, Save the Children, the United Nations Children’s Fund (UNICEF) and the United Nations Population Fund (UNFPA).

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Development of this guide was coordinated within WHO by Matthews Mathai and Nathalie Roos, with inputs from Emma Allanson, Larisa Boderscova, Anthony Costello, Pablo Duran, Karima Gholbuzairi, Priya Mannava, Assumpta Muriithi, Neena Raina, Martin Weber and Wilson Were.
Foreword

Pregnancy is a time of great anticipation for all expectant parents and their families as they envision getting to know and love a healthy baby. The presence of a long-desired baby in a woman’s womb is accompanied by thoughts and dreams about what the child will look like and how his or her future will be. Experiencing a stillbirth or the death of a baby in the final stages of pregnancy, during labour or soon after delivery is a silent tragedy for mothers, fathers and families globally.

The day of birth is potentially the most dangerous day for both mothers and their babies. Significant reductions have been made in neonatal mortality during the last two decades, but there are still an estimated 2.7 million neonatal deaths and 2.6 million stillbirths every year. Most of these losses are preventable with high-quality, evidence-based interventions delivered before and during pregnancy, during labour and childbirth, and in the crucial hours and days after birth.

Countries are increasingly collecting data that will enable the burden of stillbirths and newborn deaths to be more accurately estimated. Yet in most countries, especially where the estimated burden is the highest, there is a need to strengthen the civil registration and vital statistics (CRVS) systems for counting all births and deaths and assigning cause of death. Most stillbirths and half of all neonatal deaths do not receive a birth certificate and are not registered. Improving systems for reporting births and neonatal deaths is a matter of human rights and a prerequisite for reducing stillbirths and neonatal mortality.

By counting the number of stillbirths and neonatal deaths, gathering information on where and why these deaths occurred and also by trying to understand the underlying contributing causes and avoidable factors, health-care providers, programme managers, administrators and policy-makers can help to prevent future deaths and grief for parents, and improve the quality of care provided throughout the health system.

This guide shows the way forward for health-care facilities or whole countries to introduce a system to address the burden of stillbirths and neonatal deaths. Similar to the maternal death surveillance and response (MDSR) approach to ending preventable maternal mortality, this guide and related tools provide support for identifying cases, collecting information and analysing the data collected to recommend solutions to improve the quality of care and to implement the changes within a continuous evaluation and response cycle. This guide does not suggest setting up a new system, but building on systems already in place. The approach is in line with two of the five objectives outlined in the Every Newborn Action Plan (ENAP): Strategic Objective 2 – Improve the quality of maternal and newborn care; and Strategic Objective 5 – Count every newborn through measurement, programme-tracking and accountability to generate data for decision-making and action.

It is time to make every baby count and prevent future tragedies, by learning from and effectively responding to preventable deaths.

Dr Flavia Bustreo, Assistant Director-General
Family, Women’s and Children’s Health
World Health Organization
Executive summary

Counting the numbers more accurately, and gaining a better understanding of the causes of death are key to tackling the burden of 2.7 million neonatal deaths\(^1\) and 2.6 million stillbirths that are estimated to occur each year. Half of the world’s babies do not currently receive a birth certificate; and most neonatal deaths and almost all stillbirths have no death certificate, let alone information on causes and contextual factors contributing to these deaths.\(^2\) Many countries have limited capacity for capturing neonatal deaths beyond the level of the health-care facility, especially those countries where births are not registered, and very few countries have a system for tracking stillbirths at all, despite increasing demand for data. Consistent information about the nature and cause of death is needed for planning health systems and distributing resources, as well as for improving the quality of care at the point of service delivery.

National and regional estimates of numbers and causes of death are useful, but they do not tell the whole story.\(^3\) Examination of individual cases identifies the underlying reasons why these deaths occurred and provides opportunities to learn what needs to be done to prevent similar deaths in the future. The majority of stillbirths, particularly those that occur in the intrapartum period, and three quarters of neonatal deaths are actually preventable.\(^4\)

A mortality audit is the process of capturing information on the number and causes of stillbirths and neonatal deaths, and then identifying specific cases for systematic, critical analysis of the quality of care received, in a no-blame, interdisciplinary setting, with a view to improving the care provided to all mothers and babies. It is an established mechanism to examine the circumstances surrounding each death including any breakdowns in care that may have been preventable. Applying the audit cycle to the circumstances surrounding deaths is an established quality improvement strategy that can highlight breakdowns in clinical care at the local level as well as breakdowns in processes at the district or national level, and ultimately improve the civil registration and vital statistics (CRVS) system and quality of care overall.

This process is already being used in many countries in the form of maternal death surveillance and response (MDSR)\(^5\). This is a key strategy to collect accurate information linked to routine health systems recording how many maternal deaths occurred, where the women died, why they died, and what could be done differently to prevent similar

---

deaths in the future. The process of routine identification and timely notification of deaths is a continuous action cycle linking quality improvement from the local to the national level. Although women and their babies share the same period of highest risk, often with the same health workers present, less information has been captured for stillbirths and neonatal deaths than for maternal deaths. Even basic information about each birth and death is limited, and the practice of reviewing selected deaths is not widespread.

The WHO application of ICD-10\(^6\) to deaths during the perinatal period: ICD-PM (ICD-perinatal mortality), published at the same time as this document, provides a new system for classifying causes of death that aims to link stillbirths and neonatal deaths to contributing maternal conditions, where applicable, in a way that is consistent across all settings and that helps to standardise and increase the amount of available information on causes of death around the critical time of childbirth.\(^7\)

This guide, *Making every baby count: audit and review of stillbirths and neonatal deaths*, and the accompanying tools have been developed for use at multiple entry points within the health system, ranging from a few interested individuals at a single health-care facility to a nationally mandated programme covering all health-care facilities and communities. The tools (included as annexes to this document) use a simplified version of ICD-PM for the purpose of initiating audits in low-resource settings, with options to expand the classification in greater detail where feasible.

A couple of notes on terminology used in this report may be useful. Although the perinatal period as defined in ICD-10 encompasses antepartum and intrapartum stillbirths and early neonatal deaths (deaths occurring during the first seven days of life), this guide uses the term “perinatal” slightly more broadly, to refer to the perinatal period extending to four weeks after the delivery, thus also including late neonatal deaths (those occurring on days 8 to 28 days of postnatal life).

Furthermore, some users are familiar with the term “audit” when applied to deaths and mortality, while others are more familiar with the term “review”, as used in the context of MDSR.\(^8\) Experts who contributed to the development of this guide have suggested that the use of both of these terms is acceptable and thus they are used essentially interchangeably in many parts of this guide.

### Components of an audit system for stillbirths and neonatal deaths

The guide is structured around the key components required to establish an audit system for stillbirths and neonatal deaths.

- **Chapter 1** provides the overall rationale for conducting an audit and for the development of this guide in particular.

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\(^6\) ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th revision

\(^7\) The WHO application of ICD-10 to deaths during the perinatal period: ICD-PM. Geneva: World Health Organization; 2016.

\(^8\) WHO, 2013, op cit.
• **Chapter 2** addresses issues around definitions and the classification of causes of death, as well as examples of various systems for classifying modifiable factors related to deaths or near misses.

• **Chapter 3** describes the six steps required to establish and complete the mortality audit cycle at the facility level:
  – setting up the system;
  – collecting information;
  – analysing information;
  – recommending solutions;
  – implementing changes; and
  – evaluating and refining the process.

• **Chapter 4** gives an overview of how to incorporate deaths that occur in the community into an existing facility-based audit system.

• **Chapter 5** highlights the importance of a supportive atmosphere for a successful audit and describes how to create an enabling environment that supports reflective practice.

• **Chapter 6** provides information on expanding a mortality audit system from individual facilities to a network of facilities at regional and national levels, including linkages to civil registration systems and community surveillance systems.

The following tools, forms and additional resources accompany this guide in the form of annexes. The tools and forms come with instructions and can be modified to fit local circumstances.

• **Annex 1:** Stillbirth and Neonatal Death Case Review Form
• **Annex 2:** Births and Deaths Summary Form
• **Annex 3:** Minimum set of perinatal indicators to collect for all births and perinatal deaths
• **Annex 4:** Approaches for classifying modifiable factors
• **Annex 5:** Setting up a mortality audit steering committee
• **Annex 6:** Sample mortality audit meeting code of practice declaration
• **Annex 7:** Sample calculations for reporting
• **Annex 8:** Stillbirth and Neonatal Mortality Audit – Meeting Minutes and Action Items Form
• **Annex 9:** Steps for establishing a mortality audit for stillbirths and neonatal deaths
• **Annex 10:** Verbal and social autopsy tool for stillbirth and neonatal deaths audits in the community.
Key messages of this guide

• Auditing stillbirths and neonatal deaths requires capturing basic information on all births and deaths, as well as a more in-depth analysis of the critical factors involved in selected cases, with the aim of identifying and implementing ways to improve the quality of maternal and newborn care.

• The true burden of stillbirths and neonatal deaths has been unknown and thus silenced for too long. Improving measurement is the first step to understanding where action is needed.

• It is possible to establish a system to assess the burden of stillbirths and neonatal deaths, including trends in numbers and causes of death, and the data must be linked to action at the relevant level.

• These data can be used to provide accountability for results and compel decision-makers to pay due attention and respond to the problem of stillbirths and neonatal deaths. Champions and local leaders are required to lead the review and audit process and translate this information into effective action.

• In addition to leadership, appropriate protections, legal and otherwise, must be in place to create an enabling environment in which critical review of practices can take place.

• There is no long list of requirements needed to initiate a death review. Users only need to decide to learn from the experience and adapt the approach as needed.
Getting started
1.1 What is this guide about?

The timely dissemination of reliable data about the numbers and causes of death to those who need them for taking action is essential for planning and implementing health services (1). A systematic analysis of mortality trends and events leading to deaths can help identify system breakdowns and provide information on local solutions to address deficiencies in service delivery. This process of mortality audit and feedback shows a greater impact on health-care practices and outcomes than other quality improvement strategies, particularly in settings where the audit process includes an action plan and clear targets and when there is greater opportunity for improvement in all sectors and at all levels (2).

Maternal death surveillance and response (MDSR) is becoming an increasingly popular strategy for collecting data linked to routine health systems recording how many maternal deaths occurred, where the women died, why they died, and what could be done differently to prevent similar deaths in the future (1, 3). The process of routine identification and timely notification of deaths is a continuous action cycle that can link quality improvement from the local to the national level. Although women and their babies share the same period of highest risk, often with the same health workers present, less information has been captured for stillbirths and neonatal deaths than for maternal deaths. Even basic information about each birth and death is limited, and the practice of reviewing deaths is not widespread.

This guide sets out key steps towards introducing a system for capturing the number and causes of all stillbirths and neonatal deaths, and reviewing selected individual cases for systematic, critical analysis of the quality of care received, in a no-blame, interdisciplinary setting. The steps of the audit cycle are described, namely: identifying cases, collecting information, analysing data, recommending solutions, implementing changes, and evaluating and refining the process. When information on deaths is aggregated to demonstrate trends, and individual deaths are systematically reviewed to identify common modifiable factors, solutions emerge to address bottlenecks that may not be otherwise apparent when individual cases are viewed in isolation.

With regard to terminology used in this guide, some readers will be more familiar with the term “audit”, which is an established term in clinical practice, while others are more familiar with the term “review” as used in the context of MDSR (1). Experts who contributed to the development of this guide have suggested that the use of both of these terms is acceptable and thus they are used essentially interchangeably in many parts of this guide.

A mortality audit can have multiple entry points into the health system, ranging from a single hospital to a nationally mandated programme covering all health-care facilities and communities. This guide presumes that, at a minimum, all health-care facilities that provide care during childbirth can institute interdisciplinary review of stillbirths and neonatal deaths as part of standard practice. Around the world, more births are taking place in health-care facilities than ever before (4). This guide uses the review of deaths in health-care facilities as an entry point to a broader system-wide approach. Generally, there is more information available about deaths that occur in facilities than those that happen in the community, and it is easier for health-care providers to review and learn from them. However, there is a need to ensure that all births and deaths are counted – and count – no matter where they occur.
1.2 Why is this guide important?

Counting the numbers more accurately, and gaining a better understanding of the causes of death are key to tackling the burden of 2.7 million neonatal deaths (5) and 2.6 million stillbirths that are estimated to occur each year. Many resource-poor settings lack effective civil registration and vital statistics (CRVS) systems for counting all births and deaths and assigning cause of death. Half of the world’s babies do not currently receive a birth certificate; and most neonatal deaths and almost all stillbirths receive no death certificate, let alone information on causes of death and contextual factors contributing to them (4). Many countries have limited capacity for capturing data on neonatal deaths beyond the healthcare facility level, especially those countries where births are not registered, and very few countries have a system for tracking stillbirths at all, despite increasing demand for data.

National estimates of numbers and causes of death are useful, but they do not tell the whole story (6). Examination of individual cases provides us with underlying reasons why these deaths occurred and information about what needs to be done to prevent such deaths in the future. The majority of stillbirths, particularly those that occur in the intrapartum period, and three quarters of neonatal deaths are preventable (7). Applying the audit cycle to the circumstances surrounding deaths can highlight breakdowns in clinical care at the local level as well as breakdowns in processes at the district or national level, and ultimately improve the CRVS system and quality of care overall (Figure 1.1).

FIGURE 1.1. Relationship between mortality audit and wider quality of care and CRVS systems
A mortality audit for stillbirths and neonatal deaths also contributes to global targets and achievements. This approach is in line with two of the five objectives in the Every Newborn Action Plan (ENAP): Strategic Objective 2 – Improve the quality of maternal and newborn care; and Strategic Objective 5 – Count every newborn through measurement, programme-tracking and accountability to generate data for decision-making and action (8). The ENAP Measurement Improvement Roadmap and the Measurement and Accountability for Health Roadmap both aim to increase investment in and the capacity of national health management information systems (HMISs), of which mortality audit is a part (3, 9). Conducting a mortality audit is also a key strategy to ensure accountability for women’s and children’s health, as acknowledged by the global Commission on Information and Accountability (COIA) and the new Global Strategy for Women’s, Children’s and Adolescents’ Health 2016–2030 (10, 11). In the context of the Sustainable Development Goals (SDG) framework, auditing also provides a mechanism to track progress for SDG target 3.2, which aims to reduce neonatal mortality to at least as low as 12 per 1000 live births in all countries by 2030 (12).

1.3 Who is this guide for?

This guide will be relevant for stakeholders across the health system, including health professionals, planners and managers, epidemiologists, demographers and others who measure mortality trends, and policy-makers working in maternal and perinatal health. It may also be useful for those looking to promote linkages with CRVS systems, HMISs and community surveillance mechanisms, to ensure that every birth and death is counted. It is important that those with the power to implement the recommended changes actively participate in the process of reviewing deaths, assigning causes and identifying modifiable factors and solutions; this guide is for them.

The use of audit findings to improve health outcomes is central to the implementation of a mortality audit, both inside and outside of health-care facilities. Stakeholders at all levels who can drive change, such as community leaders, civil society and parent groups, should be involved in the processes of setting up a mortality audit system, to ensure that the recommended changes take place.

1.4 What does this guide aim to achieve?

Similar to the maternal death reviews conducted as part of MDSR, death reviews for stillbirths and neonatal deaths have multiple aims (1). These include:

- to establish a framework to assess the burden of stillbirths and neonatal deaths, including trends in numbers and causes of death;
- to generate information about modifiable factors contributing to stillbirths and neonatal deaths and to use the information to guide action to prevent similar deaths in the future; and
- to provide accountability for results and compel decision-makers to pay due attention and respond to the problem of stillbirths and neonatal deaths.
Importantly, it is not sufficient to count deaths and calculate mortality rates, or even to identify systemic problems contributing to these deaths. A mortality audit is only useful if the reviews lead to action based on the findings (13, 14). There is not a long list of requirements to begin a perinatal death review process. Instead of trying to create the perfect system on paper, start the process, learn from the experience and adapt the approach as needed.

Although the perinatal period as defined in ICD-10 encompasses antepartum and intrapartum stillbirths and early neonatal deaths (deaths occurring during the first seven days of life), this guide uses the term “perinatal” slightly more broadly, to refer to the perinatal period extending to four weeks after the delivery, thus also including late neonatal deaths (those occurring on days 8 to 28 days of postnatal life).

1.5 What does this guide include?

Chapter 2 addresses issues around definitions and the classification of causes of death, as well as different systems for classifying modifiable factors. Chapter 3 describes the steps required to establish and complete the mortality audit cycle for facility-based deaths, including:

- identifying cases
- collecting information
- analysing information
- recommending solutions
- implementing changes and
- evaluating and refining the process.

Chapter 4 provides an overview of how to incorporate deaths that occur at the community level into the audit system. Given the importance of a supportive environment for a successful audit, Chapter 5 describes how to create an enabling environment that supports reflective practice. Chapter 6 provides information on expanding a mortality audit system from individual health-care facilities to a network of linked facilities at the regional and national levels, including linkages to CRVS and community surveillance systems.

The following tools, forms and additional resources accompany this guide in the form of annexes. The tools and forms come with instructions and can be modified to fit local circumstances.

- Annex 1: Stillbirth and Neonatal Death Case Review Form
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- Annex 10: Verbal and social autopsy tool for stillbirth and neonatal deaths audits in the community.
This chapter provides definitions for the key terms relating to stillbirth and neonatal death outcomes. It also introduces systems for classifying causes of death and modifiable factors, with more information and tools provided in the accompanying annexes.
2.1 Notes on terminology

Before implementing a mortality audit system, it is helpful to understand the definitions and classification systems used for reporting deaths, as well as the contextual factors surrounding these deaths. As in other mortality surveillance systems, mortality audit for stillbirths and neonatal deaths includes basic descriptive analyses that include rates and proportions relating to pregnancy outcomes, medical causes, non-medical factors and contributing factors. This chapter provides an overview of these concepts.

In recent years, increasing attention has been paid to neonatal survival (4, 15) and, to a lesser but still notable extent, to stillbirths (16, 17). One of the key reasons for this has been increased visibility arising from improved data and improved analysis and presentation of these data for use in policy-making and programme planning, such as the generation of annual, country-reviewed estimates of the national neonatal mortality rate. These estimates are included in global reporting and tracked in accountability frameworks, now with a long-range goal detailed in ENAP to track and drive a reduction in neonatal mortality to 12 or fewer per 1000 live births, as well as a reduction in stillbirths to 12 or fewer per 1000 total births, by 2030 (18).

Determining cause of death in the absence of a post-mortem examination is challenging, particularly for stillbirths (19). Yet even in better-resourced settings, the assigned cause of death may not be programmatic or linked to obvious solutions (13, 20). The availability of programmatically relevant and technically credible estimates of what proportions of deaths are attributable to specific causes of death in each country has been another critical step in working to prevent millions of neonatal deaths (21, 22). Disparate classification systems between CVRS systems, routine HMISs and audit forms may result in duplication and inefficient documentation (23, 24). In one systematic review of 142 studies, seven different classification systems were identified for stillbirths but were applied in only 22% of studies that could have used a classification system (24). Clear guidelines and a unified, relevant classification system to assign cause of death are needed.

An emerging approach that has been used in some high-income countries is to link maternal and perinatal conditions, to better address the barriers to care affecting both mother and baby. The development of The WHO application of ICD-10 to deaths during the perinatal period: ICD-PM aims to link stillbirths and neonatal deaths to contributing maternal conditions, where applicable, in a way that is consistent across all settings (25). This will help standardize and increase information on causes of death around the critical time of childbirth. The process to assign cause of death in the context of a mortality audit should be easy to apply, comparable across settings, have a good level of agreement between observers, and result in a high percentage of classifiable cases and a low percentage of unexplained causes of death.

Please note that while ICD-PM is designated to be used for all antepartum, intrapartum and early neonatal deaths, it can also be used for late neonatal deaths, which – although falling outside the perinatal period as defined in ICD-10 – may be a consequence of events in the perinatal period.
There are also numerous ways to approach the assignment of modifiable factors relating to substandard care and contextual factors during audits of stillbirths or neonatal deaths. Modifiable factors should be assigned with the inclusion of as much detail as possible, to maximize identification of deficiencies in care and focus attention on achievable preventive strategies.

2.2 Mortality outcome definitions

There are a number of important considerations related to the measurement of stillbirths and neonatal deaths within mortality audit systems, including the definition and classification of stillbirths and the timing of neonatal deaths (26).

Definition and timing of stillbirths

Terminology around stillbirths has changed over time, with variations across settings. For international comparability, WHO recommends reporting of late fetal deaths — for example, third-trimester stillbirths — at ≥ 1000 g birth weight, ≥ 28 completed weeks of gestation and ≥ 35 cm body length, with birth weight given priority over gestational age (Figure 2.1). While birth weight and gestational age are closely linked, they cannot be used interchangeably, since there is a range of “normal” birth weights for a given gestational age and gender, with substantial regional variations (27). Therefore, a gestational age threshold has been recommended as a single parameter, because it is a better predictor of viability than birth weight, and information about gestational age is more likely to be available than birth weight for stillbirths (28). In recent decades, viability has increased in settings where intensive care is available, moving the cut-off point for a death to be defined as a stillbirth (rather than a late fetal death) earlier. Most live-born babies in high-income countries survive even if they are born as early as 25 weeks of gestation, and it is recommended that outcomes are recorded for babies born before 28 weeks (6, 23, 28). The probability of recording the baby as being alive at birth is associated with the perception of the baby’s chances of survival (26). WHO’s recommended threshold of 28 completed weeks is appropriate for mortality audits in low- and middle-income settings, but it is important to note that this would miss earlier stillbirths, thus undercounting the true burden (27).

A practical and programmatic grouping of stillbirths is as either antepartum (i.e. occurring before the onset of labour) or intrapartum (i.e. occurring after the onset of labour and before birth). When there is no fetal monitoring to confirm the presence of a fetal heart rate at the onset of labour, assessment of the skin appearance is frequently used to estimate the timing of the stillbirth (27). Signs of skin maceration begin around 6 hours after fetal death; therefore, a “fresh” or “non-macerated” appearance of the skin is used as a surrogate measure for an intrapartum stillbirth, whereas a “macerated” appearance is judged an antepartum stillbirth. However, this assessment may underestimate the rate of intrapartum stillbirths, especially in situations where access to care is delayed (23). The stillbirth rate is presented as a rate per 1000 total (live and stillborn) births (Table 2.1).
Definition and timing of neonatal deaths

The neonatal period refers to the first 28 days of life (Figure 2.1). The early neonatal period is the first 7 days after birth, and the late neonatal period extends from 7 days to 28 completed days. The first day of life, the 24 hours following the birth, is typically called “day 1” in clinical practice, or “day 0” in surveys and vital registration. In this guide we refer to the first day of life as “day 1”, and we refer to days 1–7 as the “early neonatal period”, days 8–28 as the “late neonatal period”, and days 1–28 as the “full neonatal period” (26). Deaths on the day of birth (day 1) and in the first week of life are particularly important because they account for a large number of deaths that can be targeted by interventions around the time of birth. Around three quarters of neonatal deaths are estimated to occur during the first week of life (26). Many late neonatal deaths occur at home and may not be captured in facility-level records, though they may be captured by CRVS systems with variable information on cause of death and relevant details. When deaths do occur in health-care facilities, whether in the neonatal unit, postnatal ward or paediatric ward, they should be documented and included in the audit process. Deaths that occur in the community after discharge from a health-care facility may also be considered for inclusion in the death review process if enough information is available. The neonatal mortality rate is expressed at the population level as a rate per 1000 live births (Table 2.1).

**FIGURE 2.1. Pregnancy outcome definitions**

<table>
<thead>
<tr>
<th>PREGNANCY</th>
<th>LIVEBIRTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester</td>
<td>Second trimester</td>
</tr>
<tr>
<td>Completed weeks of gestation</td>
<td></td>
</tr>
<tr>
<td>22 weeks</td>
<td>28 weeks</td>
</tr>
<tr>
<td>28 weeks</td>
<td>Postterm &gt;42 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscarriage</td>
<td></td>
</tr>
<tr>
<td>Stillbirth (early definition – ICD) Birthweight ≥500g; ≥22 completed weeks; body length ≥25cm</td>
<td>Stillbirth (international comparison definition – WHO) Birthweight ≥1000g, or if missing, ≥28 completed weeks gestation, or if missing, body length ≥35cm</td>
</tr>
<tr>
<td></td>
<td>Antepartum stillbirth Before the onset of labour</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>Perinatal death (extended definition)</td>
</tr>
</tbody>
</table>

**Pregnancy-related maternal death**

Death of a woman while pregnant or within 42 days of termination of pregnancy

Source: adapted from Lawn et al., 2011 (23).
### TABLE 2.1. Mortality rate definitions and data sources

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Numerator</th>
<th>Denominator*</th>
<th>Data sources</th>
</tr>
</thead>
</table>
| **Stillbirth rate**   | For international comparison: Number of babies born per year with no signs of life weighing ≥ 1000 g and after 28 completed weeks of gestation (ICD-10 also recommends including the number of deaths in fetuses born after ≥ 22 weeks of gestation or weighing ≥ 500 g) | 1000 total (live and stillborn) births | • CRVS  
• Household surveys  
• HMIS and audit systems (often facility-based deaths only)  
• Estimation models |
| **Neonatal mortality rate** | Number of live born infants per year dying before 28 completed days of age | 1000 live births | |
| **Perinatal mortality rate** | Definitions vary:  
  • Number of deaths in fetuses born weighing ≥ 1000 g and after 28 completed weeks of gestation, plus neonatal deaths through the first 7 completed days after birth  
  • Number of deaths in fetuses born weighing ≥ 500 g and after 22 completed weeks of gestation, plus neonatal deaths through the first 7 completed days after birth  
  • Some definitions include all neonatal deaths up to 28 days | 1000 total (live and stillborn) births | |

ICD-10: International Classification of Diseases version 10; CRVS: civil registration and vital statistics; HMIS: health management information system.

* The time period is normally calculated per year.

Source: Moxon et al., 2015 (9).

Definitions also vary for the perinatal mortality rate. Perinatal mortality refers to the number of stillbirths and deaths within the first week of life (early neonatal mortality), but the stillbirth definition varies to include stillbirths of either greater than 22 completed weeks or greater than 28 completed weeks of gestation. Some definitions of perinatal mortality also include the late neonatal period, or even up to 6 weeks (29).

### 2.3 Medical causes of death

It is important to emphasize the difference between audit data collected for review meetings and analysis, and routinely collected data that fit standard, official definitions. The official definitions – e.g. those that are used on death certificates – should not be changed for the purposes of audit. Rather, the flexibility in definitions should only be used for the purposes of death review, to generate the most effective learning cases which link to solutions and improvement of services. Annex 1 provides a death case review form with suggested programmatically relevant categories of causes of death for stillbirths and neonatal deaths.
Classifying causes of stillbirths and neonatal deaths

A globally unifying approach to the classification of stillbirths and neonatal deaths is important if we are to share a common language around the causes of stillbirths and neonatal deaths and make meaningful comparisons across settings. Thus perinatal deaths should be classified using The WHO application of ICD-10 to deaths during the perinatal period: ICD-PM (25), which builds on the features of many other classification systems (25, 30, 31) and is applicable in all settings (25, 32, 33).

Application of ICD-PM to audit

ICD-PM is an application of ICD-10 that groups the ICD codes used to classify perinatal causes of death and those used to classify the maternal condition at the time of death, to facilitate straightforward and consistent capture that makes it easy to identify where programme intervention should be targeted to impact the health of both mother and baby (25). Classifying a stillbirth or neonatal death using modified ICD-PM guidance applicable to perinatal mortality audit is a three-step process:

1. Classify the type of death based on timing as one of the following:
   - Antepartum (“macerated” stillbirth)
   - Intrapartum (“fresh” or “non-macerated” stillbirth)
   - Stillbirth, unknown timing
   - Neonatal death (hours and/or days since birth).

2. Identify the main disease or condition that caused the stillbirth or neonatal death. All of the ICD-10 codes that can be assigned to sections (a) and (b) on the death certificate (see Table 2.2) are represented in the following new broad categories, which are included on the Stillbirth and Neonatal Death Case Review Form (Annex 1) and in the Births and Deaths Summary Form (Annex 2):
   - congenital
   - antepartum complications
   - intrapartum complications
   - complications of prematurity
   - infection (select: tetanus, sepsis, pneumonia, meningitis, syphilis, diarrhoea, other)
   - other cause of stillbirth or neonatal death
   - unknown/unspecified.

3. Identify the disease or condition of the mother. The audit team should determine the maternal condition at the time of diagnosis of the perinatal death. The maternal condition at the time of perinatal death may not be the direct cause of the death but is the principal maternal condition at the time; it should be considered reasonably integrated into the pathway leading to perinatal death (e.g. hypertensive disease in a macerated stillbirth, urinary tract infection in preterm birth). If there is no maternal condition (i.e. mother is healthy), this should be documented. The definition of no contributory maternal condition identified at the time of perinatal death is “the absence of any maternal medical condition or deviation from standard intrapartum progress”. Specific conditions are grouped into the following broad categories, based on guidance in The WHO
The ICD-PM classification can be useful for a mortality audit because the focus on the mother–baby dyad highlights areas requiring programmatic intervention that will benefit both maternal and newborn outcomes. It simplifies the certification of perinatal deaths but also offers programme officers and public health workers a way to identify solutions that meet the needs of both mother and baby concurrently. The categories used in the Stillbirth and Neonatal Death Case Review Form (Annex 1) and the Births and Deaths Summary Form (Annex 2) have been collapsed to facilitate ease of data entry and analysis, but these causes of death can also be expanded to include more specific causes and categories, depending on the capacity and interest of the facility and audit team.

**Application of ICD-PM to death certificates**

Table 2.2 shows the four sections of causes of death (a, b, c, d) on a standard perinatal death certificate, as recommended by WHO. Whenever possible, causes of death should be encoded in accordance with ICD-PM classification (25). Coding rules mandate that section (a) is coded to P05–P96 (perinatal conditions) and Q00–Q99 (congenital anomalies). It should be noted that there are a number of exceptions where other codes should be used – for example, neonatal tetanus is always coded to A33 tetanus neonatorum or A50 for congenital syphilis. Assignment of the conditions in each section follows the rules for perinatal mortality coding in ICD-10 volume 2 (34).

To summarize the process, one first considers coding a cause of death using a three-character code. In most cases this is a letter and two numbers (e.g. P26 Pulmonary haemorrhage originating in the perinatal period). If appropriate, this is followed by assigning a more specific cause of death using a four-character code nested under the three-character codes (e.g. P26.1 Massive pulmonary haemorrhage originating in the perinatal period).

**TABLE 2.2. Sections of causes of death on a standard perinatal death certificate**

<table>
<thead>
<tr>
<th>Causes of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Main disease or condition in fetus or infant</td>
</tr>
<tr>
<td>(b) Other diseases or conditions in fetus or infant</td>
</tr>
<tr>
<td>(c) Main maternal disease or condition affecting fetus or infant</td>
</tr>
<tr>
<td>(d) Other maternal diseases or conditions affecting fetus or infant</td>
</tr>
</tbody>
</table>
The single main disease or condition in the fetus or infant is entered in section (a), whereas multiple other conditions can be entered in section (b). The single main maternal disease or condition affecting the fetus or infant, which, under current ICD-10 rules, can only be coded to P00–P04 (maternal conditions in perinatal death), is entered in section (c). Multiple other maternal diseases or conditions affecting the fetus or infant (P00–P04) can be entered in section (d). The assignment of three- and four-character codes for (c) and (d) is the same process as it is for the perinatal cause of death codes (a) and (b).

2.4 Collection of a minimum set of perinatal indicators

One of the key actions outlined in the ENAP is to develop a minimum set of perinatal indicators to collect and to ensure that all birth outcomes are recorded, with consistent definitions linked to vital registration and data derived from health-care facilities. Data currently collected and collated on births and birth outcomes vary widely across settings. While a separate form does not need to be completed for every birth and death to record this information, these key indicators should be recorded in a register or electronic HMIS and collated. At a minimum, it is essential to collect information on the following characteristics of each birth and death:

- maternal age
- place of delivery
- mode of delivery
- birth weight
- gestational age
- birth outcome.

Sample forms that capture these key pieces of information and further details are included in Annex 1 (Stillbirth and Neonatal Death Case Review Form), Annex 2 (Births and Deaths Summary Form) and Annex 3 (Minimum set of perinatal indicators to collect for all births and perinatal deaths). To further understand the context, it may be helpful to capture additional information relating to the health and sociodemographic status of the mother and the type of care she and her baby received. Box 2.1 lists additional information that may be relevant to consider when reviewing a death; it should be gathered during history taking and included in the patient file.
Box 2.1. Background and contextual information relevant to stillbirths and neonatal deaths for review of cases

Information on sociodemographic status:
Parents’ ages, ethnicity, occupations, education and marital status

Information on health status and care received:

Pre-conception and antenatal
• Mother’s obstetric history (gravidity/parity/previous losses/caesarean deliveries)
• Was the pregnancy planned?
• Was birth control being used?
• Mother’s medical history
• Antenatal care (if any): name of the institution that delivered care, gestational age at first visit, number of visits, was birth plan made, complications (including symptoms and signs), procedures and treatment
• Hospitalization (if any): complication, tests and results, procedures, diagnoses, treatments, problems encountered
• Barriers to care (if any): geographic, financial or cultural
• Exposure to environmental factors

Intrapartum
• Date and time of onset of labour
• Date, time and gestational age at rupture of membranes
• Place(s) where labour and delivery occurred (including the name of the institutions, if applicable)
• Management and monitoring during labour
• Date and time of onset of complications (including signs/symptoms)
• Hospitalization or consultation (record separately for each): complications, tests and results, procedures, diagnoses, treatments, problems encountered
• Date and time of birth
• Cadre who attended the birth
• Status of the baby: sex, gestational age at delivery, birth weight, Apgar score, stillborn/liveborn
• Immediate care provided to the newborn baby
• Barriers to care (if any): geographic, financial or cultural
• Timeline for the mother/family becoming aware of a problem, decision-making, transport, waiting times

Postnatal
• Choice of method of feeding, and date and time of first feed
• Date and time of onset of serious complications (including signs/symptoms)
• Hospitalization or consultation (record separately for each): complications, tests and results, procedures, diagnoses, treatments, problems encountered
• Barriers to care (if any): geographic, financial or cultural
• Timeline for the mother/family becoming aware of a problem, decision-making, transport, waiting times
2.5 Modifiable factors

A modifiable factor is something that may have prevented the death if a different course of action had been taken. Many modifiable factors involve missed opportunities within the health system. Identifying these modifiable factors, therefore, can offer potential for positive change. For example, in the case of a neonatal death it may be noted that the birth attendant did not provide bag and mask resuscitation when the baby did not respond to vigorous stimulation. In this case, there may have been a missed opportunity to avoid the situation or provide corrective action – failure to train birth attendants on resuscitation, or to provide a bag and mask in the delivery room.

Documenting the contributing and potentially modifiable factors related to each death is a priority in a mortality audit for stillbirths and neonatal deaths because it provides an opportunity to change behaviours and systems. Although at first glance a death may appear to be due to a single biological cause, further analysis usually reveals a number of contributing factors or underlying causes. Often by exploring the event and gaining a better understanding of the root causes, solutions and strategies become more apparent. Examination of these factors provides insight into whether each death may have been preventable and potential solutions that may prevent similar deaths in the future.

The terminology used to describe this concept varies, including “avoidable factors”, “elements of substandard care”, among others. “Modifiable factors” is the term used in this guide, to limit the opportunity for blame and point to elements of care that are potentially amenable to change.

There are also multiple systems and approaches for classifying modifiable factors (35). The death case review form (Annex 1) proposes a simple approach which identifies and categorizes modifiable factors in a few ways. The first proposed method uses the well-known “three delays” model (36):

- Delay 1: Were the mother, father or other family members unaware of the need for skilled care for the mother during pregnancy and birth, and for mother and baby in the neonatal period? Were they unaware of the warning signs of problems during pregnancy or in newborn infants, or were they reliant on harmful traditional medicine and practices? Were there any other sociocultural factors or barriers? (see Box 2.2)
- Delay 2: The necessary maternal and/or neonatal health services did not exist, or were inaccessible for other reasons. Was distance or cost a factor? If there was a delay in travelling to the health-care facility after a problem was identified, what were the reasons for this?
- Delay 3: The care the mother and baby received at the health-care facility was not timely or was of poor quality. Was this due to provider error, lack of supplies or equipment, or poor management?

In addition, identifying the level at which a system breakdown may have occurred provides more detail on the potential for action to prevent future deaths. The levels detailed in the death case review form in Annex 1 include:
• Family- or patient-related: e.g. late or no antenatal care; cultural inhibition to seeking care; limited or no knowledge of danger signs; financial constraints; partner restricts care-seeking; use of traditional/herbal medicine; alcohol use; attempted termination.
• Administration-related: e.g. lack of or insufficient neonatal facilities, theatre facilities resuscitation equipment, blood products or training; insufficient staff numbers; delay in anaesthesia; lack of antenatal documentation.
• Provider-related: e.g. the partograph was not used; timely action was not taken; inappropriate action was taken; iatrogenic birth; delay in referral; inadequate monitoring; delay in calling for assistance; inappropriate discharge.

Box 2.2. Assigning modifiable factors at the patient/family/community level:
a word of caution

Audit participants should be wary of placing “blame” on the patient or the family when assigning modifiable factors to a particular case. While critical delays do occur at the community level, and there can be real individual- or family-level behaviours that lead to a death, audit teams should guard against placing the burden of responsibility on the woman and/or her family. One way to guard against this is to calculate the proportion of modifiable factors that occur at the facility level and at the district/community level. If the patient-level factors are increasing or the issues remain constant over time, question whether there were any other factors at the point of care or elsewhere that could have played a role. The audit committee can also examine the recommendations that have been made and what actions have been taken. When community-related modifiable factors are identified through audit, it is important that communities are informed of the findings and that active members are involved in determining and implementing the solutions.

Identification of gaps at these three basic levels can be followed by root cause analysis to better understand underlying deficiencies in care (37). A root cause analysis helps to identify all the problems that led to or contributed to an event – in this case, the stillbirth or neonatal death under review. The purpose of this analysis is to identify the factors that contributed to the death and further assess whether there are any underlying causes to the contributing factors. This analysis may help formulate integrated strategies and recommendations. The diagrams that are created during root cause analysis are known as Ishikawa diagrams or fishbone diagrams, because a completed diagram can look like the skeleton of a fish (see Annex 4 for examples).

The root cause analysis approach is adaptable, and other methodologies have been used successfully in different settings (35). For example, the process of determining whether adequate care was provided can also be based on a criterion-based audit against national standards, as implemented in Uganda (38) and South Africa (39). Assessing the care provided against a limited set of existing standards for availability of equipment, medication and staff by level of service has the potential to be less subjective than the methods described above (38, 40). Additional guidance for classifying modifiable factors with varying levels of complexity and detail is provided in Annex 4.
3 Auditing deaths that occur at the health-care facility

This chapter provides an overview of considerations for initiating a system for reviewing stillbirths and neonatal deaths that occur at a health-care facility, and the process required to walk through each of the steps of an in-house mortality audit cycle at the health-care facility level.
3.1 Setting up the system

In many health-care facilities, local in-house mortality reviews are conducted as standard clinical practice and risk management. This is not always the case, however, even in facilities where there are large, multidisciplinary teams operating in well-resourced settings; but often some form of review is part of an ongoing quality improvement processes. A good principle is to review what already exists, start small and scale up gradually. A phased approach to scaling up may be applied: following introduction and institutionalization in one or a few facilities, expand the audit system to other locations, moving towards greater coverage (Figure 3.1). This chapter describes the process of introducing the mortality audit approach at an individual health-care facility, while the process of scaling up to a regional- or national-level system is described in Chapter 6.

A positive enabling environment at the national and/or regional level will make it easier to move through the various phases of the mortality audit process, but it is possible for an in-house process to start and thrive without initial external support from authorities at that level. In the pre-implementation phase, the right stakeholders need to be involved to establish the programme and raise awareness about it. In some settings, audits may be linked to existing quality improvement initiatives. If a quality improvement committee is already in place, it can be engaged to support the formation of a facility-level steering committee that will prepare cases for review and rotate facilitation of the audit meetings (Annex 5). This committee could be combined with an existing maternal death review committee, or just closely linked to it (Box 3.1), but either way, the committee should be well institutionalized within the system. The steering committee’s role includes the overall responsibility for operationalizing the audit policy, providing technical assistance for the implementation of audit systems, and monitoring recommendations and follow-through.

Midwives and obstetricians are in a natural position to lead the audit process, given their knowledge of the burden of intrapartum deaths. In South Africa, midwives drive the national mortality audit process, called the Perinatal Problem Identification Programme (PPIP) (41). However, recording the details of first-day and later neonatal deaths also requires crossover with other departments and specialities such as paediatrics, neonatal nursing, emergency, outpatients and pharmacy. In Brazil, for example, paediatricians hold leadership positions on perinatal review committees. In Uganda, stillbirth and neonatal death review has been successfully initiated and sustained by midwives and community representatives (42). A facility-based mortality audit committee should include representatives of various departments, and stakeholders from among the facility’s management team and the district medical office as well as a community liaison, if applicable. In some settings, the range of committee participants may be even further expanded (43). In the United States, multi-agency child death review involves coroners, law enforcement officers, child protective services and health-care providers (44), and in England, each local authority has established a multidisciplinary child death overview panel to review all child deaths (from birth to age 18) in their area (45). However, such a wide stakeholder group is not essential. Involving the legal system, in particular, can undermine a collaborative environment in which shortcomings in care are openly discussed. While accountability is needed, the mortality audit process should focus on the ability of health professionals to identify opportunities to improve the health system, not assign blame.
Within each facility, at least two individuals who are willing to lead the data collection process should be identified. Larger facilities may need a bigger data collection team to share the responsibilities and achieve full coverage. If there is only one data collector who can work only part-time for the review committee, the committee may decide to select a subset of cases for review, take a thematic approach or limit the review to cases that are most likely to be preventable (see Box 3.1 and also section 3.2, Step 1).

**Box 3.1. Linking audits for stillbirths and neonatal deaths to existing facility-based maternal death reviews**

It is important that the process for maternal and perinatal death review are coordinated and linked, rather than operating in parallel.

If maternal mortality and morbidity review meetings already exist at a health-care facility, with several maternal deaths or near misses to review at every meeting, teams may consider reviewing at a minimum a selection of intrapartum stillbirths and first-day neonatal deaths to avoid spending too much additional time in the meetings. If only a subset of all stillbirths and neonatal death cases is being discussed at review meetings, key details should be recorded for each patient. Given the higher numbers of stillbirths and neonatal deaths than maternal deaths, it might make sense to institutionalize separate but linked perinatal meetings once the review process has been established, especially in large facilities.

Annex 3 provides a minimum set of perinatal indicators that should be collected for each birth and death, and integrated within a broader surveillance system.

The steering committee and the district and facility management teams have a responsibility to nurture a culture that is conducive to a successful audit process in a no-blame environment. This will also contribute to accountability at the national level. Lessons learnt from maternal mortality audits indicate that successful ones were those led by committed health professionals, while less successful audits often suffered from poor leadership and a reluctance of staff to participate. Where poorly planned reviews had been running for some time with no action taken on the results, senior staff stopped attending meetings, which led to a sense of futility and demoralization among the more junior staff (3). Having participants agree to a code of practice for review meetings (Annex 6) and ensuring confidentiality as much as possible can contribute to an environment where the audit is more likely to be successful (46).

Once the committee is established and key actors identified, physical and financial resources may be required to adapt tools and software, and provide training to district, management and clinical staff on the new system (for more information on training, see Chapter 5). The decision of whether to adopt an electronic or paper-based system is an important one, with trade-offs on both sides. In settings with limited computer literacy and inconsistent power supplies, electronic data entry may hamper implementation (47), though some success has been seen with systems that use mobile phones (48). Regardless of the medium, the development of a user-friendly form that reflects local capacity for data entry is an essential component of this process.
3.2 The six-step mortality audit cycle

Once positive support from management is secured, the leadership of the steering committee has been appointed, and the tools are in place for data collection and for linking to regional or national systems if they exist, the process of moving through the six-step audit cycle may begin: (1) identifying cases; (2) collecting information; (3) analysing information; (4) recommending solutions; (5) implementing solutions; and (6) evaluating both the process and the outcomes, and refining the process as indicated. Each of these steps will now be described in detail.

**Step 1: Identifying cases**

The aim should be to record all deliveries, births, stillbirths and neonatal deaths that occur in the delivery ward, neonatal unit and postnatal ward, ensuring that the indicators contained within the minimum set of perinatal indicators are captured in a register or a central database (Annex 3). Trends in these data can be analysed using the calculations in Annex 7.

In some settings, audit teams may be able to rely on CRVS systems to help identify events, and the process and individuals involved in death certification at the facility level should be integrated with the mortality audit process. However, as discussed in Chapter 2, even in the presence of vital registration systems with complete coverage of most events, reporting of stillbirths and neonatal deaths may not be complete. Frequently, civil registration does not require reporting of stillbirths, or they are not well reported, similar to the poor reporting of many early neonatal deaths (4, 28). Cultural interpretations of when a baby becomes a “person” may also affect the willingness of health staff to audit particular deaths. Late neonatal deaths are often excluded from registers of neonatal deaths if the babies have been readmitted and then die on the paediatric ward rather than in the neonatal unit, but this is a missed opportunity to address preventable neonatal deaths and system gaps.

Advocacy may be needed around case definitions and expanding data capture to cover all stillbirths and neonatal deaths. This first step may be accompanied and supported by a national process to advocate for the introduction or improvement of perinatal death certificates to capture cause of death and maternal condition and link this information to local and national statistics.

Given the challenges of documentation and data collation in a high-volume health-care facility setting, specific strategies should be put in place to ensure that all deaths are captured in the routine health information system and filtered to the mortality audit committee so that cases can be selected for review and discussion at mortality audit meetings.

Whereas maternal deaths are rarer than stillbirths or neonatal deaths, and in many countries they are a notifiable event (i.e. an event that must be reported to the authorities), it is unlikely that policy will mandate for stillbirths and neonatal deaths to be notifiable at the national level. Even so, each stillbirth and neonatal death should be recorded. Generally speaking, the number of stillbirths and neonatal deaths will relate to the number of births that occur at any given health-care facility. Table 3.1 provides rough estimates of how many deaths can be expected at facilities of varying sizes (indicated by births per year) with a range of in-facility perinatal mortality rates (PMR), so that these estimates can be
compared to the actual numbers of registered perinatal deaths, as an indication of how well the system captures perinatal deaths, and how many cases are likely being missed. However, even in settings with fewer deaths, analysing a case with relevant learning points can still yield valuable information on modifiable factors and lead to improvements in the quality of care.

Table 3.1. Expected number of facility-based perinatal deaths (stillbirths and deaths in the first week of life) at various levels of mortality at the facility

<table>
<thead>
<tr>
<th>Births</th>
<th>Expected number(^a) of facility-based perinatal deaths per year for a range of in-facility perinatal mortality rates (PMRs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PMR 20</td>
</tr>
<tr>
<td>156</td>
<td>3</td>
</tr>
<tr>
<td>260</td>
<td>5</td>
</tr>
<tr>
<td>364</td>
<td>7</td>
</tr>
<tr>
<td>520</td>
<td>10</td>
</tr>
<tr>
<td>780</td>
<td>16</td>
</tr>
<tr>
<td>1040</td>
<td>21</td>
</tr>
<tr>
<td>1300</td>
<td>26</td>
</tr>
<tr>
<td>1560</td>
<td>31</td>
</tr>
<tr>
<td>2080</td>
<td>42</td>
</tr>
<tr>
<td>2600</td>
<td>52</td>
</tr>
<tr>
<td>3900</td>
<td>78</td>
</tr>
<tr>
<td>5200</td>
<td>104</td>
</tr>
</tbody>
</table>

\(^a\) Calculated as: expected number = (perinatal mortality rate) \times (no. of births per year) / 1000.

At any health-care facility, the number of perinatal deaths will be much higher than the number of maternal deaths. Depending on the staffing and workload at the facility, it may be prudent for the mortality audit committee to start by reviewing a selection of stillbirths and neonatal deaths, to reduce the length of review meetings. For more information, see Step 4: Recommending solutions.

If there is no pre-existing, current list of all stillbirths and neonatal deaths that occur at the health-care facility, this will need to be created by the mortality audit steering committee to improve capture of perinatal deaths for review. The list should include an identifying code or initials and the baby’s date of birth, to avoid duplicate entry of the same death, as well as which unit recorded the death.

The following questions can assist in the selection of sources to investigate and use in the review process:

- Where are deaths likely to occur in the facility?
• Which deaths do I want to collect more detailed information on? (e.g. all or a subset of antepartum stillbirths, intrapartum stillbirths, early neonatal deaths, late neonatal deaths, a particular range of birth weights or gestational ages, see below and Box 3.1)
• What kinds of records exist? (e.g. labour and birth registers, postnatal registers, emergency or operating theatre records, discharge logs with status of patient, paediatric registers)
• Are the records paper-based or electronic?
• Are all the records housed in one location, or are they scattered?

Once all the places where the data might be located have been identified, a plan for systematically reviewing these sources may be created that includes a schedule for checking various registers and departments.

If the burden of stillbirths and neonatal deaths is high it may not be feasible to review all cases. Further, if human resources are limited – e.g. if there is only one data collector who can work only part-time for the review committee – the committee may decide to select a subset of cases for detailed review (e.g. only the cases that take place in the first week of each month) or to take a thematic approach (e.g. for a specified number of meetings, only deaths attributed to sepsis will be reviewed, followed by a different cause of death), or to limit review to cases that are most likely to be preventable (e.g. intrapartum stillbirths and neonatal deaths among near-term babies).

**Step 2: Collecting information**

For every death, decisions must be taken as to what information is recorded, where the information is recorded, who records it, and who collates it on a periodic basis both for the death review process and for reporting to other levels within the system such as facility- and district-level administration, the national ministry of health, as well as intersectoral systems such as CRVS. It is important to limit the data collected. Having too many difficult or highly detailed questions with no apparent purpose alienates busy staff who are required to fill in the forms. If a use for the data cannot be identified, then the data should not be collected. Having a clear understanding of the data analysis plan will help with these decisions.

Ideally, deaths are reviewed within a week of the event. Depending on the interval of the mortality audit review meetings (e.g. biweekly or monthly), the total number of deliveries, stillbirths and neonatal deaths during that time period is captured on a standardized data capture form by the designated staff members. These are usually physicians or midwives, though they can be data clerks if these cadres are available. In all cases, those entering data should be trained on the system and the reasons for its use. Data abstraction/collection forms may be either paper-based or computerized/electronic, but they should include clear directions about exactly what information is to be collected. It is helpful to pilot-test and then revise these forms as needed prior to use and to allow for future review and updates. Most of the abstracted data will be quantitative, and the form should have clearly designated data entry fields. If items are pre-coded, all possible responses should be captured (including missing responses) or a space should be provided for entering other values. Because data may at times be abstracted as text, such as the description of a chain
of events that led to death, text boxes should be an option in both electronic and paper systems. They should be large enough to allow the abstractor to describe the event in full.

Key information to collect for a facility-based review is outlined in Chapter 2 (see Box 2.1). Briefly, the minimum data required cover information about the mother’s condition, the baby’s condition on admission and/or the at onset of labour (for antepartum and intrapartum deaths), the baby’s condition at birth (stillbirth or live birth), the baby’s condition on discharge from the health-care facility (alive, transferred to another facility or dead), and the date and time of birth and death (so that age at death can be calculated in hours, not just days).

A phased approach can be considered, in terms of the level of data complexity. For example, the committee at the facility can start with a form that simply captures the number of births, stillbirths and neonatal deaths, as well as details on how many were intrapartum stillbirths and intrapartum-related neonatal deaths, to assess trends over time. This is a possible first step, while gauging the willingness of the mortality audit committee to introduce a wider and more in-depth stillbirth and neonatal death review process, or to add the review of stillbirths and neonatal deaths to a more established maternal mortality or maternal near-miss audit system.

If a more comprehensive system is feasible, data captured on each death may include the programmatically relevant cause of death, linked maternal conditions, demographic data and a limited list of contributing, modifiable factors corresponding to codes for analysis and clearly linked to recommendations (see Chapter 2 and Annexes 1–4 and 7). If there is a possibility to link deaths that occur in the community to the facility’s audit system, decisions can be made about how the chain of notification will operate depending on the local context. Given the challenge of locating medical records after the fact, the necessary information on each death should be extracted from the patient file and relevant medical records as soon after the birth and death as possible. Even so, delays in documentation may occur and files may be lost. In cases where lost medical records may have provided key information related to the circumstances surrounding the death (and thus possibly related to the cause of death and modifiable factors), it may still be desirable to include the case in the mortality review meeting, in order to highlight the importance of following protocol for case notes and record-keeping.

For the majority of cases, data can be abstracted from patient notes and medical records without additional research. If interviews are being conducted by the audit committee – for example, to glean more information about a specific cause of death or contributing factors – interviewers may want to collect relevant information from mothers, family members, relatives, community members and health workers. Training on interviewing techniques may be helpful, including how to probe for information in a sensitive manner without upsetting the respondent or biasing their responses, and how to help respondents recall dates and other important information. Interviewers should also be prepared to respond to questions or requests for information from the interviewee. The interviewer should always receive consent before each interview and assure respondents that the information collected will be kept confidential by the facility staff and that the privacy of the families and the health workers involved is paramount.
Sometimes information concerning the birth and death from different sources may be contradictory. Although it is not the task of any one individual to reconcile such discrepancies, it is important that they are highlighted at the stage of data collection and synthesis, with plans to rectify inconsistencies in register data and move towards better-quality inputs. Data quality should be ensured at the data entry level. South Africa’s PPIP electronic database has a number of built-in validity checks (41). Some are automatic on the data entry page, and other validity checks can be activated once the monthly data have been entered (e.g. critical fields must be filled in before the next field can be activated for data entry, and implausible entries – such as 60 weeks gestational age, or 20 kg birth weight – are not permitted by the software. This minimizes the potential for missing or incorrect data. Data verification should happen at the facility level before local data are relayed to any higher levels.

Variations in trend data (Annex 7) – for example, increases or decreases in deliveries or care-seeking behaviours – may need to be examined further with information from the community to understand possible explanations for these changes (see Chapter 4). Innovation and technology such as software programs can help, particularly in the rapid analysis and presentation of results, but should not be the focus of the audit process or a barrier to uptake.

**Step 3: Analysing information**

It is helpful to have an analytic plan to guide the process, keeping in mind that the overall goal is to identify problems in the system that may contribute to stillbirths and neonatal deaths, especially those that could have been prevented or avoided. To accomplish this, data analysis should ideally include both qualitative and quantitative components. The quantitative analysis, based on data such as geographic location and maternal risk factors, will provide information on which groups of babies are at higher risk of death, and identify trends in mortality rates and medical causes of death. Qualitative analysis of information about contributing factors and barriers to care, among others, will provide additional insight into the problems that caused the deaths of individual babies as well as more generally providing information about groups of babies affected by similar contributing factors. For example, qualitative data can help to answer questions about individual cases such as: Did the baby die because no one realized how sick it was or because the health centre was too far away? Were the right medicines not administered or were they unavailable? Collection (by interview) and review of such qualitative data can be particularly helpful for getting more information when patient notes in a particular case are very limited, for example if cause of death is simply noted as “already dead” or “arrived too late”. The use of both types of data together will provide a more rounded view of what the problems are and help the review committee identify priorities for action.

While death reviews should not primarily be a process to produce data, there are a number of informative quantitative analyses and outcomes that can be tallied by the review committee or designated staff and presented at scheduled mortality audit meetings, as well as posted publically within the ward or unit. The minimum set of perinatal indicators that could be presented in this way include (49):

- the number of normal vaginal, assisted and caesarean deliveries;
- the number of maternal deaths;
• the number of antepartum (or macerated) and intrapartum (or fresh) stillbirths and early neonatal deaths; and
• in-facility stillbirth (intrapartum and antepartum) and neonatal mortality rates.

The number of major complications during labour and birth, and the reasons for caesarean section (fetal distress, obstructed labour, failed induction, placental abruptions, postpartum haemorrhage, postpartum infection, severe preeclampsia or eclampsia, etc.) may also be collated and presented. Audit committees, facility administrators or local policy-makers may want to pick one particular indicator to focus on and follow over time to see if outcomes improve after implementing audit recommendations.

Computer programs, such as the Perinatal Information System (50), can be designed to run analyses and produce standardized tables, graphs and maps, which may enhance the use and reporting of data (Annex 7). Although the set-up of an automated system requires an initial investment, it will save time and money in the long run. Program maintenance and plans for updating source data and program codes should be integrated into the data management plan, as well as checks within the system to avoid erroneous data entry, where possible.

Indicator tallies over time are simple and quick to prepare, but more detail could be gained from geographically mapping key details related to specific indicators – for example, if a number of women presenting with obstructed labour come from a specific area, there may be a transport or other issue affecting access to the health-care facility. Mapping cases may be time-consuming but can provide more information about the population’s care-seeking behaviour, existing social and health services and the natural environment.

For each individual case, a death case review form with key details should be completed ahead of the meeting (see Annex 1: Stillbirth and Neonatal Death Case Review Form), by compiling data from multiple sources. While the form is concise, it should include all relevant information, both medical and non-medical, as well as some standard demographic data. Although it is more efficient for a designated individual or small group to complete the whole form – including the direct causes of death, related maternal conditions and modifiable factors – before the mortality audit meeting, these sections may also be discussed and completed during the meeting itself until the designated individuals are comfortable with completing the process independently.

The review team should remain open to considering all possible problems and factors revealed by the data. Different methods of classifying modifiable factors are detailed in Chapter 2 and Annex 4. The combined quantitative and qualitative analysis will allow identification of patterns and trends of problems, both non-medical and medical, that lead to deaths. The interpretation of and action in response to the results of the quantitative analysis – i.e. information about the most common problems contributing to stillbirths and neonatal deaths – will be the job of the health-care facility staff, management and local leaders who are members of the mortality audit committee.

Additional analyses that could be helpful include the approximate number of deliveries and deaths and their distribution by place of occurrence (home, health centre, public hospital, private hospital or other level/type of hospital). Where more detailed demographic
information exists, mapping the geographic location of towns and health-care facilities, as well as roads and rivers, may also provide valuable information on access and sociodemographic factors that may be related to the deaths.

**Step 4: Recommending solutions**

One of the most challenging parts of the review process is the formulation of appropriate recommendations, but this step is critical to the process. As data and trends are examined, patterns of problems will become evident. Moving from problems to solutions requires more effort and creativity but is an integral part of the process to prevent similar deaths in the future.

The type of solutions identified will depend on the individuals responsible for the investigation, the breadth of stakeholder involvement and the level of development and local resources. The recommendations may relate to a one-off action or an ongoing activity, and they may need to balance priorities based on the burden of various causes of mortality and the feasibility of implementing the various solutions. Review committees will be able to determine from the results of their own analyses which mixture of strategies will be best suited to their circumstances, including their access to resources. However, solutions should always be SMART: specific, measurable, appropriate, relevant and time-bound. The responsibility for tracking the progress of each solution should also be assigned to specific individuals. Even if the designated person is not solely responsible for making the change, assigning implementation and monitoring tasks to individuals reduces the likelihood of failure to follow through with action.

Mortality audit meetings where the basic overview of number of deaths is presented can take place as regularly as every morning. However, a larger periodic review meeting is necessary for detailed review of select cases. To institutionalize the system, a formal platform should be created to present the findings of the audit process. In larger facilities, this meeting may already be a mandatory event across departments. In other settings, attendance may vary by shift, department and discipline, but attendance should be encouraged.

At the mortality audit meeting, a skilled, independent and accepted chairperson is needed to guide the discussion. While the tendency is to designate a senior clinician as the chairperson, such as a doctor, it is important to consider nurses and midwives for the role, and to involve them in the process. Aggregated statistics and trends should be presented, with selected individual cases also presented anonymously and without bias. The presentation of cases may include as much information as available, from antenatal care through to the point of death. The facilitator may refer participants back to best practice guidelines, where available. A discussion should follow the presentation, reflecting on the modifiable factors of specific cases, and any changes in trends from meeting to meeting. The group should attempt to reach consensus on appropriate, evidence-based strategies required to address the main gaps in care that have come to light. At this stage, a framework to define what went well and what could have been done differently to provide better care in a no-blame environment can be helpful, along with minuted notes of recommendations, suggested actions and the person responsible for implementing and/or tracking each (see Annex 8 for guidance on taking minutes at mortality audit meetings and following up on action items).
Possible actions include interventions in the health-care facility, in peripheral or linked local health services and in the wider public sector, as well as in the community. Information from facility-based quality improvement approaches may point to the need for changes in clinical practice (direct patient care) or modification of service provision at the system level, such as how to provide the necessary drugs and trained personnel at a health-care facility or perhaps the need to establish clinical guidelines for care. Community-based approaches may point to the need for the development of health promotion and education programmes as well as possible changes in community service provision, changing home practices or improved infrastructure, such as roads, bridges and communication technology. These solutions are beyond the scope of the review committee to address, and necessitate links to a regional or national audit committee or higher-level authority, and community leaders. It is important for all of these elements to be included, especially in audit systems that extend beyond a single or regional grouping of health-care facilities. Nevertheless, audit findings and actions should also always include recommendations that are achievable at the point of care.

Dissemination of audit findings is important at multiple levels. The general principle around dissemination is to get the key messages to those who can implement the findings and make a real difference towards saving babies’ lives. Some examples include: ministries of health; local and regional planners and politicians; professional organizations; leaders in peripheral sectors such as education and social security; private sector health professionals and institutions; health promotion experts; academic institutions; and local health-care managers or supervisors not involved in the mortality audit committee. If a community liaison role exists, relevant findings for the community, particularly around the first delay in seeking care, should be shared in appropriate forums (see also Chapter 4). Health-care institutions may use radio stations, local newspapers and civil society organizations to share information with community members and elicit feedback (47).

A periodic report is one way to disseminate the findings and recommendations. The report should be written in clear, easy-to-follow language, and should include some standard sections such as data trends covering numbers of births and deaths, causes and modifiable factors, as well as recommendations and the solutions enacted. The report may be kept as an internal document, copied and distributed to all staff, or it could also be shared with all relevant stakeholders and concerned community members. While the report should be clear and straightforward about the potential for improving care, it should do so without placing blame. Positive vignettes – for example, the case of a near miss that was prevented because of a gap identified and addressed by the audit committee – can be presented alongside recommendations and progress towards solutions. These case studies are helpful narratives that communicate the findings of an audit in a very practical way. Another option is a short, less formal newsletter that could be drafted by delegated members of the audit committee following each meeting, to share in a non-threatening way the recommendations arising out of the meetings and the actions taken.

**Step 5: Implementing changes**

Taking action to prevent stillbirths and neonatal deaths is the reason for the entire audit cycle. A number of problems and potential actions are likely to be identified in almost any review. These can be separated into short-, medium- and long-term actions, with specific
time frames for each. It is also important that the responsibility for implementing and/or monitoring each recommendation arising from the mortality audit meeting is assigned to one or more team members. While recommendations based on modifiable factors that fall under the purview of administration may be acted on quickly within a responsive management structure (e.g., ambulance availability or lack of resuscitation equipment), it may be more effective to first focus on the modifiable causes that are within the control of health workers (e.g., detailed history taking and correct partograph use) and then use successes emerging from subsequent mortality audit meetings as an advocacy tool to prompt management to further action. In addition to following up on items that have not been completed, it is important to celebrate progress and identify successful changes when they occur.

Lessons learnt through experience with maternal mortality audits point to three interdependent factors contributing to recommendations resulting in successful solutions. These factors were (i) individual responsibility and sense of ownership; (ii) a proactive institutional ethos that promotes learning as a crucial part of improving services and quality of care; and (iii) a supportive political and policy environment at the national and/or local level (46, 51). In programmes where staff members were disinterested, uncooperative or even obstructive, failure and disenchantment followed. Disenfranchisement and thus failure to fully participate and engage with the recommended changes has been shown to arise from an environment lacking in professionalism and self-reflective learning, where there is a fear of blame and punishment, and disillusionment with a persistent lack of action on the recommendations made in earlier meetings or reports (3). If, on the other hand, the audit takes place in a forward-looking and safety conscious culture, long-lasting improvements can be made. Healthy hospitals that support their staff understand that errors are unintentional, and in these settings learning from adverse events is encouraged, and the leadership open and fair. The importance of leadership within the enabling environment is discussed in more detail in Chapter 5. Overarching conditions that lead to implementation of recommendations from audits include good leadership, task-oriented minutes (Annex 8), staff stability, good communication with academic departments and clinics, and the existence of guidelines and protocols (52). Similarly, conditions hindering implementation included poor communication between health workers and the community, frequent staff rotation, staff shortages, unresponsive management, inadequate financial resources, poor attendance at review meetings and an absence of skilled supervisors.

Experience from maternal death reviews indicates that a multifaceted approach is needed to translate recommendations into action. In the QUARITE trial (53, 54), which showed a substantial reduction in maternal mortality in low-resource facilities in Senegal and Mali, a bundle of three interventions was implemented:

- involving opinion leaders to champion the process, the findings and the actions for change in the local health-care facility;
- engaging a quality improvement committee that would conduct case reviews and determine whether recommendations are being acted on; and
- strengthening the capacity of health-care professionals, using drills and simulations.
Step 6: Evaluating and refining

The final step in the audit cycle involves looking back to evaluate what worked and what did not, and then refining and adapting the approach in order to move forward with an improved process. Evaluation goes back into the action cycle to examine how successful it was in identifying deaths, collecting, reviewing and analysing the information, and identifying the problems that contribute to stillbirths and neonatal deaths. In general, the purpose of evaluation is to ensure that the approach used is both efficient in the way it works and effective in instituting beneficial practices.

Documenting changes over time, through an annual review meeting or report as described above, helps to identify successful components and those still needing work. Once the process has begun, maintenance and supervision is critical. Systems that can provide real-time feedback linked to data showing long-term trends (e.g. reduction in the rate of intrapartum stillbirths over a five-year period, after introduction of better quality intrapartum care) can be motivating for users. A list of questions has been developed to help users assess and reflect on progress at each stage of implementation, from creating awareness of the need for a mortality auditing process to integrating it into routine practice; this is provided in Box 3.2 (47).

In addition to the ongoing evaluation of the process of acting on the recommended solutions, as well as monitoring indicators that provide a quick snapshot of whether the system and outcomes are improving, a more detailed periodic evaluation is useful, particularly if: (i) the indicators demonstrate that outcomes are not improving despite actions being taken; or (ii) mortality rates are not decreasing. While it is important to look at reductions in mortality rates, trends in these rates are not always the best illustration of improvements in care, because there are many factors that influence the in-facility mortality rate. Improvements in the community, in the health system or in society in general, and changes in the types of delays or modifiable factors that are being identified will prove insightful. A more detailed evaluation can also be used to assess whether the system can function more efficiently. Ideally, there should also be a periodic evaluation of the quality of the information captured, particularly if the system is not linked to an HMIS and CRVS.

A summary of these six steps is provided in Annex 9 as a quick reference.
Box 3.2. Questions for reflection on the implementation and maintenance of the audit system

- How can review meetings be improved and used more effectively?
- How often and to whom is feedback given?
- What are the gaps in our feedback procedures?
- How can the feedback to service providers and senior management in the facility be improved?
- How can engagement in the audit process, the use of the findings and the application of recommendations be improved?
- How can feedback outside the facility be improved, e.g. at district or provincial levels and in the community?
- How can involvement from each of these levels be improved?
- Who is responsible for keeping the audit system together, e.g. one person, a team, formally or informally designated?
- Who is leading the audit? Who takes responsibility when the leader is not there? What kind of succession plan do we have?
- How do staffing issues such as rotations and turnover influence the audit activities?
- If lacking, how can staff stability be improved?
- What is our facility’s responsibility in reaching out to another facility or facilities to introduce and establish an audit programme?

Source: Belizan et al., 2011 (47).
4 Auditing deaths that occur in the community

This chapter provides an overview of considerations for initiating a system for auditing stillbirths and neonatal deaths that occur in the community. Family and caregiver narratives within a traditional verbal and social autopsy interview can help identify social, behavioural and health system contributors, in addition to the biological causes of death, as a means of generating information about key delays and modifiable factors.
4.1 The importance of review and response to deaths in the community

In many countries, despite high average rates of antenatal care and increasing rates of facility-based delivery, even in resource-limited settings, many births still occur at home, without any contact with health-care facilities or providers. Therefore, many stillbirths and neonatal deaths also still occur at home. Many of these families will have had contact with a health-care facility or community health worker (CHW) during pregnancy and/or delivery. Identification and review of these stillbirths and neonatal deaths occurring in the community is needed to help complete the picture of why these deaths are occurring and how they can be prevented. Identification and analysis of these deaths requires the facility-based and district-level mortality audit committee and the community to be accountable to each other for sharing information and enacting changes.

Factors contributing to stillbirths and neonatal deaths in the community may be different from those contributing to facility-based deaths and may not be identified by the facility-based mortality audit process. For example, reviews of deaths occurring in the community may identify barriers to care that may not have been faced by individuals who were able to reach and receive care at health-care facilities.

Many stillbirths and neonatal deaths can be attributed, at least in part, to factors that occur in the community, such as poverty and poor access to services, poor social and nutritional status of girls and women, harmful practices around pregnancy and childbirth, and perceptions about and use of health services. Yet everyone in the community wants healthy children. Thus, whatever approach is used, it is important that the people whose lives will be affected by the findings of the review process feel that their voices will be heard when solutions are being developed.

The process of setting up a system for identifying, reviewing and responding to stillbirths and neonatal deaths at the community level is also intrinsically valuable for the connections it fosters among stakeholders in the community, at health-care facilities and within the public health infrastructure.

4.2 Setting up the system

There are two primary additional roles that must be competently filled when setting up a process for community mortality audits, including designated community-based “identifier-reporters” and reviewers. In addition, a mechanism for transmission of information must be in place. These three key components of the system for auditing deaths that occur in the community are discussed below.

Identifier-reporters

Identifier-reporters are those who will be informed of or able to identify stillbirths and neonatal deaths in the community as soon as they occur and then promptly relay information about them to the health system. These could include CHWs (who may be volunteers or salaried workers), community or village leaders, community representatives appointed or elected specifically for this purpose, or individuals employed by another existing initiative.
(e.g. individuals who conduct routine home visits during pregnancy and the postnatal period). To facilitate their role as reporters, in order to effectively relay the information, they should be formally connected to the health system through a primary health centre, hospital or district office.

Where a public health system already has a network of CHWs in place, it may be effective to train them to take on the identifier-reporter role. Many countries, however, do not have unified networks of CHWs with sufficient coverage. Alternatively, identification/notification programmes could be run through district or sub-district networks of identifier-reporters to capture stillbirths and neonatal deaths in smaller areas. For example, in Cameroon, several programmes have worked with village mothers’ associations or women’s associations to assist community-level identification of programme-related outcomes.

It may be possible in some settings to integrate the reporting of stillbirths and neonatal deaths within other existing public health surveillance efforts. Community-based maternal death surveillance and response (MDSR) and integrated disease surveillance and response systems may provide platforms for expansion to include perinatal deaths. In Indonesia, for example, a training programme for professional midwives to be deployed in villages facilitated the initiation of community-based perinatal death review (55).

Other public health programmes, including those outside maternal, newborn and child health, may also provide these opportunities. For example, if a region has an ongoing polio vaccination campaign to target remote communities, it may be possible to train the community-based volunteers or campaign staff to identify stillbirths and neonatal deaths in these communities and notify the health system of their occurrence. For example, the “Reaching Every District” (RED) strategy was undertaken by a group of immunization-targeting partners of WHO in 2002 to improve surveillance by re-establishing outreach services to communities in both urban and rural areas (56).

A variety of reporting mechanisms can be designed to successfully relay information from community-based identifier-reporters to the public health system, as discussed in the section on transmission of information, below.

**Reviewers**

Reviewers are community representatives who participate in perinatal mortality audits. The composition and roles of the membership of facility-based or national-level steering committees for these audits are described in Annex 5. There are a few additional considerations that are particularly important to the community, including representation, communication and advocacy.

The first consideration in the selection of reviewers of stillbirths and neonatal deaths in the community is that of representation of the community perspective on these deaths. Including a member of the community in the facility-based review committee may help gather more complete information from the community’s perspective on what led to each stillbirth or neonatal death. For example, a CHW participating in a review may be able to contribute information on why a family did not seek care earlier or why transportation may have been delayed.
The second consideration is that of communication with the community. Including someone with the capacity to provide feedback on the findings of the perinatal death review to the community has the potential to build trust between the public health system and the community, and increase the likelihood of successful completion of community-based interventions designed in response to review findings. Care must be taken to select an appropriate person for this critical role, as the relationship between the community and the public health system may be jeopardized if communication is not done well. For example, an unskilled communicator may assign blame to particular individuals who provided care for a terminal illness or health problem during pregnancy or childbirth; this could have serious consequences for both the individual’s safety in the short term and trust between the community and the health system in the long term.

The third consideration is that of ensuring advocacy on behalf of the community. The inclusion of community representatives with decision-making power in the reviews could increase the likelihood of appropriate community-based interventions being implemented to prevent future perinatal deaths, and of community members supporting any proposed community-based interventions.

**Transmission of information**

The last consideration in getting started with a community-based perinatal death review process is to set up a mechanism for the transmission of information.

A very important consideration is how community-based identifier-reporters will notify the health system of a stillbirth or neonatal death that has occurred. There are two major ways to structure this transmission of information from the community: (i) report directly to a specific health-care facility (also known as reporting “in series”) or (ii) report to the lowest level of the public health administration, such as the county, district, sub-district or parish health office (also known as reporting “in parallel”).

Community reporting through local health-care facilities, or reporting in series, has multiple potential advantages:

- Setting up infrastructure for community-based reporting through health-care facilities has clear potential to improve the frequency and quality of communication between health-care facilities and the communities they serve.
- Reporting “in series” has the potential to decrease the chance of duplicate reporting of a particular perinatal death.
- Centralizing the review of stillbirths and neonatal deaths to include both facility- and community-based deaths allows the formulation of recommendations and interventions that address modifiable factors in both facilities and communities.

Community reporting through local health-care facilities may not be feasible if the local health-care facility does not have a functional mortality audit committee in place. Similarly, it may not be advisable if the community of interest does not have realistic access to quality facility-based care, if the relationship between a community and its health-care facility is so poor as to disincentivize reporting, or if the public health leadership prefers communities to report directly to district health offices or other local public health infrastructure.
The most effective mechanism for information flow may partially depend on the way in which death reporting from the community is envisioned to take place by the ministry of health, and the availability of any existing systems for reporting from the community. For example, death identification and notification via mobile technology has the potential to improve rates of timely reporting from the community, and may be better suited to reporting “in parallel” to district health offices if no specific individual(s) can be identified at the health-care facility level to receive these reports or if a data capture system already exists at the district health office.

4.3 The six-step mortality audit cycle from the community perspective

Once identifier-reporters, reviewers and the mechanism for information transmission have been selected and established, the process of a mortality audit that includes deaths that occur in the community can begin. The remainder of this chapter will consider the same six steps of the perinatal death audit cycle, as described in Chapter 3, but from the perspective of the community.

Step 1: Identifying cases for review

There are three sub-steps within the process of identifying cases for review: (1) ensuring a strong mechanism for identification of all deaths; (2) ensuring a strong mechanism for notification and reporting of all deaths; and (3) selecting cases to review from among all occurring cases.

Step 1.1: Identification of all deaths

Cases may be identified by community-based identifier-reporters through varied means of active surveillance. They should aim to capture all stillbirths and neonatal deaths in their communities, regardless of where the deaths and care prior to death occurred. Box 4.1 describes the “Saving Mothers, Giving Life” project to reduce maternal and newborn mortality through community involvement in mortality surveillance and response, as implemented in Uganda.

Community-based identifier-reporters can make use of several sources of information about the occurrence of stillbirths and neonatal deaths. In small communities, rumours and word-of-mouth communication at small community social gatherings may be a good source of information. Household visits, whether done through perinatal death review or another programme (such as routine home visits for pregnancy and newborn care), may be a much more complete source of information about pregnancies and their outcomes, including stillbirths and neonatal deaths. Questions about recent stillbirths and neonatal deaths can be added to any existing standard sets of questions for volunteers or CHWs employed by partner programmes, with appropriate training. Lastly, demographic surveillance sites are likely to be a more complete source of information about stillbirths and neonatal deaths, although such surveillance systems are not common worldwide.

Once a stillbirth or neonatal death has been identified, the community-based identifier-reporter should transmit the information they have about this death to a pre-designated
focal point either at the local health-care facility, the district health office or other local public health body, in accordance with the agreed mechanism for information transmission (see “Transmission of information” in section 4.2 above, and Step 1.2 below).

Only after all deaths are captured will the committee be able to make a representative selection of deaths to be reviewed (see Step 1.3).

**Box 4.1. Case study in identification: Saving Mothers, Giving Life in Uganda**

Uganda was one of two countries selected for a pilot project – Saving Mothers, Giving Life (SMGL) – to rapidly reduce maternal and neonatal deaths through community- and facility-based interventions. The SMGL model employs a comprehensive approach that builds on existing district health systems and implements evidence-based practices to improve maternal and perinatal survival.

Through the SMGL initiative, over 4000 village health teams (government cadres of mostly volunteer CHWs) were trained, one team for each 100–300 households, to identify any deaths of women of reproductive age and neonatal deaths through routine monthly monitoring visits. Currently, about 3800 village health teams continue to report monthly the number of deaths among women of reproductive age and newborns identified in the previous 30 days. Their reports are compiled and submitted to sub-district health coordinators. Approximately six to eight weeks after a death report, the household is visited by a team trained in verbal autopsy (VA) procedures. Complete VAs are used to identify causes of neonatal death and contributing factors, thus obtaining information critical to designing interventions to prevent future deaths.

**Improving the system: lessons learnt**

In establishing a district-level maternal and neonatal death surveillance system in Uganda, partners learnt that:

- **Identification of maternal and neonatal deaths is enhanced through continuous cross-checking of deaths between facilities and communities.**

- **Continuous supervision and quality assurance of the SMGL maternal and neonatal mortality surveillance system needs to be carefully planned, implemented and maintained.** This includes clear case definitions, periodic reminders on both the importance of and the process for reporting, accountability, monitoring results, information sharing and linkages with action.

- **Real-time data on maternal and neonatal deaths in communities were used at village health team meetings to advocate for increasing prevention and community mobilization activities.** The leadership of Kibaale district allocated resources for building a bridge that helped connect several communities with high mortality rates to the main road and thus improved access to emergency obstetric care.

The Ministry of Health is planning to scale up the MDSR and neonatal death surveillance and response from the four districts where SMGL was implemented to other, non-SMGL districts. The Uganda adaptation of the WHO maternal death surveillance and response (MDSR) guidance (I) was launched in September 2015. It is based on the experience in the SMGL-supported districts and includes the tools, standard operation procedures and monitoring processes developed and refined by the project. The verbal and social autopsy tool used for gathering information about perinatal deaths is included in Annex 10.

Source: MDSR Action Network, 2016 (57).
Step 1.2: Notification and reporting of deaths

Deaths may be reported through mobile networks, paper forms or oral reports. The choice of method depends on what will best facilitate the reliable transmission of information from identifier-reporters to the public health system in the local context.

The information initially captured about a death in the community may be different from the information initially captured about a death in a health-care facility. For deaths in health-care facilities, the aim is to capture all information contained within the minimum set of perinatal indicators (Annex 3). For deaths in communities, in contrast, the main goal is just to notify the health system of the death itself by reporting it through appropriate channels (as selected when designing the mechanism for transmission of information: see section 4.2: Setting up the system). The specific information to be initially collected in the case of deaths in the community must be tailored to the level of education of the identifier-reporters, and will likely need to be minimized in order to encourage expedient transmission of information about the death.

Box 4.2 presents a case study from South Kalimantan, Indonesia.

Box 4.2. Case study in notification and reporting: Safe motherhood in South Kalimantan

In 1995, the Indonesian Ministry of Health introduced additional safe motherhood services in three rural districts of South Kalimantan, which included initiation and support of maternal and perinatal death review processes. Village midwives were deployed to live in communities and were responsible for identifying and reporting all maternal and perinatal deaths in each community to the health centre. Midwives learned about these deaths either through their role in caring for the women before the deaths occurred, or because they had received reports from village leaders or traditional birth attendants.

Following a post-mortem interview, and follow-up investigation to document any health services the woman or baby received before their death, the village midwife assigns a cause of death and reports it directly to a health centre, where a senior midwife or doctor checks that the information collected is complete and consistent, and verifies the accuracy of the cause of death. All interview forms and data collected are sent to the district health office.

Source: Supratikto et al., 2002 (55).

Step 1.3: Selecting cases for review

Once all identified cases have been reported, the information about those cases can be compiled at the facility level for analysis and review, then either all cases or a selection of cases can be prepared for presentation and discussion at a multidisciplinary review meeting.

To ensure time for adequate review, and given the unfortunately high numbers of perinatal deaths in many environments, it is often necessary to select a small number of cases.
There are several strategies available for case selection. One strategy is to select those deaths with the most information available for discussion since, by extension, these cases are most likely to yield fruitful discussions. A study of community neonatal death audits in Uttar Pradesh, India, for example, defined selection criteria for deaths to include, among others, the occurrence of the death within the past year and the willingness of the family of the deceased newborn to discuss the circumstances leading up to death (58). Another strategy is to select a representative “case mix” of perinatal deaths (13). In the safe motherhood project in Indonesia, for example, cases are selected on the basis of the nature of the problems identified and the frequency with which the medical causes of death occur (55).

**Step 2: Collecting information**

It is particularly important in communities to ensure that sufficient data are collected to contribute to a meaningful understanding of deaths. This may be challenging because, in the context of the community, programmes must often rely exclusively on lay people as both the sources and the collectors of information. Successful collection of information will pave the way for effective perinatal death review and formulation of solutions. Four key considerations are discussed here.

(i) *From whom should the information be collected?*

If the death occurred in the community without any contact with a health-care facility, then the family and any non-facility-based care providers will be the only sources of information. If the death occurred in a facility or after contact with a facility, these facility-based data should also be collected, as described in Chapter 3.

It is also important to bear in mind who will be willing and able to provide the best information. If the mother of the deceased is still living, she is likely to be the source of the most comprehensive information. If the mother is also deceased, consider those who lived with the mother (e.g. her spouse, her mother, her sisters, other wives if applicable) at the time surrounding the perinatal death. If possible and applicable, information should also be obtained from those who provided care to the mother and baby during pregnancy, labour and/or delivery.

Non-facility-based care providers may include trained midwives, lay midwives, doulas, traditional healers and relatives. They can also provide extremely important information and should be included in the data collection process whenever possible.

(ii) *Who should collect the information?*

It may be that the initial identifier-reporter of the death will be the same person assigned to collect further information about the death when the family and/or care providers are available for interview. In some cases, however, there may be reasons to assign different people to collect this information.
It may be easier for an information collector/interviewer from outside the community than for community-based reporters to obtain sensitive information. Although CHWs living in the community may be the most reliable source of information on the occurrence of any death in their community, they may not be able to obtain the most reliable information about factors that may have contributed to that death if family members are hesitant to share information about stigmatized topics with members of their own community. Additionally, if the identifier-reporter was involved in the woman’s care, their presence during more detailed data collection could bias the responses from the woman or her family. Non-medical interviewers may be preferred.

It may also be more practical to designate separate information collectors/interviewers. The most frequent method of information collection about community-based deaths is through verbal autopsy (VA), discussed below. VA requires training, and the quality of information gained may improve with practice. Therefore, it may be ideal to have a large cadre of community-based death identifier-reporters and a smaller, more intensively trained and practised cadre of VA interviewers.

(iii) What information should be collected?

VA provides a thorough, structured way to collect valuable information about stillbirths and neonatal deaths that can be used in the context of a review of a specific perinatal death to identify causes of death and contributing factors, and to provide data that will help to develop strategies to prevent future deaths.

VA is a structured interview using a questionnaire administered to caregivers or family members of the deceased (often the mother, in the case of stillbirths and neonatal deaths) at or near the time of death to elicit information about signs and symptoms and their durations, as well as other pertinent information about the period before the death (Annex 10). The VA also usually includes a social autopsy which explores the social, cultural, behavioural and health systems issues that may have contributed to the death.

Annex 10 of this guide includes a verbal and social autopsy questionnaire from a community-based surveillance project that can be used to conduct interviews specifically related to stillbirths and neonatal deaths. When more contextual factors are needed to examine circumstances surrounding the time of death, social autopsy is a useful tool. The verbal and social autopsy tool included in this guidance contains elements of both verbal and social autopsy, including questions about the health status of the mother, details about her labour and delivery, a structured symptom and duration checklist, an open narrative section and detailed information about the three delays, which are described in section 2.5.

The purpose of VA is to identify the causes and contributing factors for the stillbirth or neonatal death in the community where no higher-quality data sources or more definitive diagnostics exist. VA can provide information to help perinatal mortality audit committees identify factors contributing to stillbirths and neonatal deaths in the community. VA may also be used for deaths that occurred in facilities, when additional information from caregivers needs to be included in the review.
(iv) When should information be collected via verbal and/or social autopsy?

The period of time passing between the death and the verbal and social autopsy is known as the “recall period”. The goal is to select a recall period that will be long enough to allow adequate mourning, but not so long that a respondent’s ability to recollect and report relevant information will be impaired. A systematic review by WHO of VA practices internationally found a wide range of recall periods, with some programmes performing interviews “as soon as possible” and others waiting for a “minimum of four weeks” to allow an adequate mourning period, while the maximum recall period ranged from “six months to an indefinite amount of time” (59). A recall period of 1 to 12 months is generally considered acceptable, and a validation study of adult deaths demonstrated no significant effect on sensitivity or specificity using differences in length of recall period of 1 to 21 months (60), though accurate recall periods for adult and perinatal deaths may differ. Generally, shorter recall periods are preferable, and recall after periods of more than 1 year should be interpreted with caution (61). The goal is to achieve timely reviews in order to inform recommendations and interventions to prevent future perinatal deaths; therefore, we recommend performing verbal and social autopsy as soon after the death as is culturally acceptable.

Step 3: Analysing information

Community stillbirths and neonatal deaths can be included in perinatal death reviews at the facility level, at dedicated community-level review meetings, at district level meetings or through a combination of all three. Community representation at perinatal mortality audit meetings is discussed under “Reviewers” in section 4.2: Setting up the system. During review of cases of perinatal deaths that occurred in the community, the audit team can use verbal and social autopsy results to assign a probable cause of death using standardized international certification and coding methods, and to identify any delays in receiving care that contributed to the death. This information can then be added to the compiled list of all deaths, as discussed in Chapter 3.

At the facility level, district level and higher, numbers of stillbirths and neonatal deaths in the community can be added to those identified in facilities. These summary statistics can be compared with expected numbers of stillbirths and neonatal deaths to evaluate the completeness of data and provide the basis for recommendations even if each death is not individually reviewed. The suggested minimum list of data elements that should be compiled to form these summary statistics is included in Annex 3.

In addition to the standard analyses applied to all deaths, there are several analyses that may be particularly helpful or revealing when applied to deaths that occurred in the community. Trends over time can help identify where seasonality is occurring within deaths at the community level, and whether or not such seasonal trends are observed at the facility level. This may help characterize the impact of malaria, for example, in an area undergoing changes in mosquito control. Time-related trends may also be extremely valuable at the single-day level; a preponderance of deaths at night, for example, may provoke a discussion of whether barriers to seeking or receiving care are greater at night, and how those barriers might be mitigated.
Geospatial analyses may be very beneficial at the community level. Geolocalization of deaths in the community may visually highlight areas without adequate access to care, or may help characterize particular transportation barriers.

**Step 4: Recommending solutions**

Recommending realistic solutions to reduce deaths in the community is challenging. The characteristics of high-quality recommendations are covered in Chapter 3, but there are at least two aspects of recommending solutions that are worth addressing with particular ramifications for the community: capacity and communication.

**(i) Capacity to implement a recommendation**

This is an extremely important consideration when formulating a recommendation that impacts the community. If a recommendation is formulated in collaboration with community leaders and in partnership with community members empowered to make the recommended change, it can be powerful and effective. In contrast, however, if recommendations that the community has no ability to enact are “handed down” to the community from a perinatal mortality audit committee, they can cause distrust between the community members and the health system.

**(ii) Communication with the community**

This is also of highest priority. Results and recommendations of perinatal mortality audits must be disseminated in a way that communicates information effectively, sensitively and via a medium that is accessible to all community members. Perhaps most important is the principle of community-based dissemination: when communities of lay people are left out of the plans for information dissemination, this represents a lost opportunity for enhancing relationships and building capacity for positive change within the community.

Effective communication with the community can be enhanced early on in the process through the selection of appropriate community representatives to participate in the perinatal mortality audit committees. Communication and capacity can both be enhanced by early involvement of community leaders, especially in formulating recommendations. Lastly, communication is enhanced by using forms of media favored by the community, which may include radio, television, theatre and murals, in addition to written materials.

**Steps 5 and 6: Implementing changes, evaluating and refining**

Intentional, consistent involvement of the community in perinatal death audit can help reduce perinatal deaths at both facility and community levels. Recommended solutions are most likely to be implemented successfully when a community participates in perinatal death review and in formulating the solutions, when the solutions are within the community’s capacity to enact, and when the process is undertaken in an environment of consistent, strong communication between the community and the local health-care facility.

Creating a mechanism of public accountability for implementing recommendations can be a trust-building, empowering aspect of communication and can contribute to participatory evaluation of changes, involving the community. For example, a perinatal death
A community-level “Social Audit for Community Action” was conducted in rural Uttar Pradesh, India (13). Community members from 152 villages were asked to recall the causes of deaths among children under 5 years of age in the prior year and identify preventive measures that could have been taken by the family or community. Intrapartum-related events accounted for 13.5% of neonatal deaths. Delay in recognizing the seriousness of the problem and arranging for transport and funds were identified as major contributors to neonatal deaths and were targeted for behaviour change by the community mobilizers. Another study to examine the feasibility of community audit was undertaken in Shivgarh, Uttar Pradesh, and involved in-depth interviews with family members of deceased neonates, and focus group discussions with family and community members. Both approaches involved the community in identifying modifiable factors in each death and discussing solutions, and the presence of an educated/experienced community member or health worker served as a catalyst (13). Community neonatal death audit was found to be acceptable and feasible.

In South Africa, a dynamic “Partnership Defined Quality” process was applied to address surging neonatal and infant mortality rates in a peri-urban township in Durban. Unique to quality improvement efforts, the process fostered active partnerships between healthcare providers and community members through dialogue, planning and collective action by learning from what went wrong and lessons emerging from the facility-based mortality review at the local hospital and health centres. Documented improvements in the quality of care resulted in increased trust from the community and demand for maternal and newborn services (62).
Simply holding meetings and discussing deaths does not necessarily enable change or improve quality of care. Leadership and supervision within a supportive environment are essential to ensure the completion of the audit cycle. This chapter describes legal and supervisory considerations and educational models that help provide opportunities for positive change.
5.1 Creating an enabling environment to effect change

Evidence from countries that have functional mortality audit systems for maternal deaths, stillbirths and neonatal deaths shows the importance of an enabling environment for implementation of change at all levels. Change is undertaken by individuals doing the right thing at the right time. How does this change occur?

Interventions are not implemented in a vacuum; individuals must be held accountable with appropriate follow-up, and change agents are needed to lead the way. At the national level, support from senior managers in the ministry of health is essential. As individuals within facilities or through a formal stewardship body at national level, leaders have the ability to create a culture of accountability at all levels. This should involve correction but also celebration, affirmation, encouragement and reward (47). Supportive administrators and health professionals can make all the difference between success and failure (3).

In practical terms, one way of creating this environment at the national level is by linking mortality audit for stillbirths and neonatal deaths to maternal audit where MDSR is being implemented, in concert with national health goals and mortality reduction targets. A national implementation plan may be guided by a working group at the ministry of health, with involvement of other key experts. Understanding the linkages and interactions between ministries and their partners is critical to the development of multisectoral programme coordination and implementation. Under the guidance of the ministry of health, the roles and responsibilities of various departments, ministries, professional associations, the private sector and other relevant partners should be identified. The active involvement of professional associations (e.g. neonatologists, obstetricians, paediatricians, midwives and nurses) is critical, as is the participation of other stakeholders (e.g. hospital administrators, social scientists, epidemiologists, information system specialists, health planners, monitoring and evaluation personnel, civil society representatives).

5.2 Legal and ethical issues

Legal protection

To ensure that a mortality audit is initiated in a safe environment for open discussion among staff, it is important to consider the legal and ethical issues that come into play when investigating stillbirths and neonatal deaths. The laws and customs of a particular country or culture can have a significant impact in terms of facilitating or hindering access to information, the involvement of families and health professionals, the conduct of the review, and the ways the findings are used. In some countries with a high level of malpractice litigation, fear of lawsuits has limited data collection and the use of mortality audit processes.

While the principles of mortality auditing may be standard across settings, legal aspects can vary from one country to another. In addition to having participants agree to and sign a code of practice before each review meeting (Annex 6), it may be beneficial to have administrators seek local legal counsel early in the process of establishing a mortality audit committee and process, to ensure the protection of staff and patients throughout the process. If a supportive health policy framework already exists for maternal death review, this
will help facilitate the process for stillbirth and neonatal mortality auditing also. It is essential that there are separate processes for handling legal misconduct and professional discipline that are independent of the mortality audit process.

**Access to information**

Local mortality audit committee members will usually be the only people in the review process who know the names of the mother and baby and the health workers involved in the case. Names may be on the initial report forms to help identify and locate cases and to avoid duplication; however, they should be replaced by case numbers as soon as possible, to protect confidentiality of the patient and staff involved. The minutes of the meetings should be kept in such a way that there can be no linkage to actions taken related to specific individuals or cases. This is the responsibility of the local data collectors or review coordinator. In addition, any possibly identifying information should be removed from all records, notes and reports before they are sent to any other individuals or groups for further review or completion. Staff must maintain confidentiality and ensure that all materials are kept in a secure locked space when not in use.

**Use of the results**

The goal of both the approaches presented in this guide is to identify why stillbirths and neonatal deaths occur, so that changes can be made to prevent similar events in the future and reduce mortality rates. The purpose is not to cast blame. In fact, once the data are collected, it is not even necessary to know the identities of the patients or practitioners. Mortality audits for stillbirths and neonatal deaths should not be used to blame or punish individuals, groups or institutions. They are not designed to discipline providers or review their qualifications. Reviews that are carried out in a manner seeking to attribute blame for an adverse event are unlikely to get the willing cooperation of health-care providers. Health workers do need to be accountable for their actions. However, accountability can be encouraged by carrying out any of the approaches in a way that seeks to improve care by educating both the health-care providers and the community. Occasionally it will be necessary for appropriate persons (e.g. supervisors, licensing boards, general medical councils) to take action against health-care providers who are persistently negligent, despite efforts to encourage and train them. However, a process that reviews the factors leading to stillbirths and neonatal deaths necessitates legal protection and should be separate from any disciplinary processes.

**Ethical considerations**

Privacy is an ethical consideration that is important for both families and health workers. The baby’s family has the right to privacy, although it may frequently be impossible to investigate a stillbirth or neonatal death and maintain complete privacy. Families and health workers need to be assured that, as much as possible, their privacy will be maintained. The identities of the babies whose deaths are being investigated, their families and the health-care providers involved in their care should be kept confidential, known only to those doing the actual investigation. Data collection forms, case summaries, review meeting minutes and any reports or other dissemination of results should contain no personal identifiers.
In addition, review committee members should be instructed not to disclose any confidential information about cases (including names of family or medical or other staff involved, or any details of the discussions or findings of the review process) outside the review group. Ideally, anyone with access to any information that contains personal identifiers should sign a confidentiality agreement, stating that they will not disclose this information. All records of the cases reviewed and any discussion should be kept secure; hard copies of information should be kept in locked cabinets/offices, and electronic data kept in password-protected files. In some types of review, such as confidential enquiries, complete anonymity is the rule. However, in others, such as facility- and community-based case reviews, the identity of both the deceased and the health workers involved in the care are typically known, though care is taken to remove identifying markers in the notes as soon as possible.

5.3 Developing and disseminating policy and guidelines

A clear, supportive policy has been one of the prerequisites for success in maternal mortality audit (46, 51). In some cases this has also involved an enabling legal framework, which may need to be in place before the process begins. Any fear of participation in such audits can be removed by affording legal protection for assisting in such enquiries while ensuring cases of gross malpractice will continue to be dealt with by the existing legal procedures. National guidelines for how to set up an audit committee and conduct meetings, clear guidance on information transmission, and standardized tools are also helpful. Clear norms and practice standards for each level of the health system may facilitate a more objective assessment of modifiable factors associated with each death (38, 63). These will require periodic review and updating as new evidence emerges, as with the national clinical guidelines. This process can be led by the national steering committee with ministry of health guidance.

National guidelines for stillbirth and neonatal death mortality audit may mandate that particular staff members are designated at various levels to oversee the system and that the associated tasks and responsibilities are included in their job descriptions. In settings where midwives provide the majority of care at birth and during the postnatal period, the system should be developed in such a way that midwives can complete the process from start to finish and provide leadership at all levels. If resources permit, an outreach person or regional coordinator who is familiar with the tools and meeting structure can serve as a liaison between clinical staff, senior management and district decision-makers. This person can be a valuable resource, especially in ensuring that recommendations result in actions that are followed up. This system has been one of the key drivers of institutionalization and successful outcomes in South Africa (41, 47).

5.4 Staff training, ongoing supervision and leadership

District health staff, administrative staff, health workers and other relevant stakeholders require training specific to their role in the audit process and the level of implementation of the audit system. This training may be conducted by the ministry of health or through professional associations. In Uganda, both the Association of Gynaecologists and Obstetricians and the Uganda Paediatric Association have been involved in training on the national
Maternal and Perinatal Death Review Guidelines (48). In South Africa, a PPIP coordinator appointed by the national Medical Research Council oversees all provincial training with a colleague and provides ongoing follow-up such as ensuring that the facilities send their data to the central database (41). Yearly provincial workshops are held to show the staff at health-care facilities how to install the audit software program, enter data and fill in the data collection tools, perform data validity checks and do basic analyses of common indicators.

Experience has shown that it is important to explain at the outset to those involved at each level of the review process why specific pieces of information need to be collected and for what purposes, so that data are collected for a reason and not for their own sake. Training should also include an overview of a death review meeting, and guidance on appropriate conduct, including confidentiality. If time allows, the training may also include continuing medical education on management of common maternal and perinatal conditions.

Frequent staff rotation of nurse-midwives in maternity and newborn units can have an impact on service delivery, and can be detrimental to the success of the mortality audit process. A key enabling factor is to create, recognize and reward core leadership skills among experienced midwives, nurses, clinical officers, anaesthetists and medical staff who represent the institutional memory and continuity as well as relevant clinical knowledge and skills. These individuals would be the key leaders on the mortality audit steering committee, responsible for orienting new staff, providing guidance in clinical areas for less experienced staff and able to feed in most effectively to audit discussions because of their experience and credibility within the institution. It is important to remember that leaders may or may not be managers, and they are most likely to be role models for effective teamwork for the rest of the staff. The success of an audit process depends on these individuals to build teams and implement solutions rather than assign blame.
To facilitate wide-reaching change and promote accountability at all levels of the system, it is important for policy-makers to seize opportunities to create a standardized national mortality audit system. This chapter describes the creation of a mortality audit infrastructure and systems that link to existing data architecture and policy response beyond individual health-care facilities.
6.1 Moving from single facilities to regional and national levels

Once local systems for comprehensive and systematic review of stillbirths and neonatal deaths have been institutionalized as routine practice with documented changes in practice and quality of care, other facilities, districts or health regions within a country may take note and explore the feasibility of adopting a similar approach. With some additional resources to coordinate this standardized system, data can be centrally collated, tracked and disseminated.

A larger number of deaths enables a more detailed analysis to be undertaken with a broader population base, potentially enabling triangulation with other data sources such as CRVS and the HMIS. In some cases, a central (national-level) committee may just gather data from facility-based reviews and report broad trends, but in other cases a separate review process might also be put in place at a district or regional (subnational) level. One benefit of a regional-level review is that the forms can be made anonymous, and assessors from other facilities can review cases, providing an independent opinion and recommendations. At this level, general lessons may also be derived which reveal systemic bottlenecks and thus highlight a path towards broader changes. For example, the results may point to the need for regional review of pre-service training procedures or transport systems.

If a decision is made to undertake a national audit programme with leadership from the central level, there are a number of factors to be considered in a phased approach (5), including:

• **Who leads?** Will coordination take place at the national level or through regional committees, or both? Will it be governed by the ministry of health exclusively, associations of health professionals or a multistakeholder group that includes partners, civil society, community representatives, etc.?

• **Where are deaths identified?** Does the system cover just public-sector health-care facilities or all facilities? Are deaths that occur in the community included? If so, how is information gathered about those deaths? How does the mortality audit system feed into or get information from the HMIS and/or CRVS?

• **What is the scope of implementation?** Do single facilities conduct reviews on their own, or are they done within practice groupings or districts, or both? Is implementation mandated or voluntary?

• **What is the depth and breadth of the review process?** Does the committee review a selected sample of cases, all deaths or all deaths and near misses? How does the committee decide which cases to review and how often?

Figure 6.1 illustrates the dimensions of this phased introduction of mortality audits from single facilities to the national level.

Experiences from high-income countries such as Australia (64, 65), New Zealand (66), the Netherlands (67–69) and the United Kingdom have shown the potential for sustained, widespread implementation when there is high-level national leadership. Where local drivers exist without an overarching national or regional coordinating body, national systems can still arise from the ground up, as seen in South Africa (13, 41).
Even if the ministry of health leads the national review process, a multistakeholder committee should be established, including representatives of health professional associations, communities, various departments and facility management, as well as the district medical office and community liaison, if applicable (see Annex 5 for a more detailed list of potential participants). This structure can be similar to the local level, with broad representation across disciplines but with more capacity for programme management and system-wide change (43).

While a standardized national mortality audit system for stillbirths and neonatal deaths may be a goal, the final structure and scope of any mortality audit system will differ in facilities and regions according to the local context and challenges. Implementation strategies should, therefore, be adaptable and easily customized even within countries. This chapter addresses some of the key ingredients of a national perinatal mortality audit system.

**FIGURE 6.1. Dimensions of a phased introduction of mortality audits for stillbirths and neonatal deaths**

<table>
<thead>
<tr>
<th>Place of deaths identified</th>
<th>Single facilities</th>
<th>Districts or groups of facilities</th>
<th>National coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scope of review process</strong></td>
<td>Tertiary facilities</td>
<td>All government facilities</td>
<td>All facilities</td>
</tr>
<tr>
<td>Sample of deaths, e.g. intrapartum only</td>
<td>All deaths</td>
<td>All deaths and near-misses</td>
<td></td>
</tr>
<tr>
<td>All government facilities</td>
<td>All facilities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All facilities and communities</td>
<td>All facilities and communities</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Source: adapted from WHO, 2013 (1).*
6.2 Collating data and linking to existing information infrastructure

A data flow algorithm may be useful for assigning responsibility to named people along the path of data collection (see Figure 6.2). This brings the vital step of accountability into the process. Different individuals may be involved depending on the size of the facility, the capacity for electronic data collection and the level of integration with existing information systems. The staff responsible for each stage could be physicians, midwives or data clerks, but there should be clearly designated individuals trained on the system, with the mortality audit coordinator or steering committee overseeing the process, including integration with CRVS and the HMIS.

Reports emerging from single-facility mortality audit committees can be collated and linked to other outputs. A multi-facility review report may have broader audiences: all the facilities involved in the review, other facilities in the area (public and private), various decision-makers, insurance companies and teaching institutions, as well as national authorities and the public. A national confidential enquiry will produce a comprehensive report that is widely distributed to all its stakeholders, including being available to the public. The frequency of publication of these reports will depend on the number of cases reviewed and the willingness of stakeholders to write, edit and publish findings. However, remedial action does not need to wait for the report to be published. Sometimes the findings of a single case review can reveal a significant problem that needs to be addressed immediately. The frequency and importance of other problems may only become apparent after the information from the qualitative review is quantitatively analysed.

The ENAP Measurement Improvement Roadmap (2015–2020) has outlined tools to be developed and has created an opportunity to embed improved newborn data and tools into national health systems through World Health Assembly (WHA) commitments to improve the use of key newborn data in countries (18). Progress in meeting milestones is reviewed annually at the WHA – the establishment of this annual reporting obligation has supported a transparent accountability mechanism with a specific focus on the use of newborn data. Mortality audit, in addition to improved birth and death registration, promoting a minimum set of perinatal indicators to be collected, and actions to test, validate and institutionalize proposed coverage indicators, is a key component of this improvement agenda. The roadmap presents a unique opportunity to strengthen routine HMISs, linking these data with CRVS and population-based surveys (9).
Fig. 6.2. Example of data flow in a mortality audit system for stillbirths and neonatal deaths

See Annex 3 for the minimum set of perinatal indicators

See Annex 1 for the case information form

See Annex 7 for how to generate summary statistics

See Annex 2 for a case summary form

See Annex 8 for the sample minute meetings and follow-up form

Raw data collected and entered into facility birth and death register and/or HMIS system

Transfer of data from the register to the case information form

Case information form transferred to database (if electronic system)

Cases for given time period collated into summary form

Mortality audit systems allow discussion of information and potentially changes to the causes of death and modifiable factors assigned

Codes edited on the electronic system (if applicable)

Data collated and sent to district/ regional/or national coordinator

Source: adapted from Rhoda et al., 2015 (41)
6.3 Ensuring appropriate resources and logistical support

The scope of a national mortality audit process for stillbirths and neonatal deaths will depend on the number of deaths, the resources required and the capacity of the system to deliver it. Having a sense of the ideal number and frequency of training programmes, steering committee meetings and consolidated reports will help establish a budget for setting up and running the system. While deciding on such issues, the steering committee may find it helpful to draw on the experience of other groups or countries that have instituted a similar review approach. A national annual report is extremely helpful to track progress in outcomes and actions on recommendations, but this does require dedicated staff time. Sustained funding is required for a national steering committee to meet and follow up on the progress of recommendations. Resources are also required to address gaps in the system, including targeting districts that are not yet using the system – usually weaker or poorer-performing facilities or districts. While there is an extra cost of central data collation, it is less than the returns on efficiency and impact in the health system overall.

Conclusion

There is growing demand for information about how to implement and scale up mortality auditing for stillbirths and neonatal deaths as a central element of a quality improvement strategy; audit emerged as the third priority in the development domain for the post-2015 research agenda (70). These remaining research questions go beyond overarching quality improvement jargon and seek answers to specific, practical implementation questions. Many of the questions about impact, best practices for managing review meetings and how to follow up on action items in busy maternity units are also similar to questions raised in the context of maternal death reviews, and the two should be linked, especially where there are fewer maternal deaths. In many low-income settings, the lack of community participation is also a critical gap and a challenge for an equitable process with a positive impact on the families most at risk. There are a number of community participation mechanisms that could be adapted and tested with the aim of building a more comprehensive, effective audit practice.

Each death that is reviewed has the potential to tell a story about what could have been done differently to identify the solutions that should have been available for each woman and baby. Though inputs are needed at every level of the health system and beyond, health workers have the power to change what is in front of them. The system requires leaders to champion the process, especially to ensure a no-blame environment, and to access change agents at other levels to address larger, systemic concerns. It has been suggested that we are entering the third revolution in global public health: from metrics and evaluation to accountability, and now to improved quality of care (71). The mortality audit approach has grown out of the knowledge of the importance of the first two themes to address the third. The benefits of audits and feedback have been acknowledged by development partners and governments for their success in preventing further unnecessary deaths of mothers; these tools should also now be used to prevent the deaths of their babies.
References


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</tbody>
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# Annex 1: Stillbirth and Neonatal Death Case Review Form (and guidance for completion)

**Annex 1a: Stillbirth and Neonatal Death Case Review Form**

<table>
<thead>
<tr>
<th>Section 1: Identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 ID # mother</td>
</tr>
<tr>
<td>1.2 ID # baby</td>
</tr>
</tbody>
</table>

| 1.3 Facility name:        |

<table>
<thead>
<tr>
<th>1.4 Type of care available:</th>
</tr>
</thead>
</table>

| 1.5 District name:         |

<table>
<thead>
<tr>
<th>1.6 Referred</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Section 2: Pregnancy progress and care</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>2.1 Obstetric history</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>2.2 Mother’s age</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>2.3 Type of pregnancy</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>2.4 Antenatal care number of visits</th>
</tr>
</thead>
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<table>
<thead>
<tr>
<th>Section 3: Labour and birth</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>3.1 Mother’s LMP</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>3.2 Date of birth</th>
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</table>

<table>
<thead>
<tr>
<th>3.3 Gestational age</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>3.4 Place of delivery</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>3.5 Onset of labour</th>
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</table>

<table>
<thead>
<tr>
<th>3.6 Fetal heart sounds on admission</th>
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<tr>
<th>3.7 Paragraphe used</th>
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<table>
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<tr>
<th>3.8 Mode of delivery</th>
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</thead>
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<table>
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<tr>
<th>3.9 Time between decision for action and birth</th>
</tr>
</thead>
</table>
### Section 4: Details of the death

#### 4.1 Date of death

<table>
<thead>
<tr>
<th>DD</th>
<th>MM</th>
<th>YYYY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 4.2 Type of death (circle one)

- neonatal death
- intrapartum stillbirth
- antepartum stillbirth
- stillbirth, unknown timing

#### 4.3 Main maternal condition

- none identified

#### 4.4 Cause of death (circle one)

- a. congenital
- b. antepartum complications
- c. intrapartum complications
- d. complications of prematurity
- e. infection
  - Tetanus
  - Sepsis
  - Pneumonia
  - Meningitis
  - Syphilis
  - Diarrhoea
  - Other, specify if known:
- f. other, specify:
- g. unknown/unspecified

#### Section 5: Critical delays and modifiable factors

##### 5.1 Critical delays

- delay 1. not identified
- delay 2. not identified
- delay 3. not identified

- 1. delay recognizing need for care:
- 2. delay seeking care:
- 3. delay receiving care:

##### 5.2 Modifiable factors

- Family-related
  - none identified
  - specify:

- Administration-related
  - none identified
  - specify:

- Provider-related
  - none identified
  - specify:

- other
  - none identified
  - specify:

### Actions to address the critical delays and modifiable factors

[Blank space for actions]

Form completed by: ____________________________

Date: ____________________________

---

c/s: caesarean section; CVD: cephalic vaginal delivery; ELBW: extremely low birth weight; EmOC: emergency obstetric care; HAART: highly active antiretroviral therapy; HIV: human immunodeficiency virus; IPT: intermittent preventive treatment; LBW: low birth weight; LMP: last menstrual period; NVP: nevirapine prophylaxis; TT: tetanus toxoid; VLBW: very low birth weight
### Reference page: Maternal conditions

<table>
<thead>
<tr>
<th>ICD-PM maternal condition group</th>
<th>Main maternal conditions included in group</th>
</tr>
</thead>
</table>
| M1: Maternal complications of pregnancy | 1. incompetent cervix  
2. preterm rupture of membranes  
3. oligohydramnios / polyhydramnios  
4. multiple pregnancy  
5. maternal death  
6. malpresentation before labour  
7. other complications of pregnancy |
| M2: Complications of placenta, cord and membranes | 1. placenta praevia  
2. other forms of placental separation and haemorrhage  
3. placental dysfunction, infarction, insufficiency  
4. fetal–placental transfusion syndromes  
5. prolapsed cord / other compression of umbilical cord  
6. chorioamnionitis  
7. other complications of membranes |
| M3: Other complications of labour and delivery | 1. breech delivery and extraction  
2. other malpresentation, malposition, and disproportion during labour and delivery  
3. forceps delivery / vacuum extraction  
4. caesarean delivery  
5. precipitate delivery  
6. preterm labour and delivery  
7. other complications of labour and delivery |
| M4: Maternal medical and surgical conditions; noxious influences | 1. pre-eclampsia / eclampsia  
2. gestational hypertension  
3. other hypertensive disorders  
4. renal and urinary tract diseases  
5. infectious and parasitic disease  
6. circulatory and respiratory disease  
7. nutritional disorders  
8. injury  
9. surgical procedure  
10. other medical procedures  
11. maternal diabetes including gestational diabetes  
12. maternal anaesthesia and analgesia  
13. maternal medication  
14. tobacco / alcohol / drugs of addiction  
15. nutritional chemical substances  
16. environmental chemical substances  
17. unspecified maternal condition |
| M5: No maternal condition | 1. no maternal condition identified (healthy mother) |
Annex 1b. Guidance for completing the Stillbirth and Neonatal Death Case Review Form

Purpose of form: To assist perinatal death review (also known as “perinatal mortality audit”) meetings/committees in reviewing a perinatal death, to provide information about the death, and to identify critical delays and modifiable factors that can be targeted with interventions to prevent future deaths. The form is designed so that the “normal” answers appear on the left and the “abnormal” answers appear on the right, making it easier to identify problem areas.

Time of completion: Sections 1–4 should ideally be completed by a committee in advance of the perinatal death review meeting, for discussion during the meeting. In some settings it may be completed during the meeting itself. If this is the case, ensure that all relevant files and patient notes are available at the meeting.

Section 5 should be completed and discussed at the review meeting.

Section 1: Identification

1.1: Mother’s ID: Put an identifier for the mother here. Include ID numbers that are used by your health-care facility. If there are potential legal ramifications linked to audit records, do not use this identifier and instead just number the cases discussed sequentially.

1.2: Baby’s ID: Include ID numbers that are used by your health-care facility. If no standard ID numbers are used, put the baby’s name instead. If the baby has no name, put mother’s name + “boy” or “girl”. If there are multiple babies for the same mother, add “boy No. 1” or “girl No. 1” as needed.

1.3: Facility name: Put the name of the facility where the stillbirth or neonatal death took place. If it is being reviewed at a different facility, add “reviewed at facility: ____” to clarify.

1.4: Type of care available: Circle the type of care available at the time the woman presented for care.

Type of care is defined according to the World Health Organization classification of basic emergency obstetric care (BEmOC) and comprehensive emergency obstetric care (CEmOC).

To classify care as “basic”, it must provide all of seven essential interventions:

1. administration of parenteral antibiotics to treat infection
2. administration of magnesium sulfate for treatment of eclampsia and pre-eclampsia
3. administration of oxytocin for postpartum haemorrhage
4. manual removal of the placenta
5. assisted or instrumental vaginal delivery
6. removal of retained products of conception
7. neonatal resuscitation.
To classify care as “comprehensive”, it must provide the seven essential interventions listed above and the following two additional interventions:

1. blood transfusion
2. surgery (i.e. caesarean section).

1.5: District name: Put the name of the district where the facility at which the mother delivered is located. This may not be the district that the woman is from.

1.6: Referred:

- Circle “not referred” if the woman or baby presented from home;
- If the woman or baby were referred from another hospital, health centre or clinic, write the name of that facility on the line for “referred in from”.
- If the woman or baby were referred out to another hospital or other facility, write the name of that hospital or other facility on the line for “referred out to”.

Section 2: Pregnancy progress and care

2.1: Obstetric history:

- For “all pregnancies”, put the total number of pregnancies, irrespective of gestational age, including the most recent pregnancy. Pregnancies with twins or other multiples are counted as one pregnancy.
- For “all births” put the total number of deliveries the woman has had of babies of gestational age 28 weeks or more. Include the delivery of the fetus or neonate being discussed. Deliveries of twins or other multiples are counted as one delivery.
- For “total live births”, put the total number of live births the woman has had. Include the delivery of the fetus or neonate being discussed. If both were born alive, twins are counted as two living children, with the same for higher-order multiples.
- For “dead”, put the number of the mother’s deceased children. Include the fetus or neonate being discussed. If both are deceased, twins are counted as two deceased babies.
- For “stillbirths”, put the number of the mother’s stillbirths of gestational age of 28 weeks or more. Include the fetus or neonate being discussed. If both are deceased, twins are counted as two deceased babies.
- For “neonatal deaths”, put the number of the mother’s deceased babies that died within 28 days of life.
- For “abortions”, put the total number of abortions for the woman, whether induced or spontaneous. If a stillbirth is being discussed, include this stillbirth in the number.

2.2: Mother’s age: Put the woman’s age in completed years. For example, a woman of 23 years and 10 months of age would be entered as “23”.

2.3: Type of pregnancy: Circle the type of pregnancy with the fetus or neonate being discussed:

- “singleton” if a pregnancy with one fetus;
- “twin” if a pregnancy with two fetuses;
- “higher multiple” if more than two fetuses (if more than two fetuses, put the number of fetuses next to the equals sign);
• “unknown” if the total number of fetuses is/was not known.

2.4: Antenatal care: Circle the total number of antenatal care visits the woman had during her pregnancy with the fetus or neonate being discussed: 4 or more; 3; 2; 1; no visits; unknown.

2.5: Malaria prophylaxis: Circle the number of intermittent preventive treatments (IPT) for malaria the woman received during her pregnancy with the fetus or neonate being discussed:
- “not needed” if malaria prophylaxis was not medically indicated due to lack of malaria in her residence during pregnancy;
- “IPT3+” if she received at least three treatments;
- “IPT2” if she received only two treatments;
- “IPT1” if she received only one treatment;
- “not received” if she did not receive any IPT in an area where it is indicated;
- “unknown” if there is no information on her receipt of treatments.

2.6: Tetanus toxoid vaccination: Circle the number of TT doses the woman received during her pregnancy with the fetus or neonate under discussion:
- “TT2+” if she received at least two TT doses in this pregnancy or at least 5 TT doses in her lifetime;
- “TT1” if she received one dose;
- “not received” if she did not receive any TT doses;
- “unknown” if there is no information on her receipt of TT doses.

2.7: HIV status: Circle to indicate the woman’s HIV status:
- “HIV-negative” if she was tested and found to be negative;
- “HIV-positive” if she was tested and found to be positive, or was known to be positive prior to pregnancy (and proceed to 2.7.1 below);
- “not done” if no HIV testing was performed during pregnancy;
- “unknown” if the HIV status and testing status are unknown.

2.7.1: If the woman was found to be HIV-positive or known to be HIV-positive prior to pregnancy, circle to indicate what action was taken:
- “NVP” if she received nevirapine prophylaxis for delivery
- “HAART” if she received highly active antiretroviral therapy during her pregnancy
Next to “other”, write whether:
- any additional treatment was received for HIV or its complications
- no treatment was received
- treatment was received but the type was unknown.

Do not complete line 2.7.1 for any woman who was not known to be HIV-positive.

2.8: Syphilis test: Indicate the status of the woman’s syphilis test:
- “negative” if she was tested for syphilis and found to be negative
- “syphilis-positive” if she was tested and found to be positive
- “not done” if no syphilis testing was performed during pregnancy
- “unknown” if the syphilis status and testing status are unknown.
Section 3: Labour and birth

3.1: Mother’s LMP: Enter the date of the woman’s last menstrual period here, or circle “unknown”.

3.2: Date of birth: Record the date of the birth here, whether live or stillborn.

3.3: Gestational age: Enter in weeks and days at the time of birth (live or stillbirth), using the LMP.

Choose gestational age to record in this order:
1. If there is a gestational age based on early ultrasound, enter this.
2. If there is no gestational age based on early ultrasound, enter the estimated gestational age according to woman’s recollection of her LMP.
3. If there is no gestational age estimate either based on ultrasound or the woman’s recollection, circle “unknown” (DO NOT enter gestational age based on late ultrasound or estimated by size at delivery).

3.3.1: Method of determination: Circle the method by which this gestational age was calculated. Additionally, circle “sure” or “unsure” for the LMP dates, depending on the woman’s stated level of certainty. If the woman’s certainty is not stated, or if another method was used, write this in the “other, specify” box.

3.4: Place of delivery. If delivery was at a facility, enter the facility’s name on this line.

3.4.1: Attendant at delivery:
- Circle “midwife” if delivery was attended by a trained midwife.
- Circle “nurse” if delivery was attended by a nurse with midwifery skills.
- Circle “doctor” if delivery was attended by a physician.
- If the delivery was attended but none of the provided options fit, write in the type of attendant in the “other” box (e.g. traditional birth attendant, community health worker, relative).
- Circle “no one” if no one other than the woman was present at the delivery.
- Circle “unknown” if delivery attendance is not known.

3.5: Onset of labour: Circle to indicate the appropriate information:
- “spontaneous” if labour began without artificial aid
- “induced” if labour was brought on with the use of drugs
- “c/s before onset” if a caesarean section was done before the onset of labour
- “unknown” if unsure.

3.6: Fetal heart sounds on admission:
- If fetal heart sounds (fetal heart tones) were auscultated on admission and were not present, circle “no”.
- If fetal heart sounds (fetal heart tones) were auscultated on admission and were present, circle “yes” and write what they were recorded as on admission.
If fetal heart sounds were not auscultated on admission or if this information is not available, circle “unknown”.

3.7: Partograph used: Circle to indicate the appropriate information:

- “no” if a partograph was not used during delivery;
- “yes” if a partograph was used during delivery, and write any relevant additional comments (e.g., write “incomplete” if it was used for only a portion of delivery or does not include all standard information on a partograph);
- “unknown” if this information is not available.

3.8: Mode of delivery: Circle to indicate the appropriate information for the fetus or neonate being discussed.

- “CVD” for cephalic vaginal (or normal) delivery
- “assisted vaginal delivery” if vacuum and/or forceps were used
- “caesarean” if indicated
- “other” if indicated, and describe (e.g., breech delivery)
- “unknown” if this information is not available

More than one answer can be chosen, as appropriate (e.g., failed use of vacuum or forceps followed by a caesarean section).

3.9: Time between the decision for action and the birth: If mode of delivery was anything other than “CVD”, circle the amount of time it took from making the decision that a normal delivery is not longer possible/appropriate to achieving the actual birth by way of assisted/surgical delivery. If delivery was “CVD”, circle “n/a” for not applicable.

3.10: Apgar score: Record the scores at 1 and at 5 minutes. Next to these, circle “6 or more” or “5 or less” as indicated by the score. If either of these scores is not available, circle “unknown” for that score.

3.11: Circle to indicate actions related to resuscitation:

- “not needed” if not indicated by Apgar scores or clinical state;
- “bag + mask” if performed;
- “not done” if resuscitation was indicated but not performed;
- “other” and record whether the following forms of resuscitation were performed:
  - stimulation
  - suction
  - intubation
  - CPR
  - other forms of resuscitation (record);
- “unknown” if this information is not available.

3.12: Sex of baby: Circle “male”, “female” or “unknown” as indicated.

3.13: Birth weight: Record the total birth weight, and circle the appropriate category of birth weight, or “unknown” if birth weight is not available. The acronyms stand for:

- LBW: Low birth weight (1500–2499 g)
• VLBW: Very low birth weight (1000–1499 g)
• ELBW: Extremely low birth weight (< 1000 g)

**Section 4: Details of the death**

4.1 and 4.1.1: Record the date and time of death.

4.2: Type of death: Circle to indicate the appropriate category based on the following definitions.

- “Neonatal death” is the death of a baby born alive but who died within the first 28 days of life.
- “Intrapartum stillbirth” is the death of a fetus who was alive at the onset of labour but who died before delivery. This can be determined by the presence of fetal heart sounds (fetal heart tones) on admission or prior to delivery, or by appearance of a “fresh” stillbirth (intact skin and fetus on delivery).
- “Antepartum stillbirth” is the death of a fetus before the onset of labour. This can be determined by “macerated” appearance of the fetus upon delivery, in combination with absence of fetal heart sounds on admission.
  - Absence of fetal heart sounds on admission does not necessarily indicate an antepartum stillbirth, if the woman was admitted with labour already in progress.
  - Presence of fetal heart sounds on admission of a labouring woman does exclude the possibility of an antepartum stillbirth.
- “Stillbirth, unknown timing” should be circled if it is not possible to tell the time of death of the fetus.

4.3: Main maternal condition: Enter in writing the main maternal condition followed by the letter and number code corresponding to it, found on the maternal conditions reference page. If unknown circle “unknown”.

4.4: Cause of death: Identify the relevant cause of stillbirth or neonatal death by circling the appropriate letter below this item (a–g). For infections (e), circle the most appropriate response.

After choosing a main cause of stillbirth or neonatal death, indicate the maternal condition in the relevant M1–M5 category, using the numbers provided on the accompanying reference page. If the mother was healthy, enter 1 in the M5 column corresponding to the cause of stillbirth or neonatal death. Check “other” if none of the maternal conditions codes fit, and check “unknown” if the mother’s condition is unknown.

**Section 5: Critical delays and modifiable factors**

5.1: Critical delays: Circle any delays in care that are recognized during the review of the case, as described below.

- Delay 1: Delay in the decision to seek care (e.g., a woman may labour at home for too long because she and/or her family are afraid to come for care, are concerned about the cost of care, or do not recognize developing problems).
• If a “delay 1” is present, circle “delay 1” and describe the delay at the end of this line.
• If no delay 1 is identified, circle “not identified”.

• Delay 2: Delay in reaching care (e.g., a labouring woman may not be able to find or afford expedient transportation to a care facility).
  – If a “delay 2” is present, circle “delay 2” and describe the delay at the end of this line.
  – If no “delay 2” is identified, circle “not identified”.

• Delay 3: Delay in receiving adequate care (e.g., a labouring woman may arrive at a hospital where no clinicians are available to provide any care to her, or her transfer between lower- and higher-level facilities may take too long to provide effective care and prevent stillbirth).
  – If a “delay 3” is present, circle “delay 3” and describe the delay at the end of this line.
  – If no “delay 3” is identified, circle “not identified”.

5.2: Modifiable factors: This section relates to modifiable factors in terms of levels of system failure. These may be helpful to identify interventions to prevent future deaths.

• Family-level factors: Did the family of a victim of neonatal death not understand when to seek care for their infant? Should families in their community receive any educational campaign, or resources to help get them to a health-care facility sooner?
  – If a family-level modifiable factor is present, circle “family-related” and describe the factor(s) next to “specify”.
  – If no family-level modifiable factor can be identified, circle “none identified”.

• Administration-level factors: Was transfer between lower- and higher-level facilities inhibited by administrative barriers? Was there a stock out of any needed drugs or equipment?
  – If an administration-level modifiable factor is present, circle “administration-related” and describe the factor(s) next to “specify”.
  – If no administration-level modifiable factor can be identified, circle “none identified”.

Provider-level factors: Was a provider unable to give adequate resuscitation? Are there needs for training or additional resources for provider use?

  – If a provider-level modifiable factor is present, circle “provider-related” and describe the factor(s) next to “specify”.
  – If no provider-level modifiable factor can be identified, circle “none identified”.

**Actions to address critical delays and avoidable factors:**

This section is the least structured part of the form, but potentially the most important.

Participants in the perinatal death review should work together to highlight the critical delays and avoidable factors that can be targeted by interventions to avoid similar deaths in the future. It is particularly helpful to ask the question: What could actually be done to prevent a critical delay or avoidable factor?
The group should generate and write down specific actions required to mitigate these critical delays and avoidable factors in future cases, attaching additional pages as needed.

Form completed by: Adding a contact name here, as well as contact information, can be very helpful to future people reviewing the forms in the future.

Date: Add the date on which the review was completed.

Abbreviations: c/s: caesarean section; CVD: cephalic vaginal delivery; ELBW: extremely low birth weight; EmOC: emergency obstetric care; HAART: highly active antiretroviral therapy; HIV: human immunodeficiency virus; IPT: intermittent preventive treatment; LBW: low birth weight; LMP: last menstrual period; NVP: nevirapine prophylaxis; TT: tetanus toxoid; VLBW: very low birth weight
Annex 2: Births and Deaths Summary Form
(and guidance for completion)

Annex 2a: Births and Deaths Summary Form

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<td>1.2 Data for the month of:</td>
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<td>1.3 District name:</td>
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<th>Section 2: Cause of death</th>
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<tr>
<td>2.1 Cause of death: antepartum stillbirths</td>
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<tr>
<td>2.2 Cause of death: intrapartum stillbirths</td>
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<tr>
<td>2.3 Cause of death: neonatal deaths</td>
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### Section 2: Cause of death

#### 2.1a Cause of death: antepartum stillbirths

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#### 2.1b Cause of death: intrapartum stillbirths

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#### 2.1c Cause of death: neonatal deaths

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CVD: cephalic vaginal delivery
Annex 2b. Guidance for completing the Births and Deaths Summary Form

Purpose of form: To assist a facility to document births and perinatal deaths.

Responsibility for completion: Once per month by the facility data clerk or statistics department. Additionally, numbers generated on this form can be compared between months to obtain trends. At every perinatal death review meeting/committee meeting, these data can be reviewed to identify similarities in cases reviewed and overall trends. This may help guide prioritization of actions or interventions recommended by the perinatal death review committee/meeting.

Section 1: Identification

1.1: Write facility name here.

1.2: Write the month and year for which these data were collected.

1.3: Write the name of the district where the facility is located.

1.4: Births

Column 1: Total Births: Write the total number of births in each of the categories, including both live and stillbirths (including any live births of neonates who later died).

Column 2: Stillbirths: Write the total number of stillbirths (SB) in each category, as defined here:

- “Antepartum SB” is the death of a fetus before the onset of labour.
  - This can be determined by “maceral” appearance of the fetus upon delivery (i.e. tissue degeneration, starting with skin changes), in combination with absence of fetal heart sounds (fetal heart tones) on admission.
  - Absence of fetal heart sounds on admission does not necessarily indicate an antepartum stillbirth, if the mother was admitted with labour already in progress.
  - Presence of fetal heart sounds on admission of a labouring woman does exclude the possibility of an antepartum stillbirth.

- “Intrapartum SB” is the death of a fetus who was alive at the onset of labour but who died before delivery.
  - This can be determined by the presence of fetal heart sounds (fetal heart tones) on admission or prior to delivery, or by “fresh” appearance of a fetus upon delivery (i.e. intact skin and fetus on delivery).

- “Unknown SB” is the category for those stillborn fetuses for whom it is not possible to tell the timing of the death.
1.5: Multiple pregnancies:
In the “pregnancies” box, write the total number of pregnancies of at least two fetuses (e.g. twins, triplets).

In the “babies” box, write the total number of fetuses or neonates who resulted from these pregnancies. Include those born alive as well as stillborn.

For example, suppose that in one month a hospital delivered 10 women who had pregnancies with more than one fetus. Suppose that of these 10 women, 8 delivered live twins, 1 delivered stillborn twins, and 1 delivered live triplets. In this example, the “pregnancies” box would have the number “10” and the “babies” box would have the number “21”.

1.6: Born before arrival: Enter the total number of stillbirths and live births that occurred before arrival at the facility.

1.7: Mode of delivery: Write in each box the total number of deliveries by cephalic vaginal delivery (CVD), vacuum-assisted, forceps-assisted, caesarean and unknown mode.

1.8: Gestational age: Write in each box the total number of:
• term deliveries: deliveries at gestational ages 37–42 weeks
• post-term deliveries: deliveries at gestational ages > 42 weeks
• extremely preterm deliveries (‘ext preterm’): deliveries at gestational ages < 28 weeks
• very preterm deliveries: deliveries at gestational ages 28–32 weeks
• moderate-to-late preterm deliveries (“mod preterm”): deliveries at gestational ages 32–37 weeks.

1.9: HIV status: Record the numbers of HIV-negative mothers, HIV-positive mothers, and mothers of unknown HIV status served by the facility in the past month.

1.10: Syphilis serology: Record numbers of syphilis-negative mothers, syphilis-positive mothers, and mothers of unknown syphilis status served by the facility in the past month.

1.11: Maternal age: Record the numbers of mothers served by the facility in the past month within each of the age groups shown on the form, as well as number of mothers for whom age group was unknown.

Section 2: Cause of death

2.1a Cause of death – antepartum stillbirths: Tally the number of causes of antepartum stillbirths in each of the listed categories in the past month at this facility. If M1–M5 designations were used, total each of those. If M1–M5 designations were not used, enter all in the “other” column provided. Tally any unknowns in the “unknown” column.

If a facility has stillbirths for which antepartum versus intrapartum status is unknown, record these separately in the empty space to the right of the antepartum deaths list, along the same rows.
2.1b: Cause of death – intrapartum stillbirths: Tally the number of causes of intrapartum stillbirths in each of the listed categories in the past month at this facility. If M1–M5 designations were used, total each of those. If M1–M5 designations were not used, enter all in the “other” column provided. Tally any unknowns in the “unknown” column.

2.1c: Cause of death – neonatal deaths: Tally the number of causes of neonatal deaths in each of the listed categories in the past month at this facility. If M1–M5 designations were used, total each of those. If M1–M5 designations were not used, enter all in the “other” column provided. Tally any unknowns in the “unknown” column.
Annex 3: Minimum set of perinatal indicators to collect for all births and perinatal deaths (and guidance for completion)

Annex 3a: Minimum set of perinatal indicators to collect for all births and perinatal deaths

### Section 1: Identification

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<tr>
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<tbody>
<tr>
<td>1.1</td>
<td>ID # mother</td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td>ID # baby</td>
<td></td>
</tr>
<tr>
<td>1.3</td>
<td>Facility name:</td>
<td></td>
</tr>
<tr>
<td>1.4</td>
<td>District name:</td>
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### Section 2: Pregnancy progress and care

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>2.1 Obstetric history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.2 Mother’s age</td>
<td></td>
<td>y</td>
</tr>
<tr>
<td>2.3 Type of pregnancy</td>
<td>singleton</td>
<td>twin</td>
</tr>
<tr>
<td>2.4 Antenatal care number of visits</td>
<td>4 or more</td>
<td>3</td>
</tr>
<tr>
<td>2.5 HIV status</td>
<td>HIV-negative</td>
<td>HIV-positive</td>
</tr>
<tr>
<td>2.5.1 HIV-positive action</td>
<td>NVP</td>
<td>HAART</td>
</tr>
</tbody>
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### Section 3: Labour and birth

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>3.1 Mother’s LMP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.2 Date of birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.3.1. Time of birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.3 Gestational age</td>
<td>weeks</td>
<td></td>
</tr>
<tr>
<td>3.3.1. Method of determination</td>
<td>sure LMP dates</td>
<td>unsure LMP dates</td>
</tr>
<tr>
<td>3.4 Place of delivery</td>
<td>facility</td>
<td>home</td>
</tr>
<tr>
<td>3.5 Attendant at delivery</td>
<td>midwife</td>
<td>nurse</td>
</tr>
<tr>
<td>3.6 Mode of delivery</td>
<td>CVD</td>
<td>assisted vaginal</td>
</tr>
<tr>
<td>3.7 Sex of baby</td>
<td>male</td>
<td>female</td>
</tr>
<tr>
<td>3.8 Birth weight</td>
<td>g ≥ 2500</td>
<td>1500–2499</td>
</tr>
<tr>
<td></td>
<td>LBW</td>
<td>VLBW</td>
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### Section 4: Details of the death

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>4.1 Date of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.2 Time of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.2 Type of death (circle one)</td>
<td>neonatal death</td>
<td>intrapartum stillbirth</td>
</tr>
</tbody>
</table>

CVD: cephalic vaginal delivery; ELBW: extremely low birth weight; HAART: highly active antiretroviral therapy; HIV: human immunodeficiency virus; LBW: low birth weight; LMP: last menstrual period; NVP: nevirapine prophylaxis; SB: stillbirth; VLBW: very low birth weight
Annex 3b. Guidance for collecting the minimum set of perinatal indicators for all births and perinatal deaths

**Purpose of form**: To identify the minimum elements that should be collected on every birth and death that occurs in the health-care facility. The form does not have to be used in addition to routine data collection if all of these elements are already being captured in another place (e.g. the register or electronic health management information system).

**Time of completion**: The form should be completed as close to the time of birth and discharge/death as possible. This information is to be compiled before or at the initiation of the perinatal death review meeting (also known as “perinatal mortality audit meeting”) if not possible in advance of the meeting.

**Section 1: Identification**

1.1: Mother’s ID: Put an identifier for the mother here. Include ID numbers that are used by your health-care facility. If there are potential legal ramifications linked to audit records, do not use this identifier and instead just number the cases discussed sequentially.

1.2: Baby’s ID: Include ID numbers that are used by your health-care facility. If no standard ID numbers are used, put the baby’s name instead. If the baby has no name, put mother’s name + “boy” or “girl”. If there are multiple babies for the same mother, add “boy No. 1” or “girl No. 1” as needed.

1.3: Facility name: Put the name of the facility where the stillbirth or neonatal death took place. If it is being reviewed at a different facility, add “reviewed at facility:____” to clarify.

1.4: District name: Put the name of the district where the facility at which the mother delivered is located. This may not be the district that the mother is from.

**Section 2: Pregnancy progress and care**

2.1: Obstetric history:

- For “all pregnancies”, put the total number of pregnancies, irrespective of gestational age, including the most recent pregnancy. Pregnancies with twins or other multiples are counted as one pregnancy.

- For “total live births”, put the total number of live births the woman has had. Include the delivery of the fetus or neonate being discussed. If both were born alive, twins are counted as two living children, with the same for higher-order multiples.

- For “dead”, put the number of the mother’s deceased children. Include the fetus or neonate being discussed. If both are deceased, twins are counted as two deceased children.

2.2: Mother’s age: Put the woman’s age in completed years. For example, a woman of 23 years and 10 months of age would be entered as “23”.

2.3: Type of pregnancy: Circle the type of pregnancy with the fetus or neonate being discussed:

- “singleton” if a pregnancy with one fetus;
- “twin” if a pregnancy with two fetuses;
- “higher multiple” if more than two fetuses (if more than two fetuses, put the number of fetuses next to the equals sign);
- “unknown” if the total number of fetuses is/was not known.

2.4: Antenatal care: Circle the total number of antenatal care visits the woman had during her pregnancy with the fetus or neonate being discussed: 4 or more; 3; 2; 1; no visits; unknown.

2.5: HIV status: Circle to indicate the woman’s HIV status:

- “HIV-negative” if she was tested and found to be negative;
- “HIV-positive” if she was tested and found to be positive, or was known to be positive prior to pregnancy (and proceed to 2.5.1 below);
- “not done” if no HIV testing was performed during pregnancy;
- “unknown” if the HIV status and testing status are unknown.

2.5.1: If the woman was found to be HIV-positive or known to be HIV-positive prior to pregnancy, circle to indicate what action was taken:

- “NVP” if she received nevirapine prophylaxis for delivery
- “HAART” if the mother received highly active antiretroviral treatment during her pregnancy
- Next to “other”, write whether:
  - No treatment was received
  - Any additional treatment was received for HIV or its complications
  - Treatment was received but the type was unknown.

Do not complete line 2.5.1 for any woman who was not known to be HIV-positive.

**Section 3: Labour and birth**

3.1: Mother’s LMP: Enter the date of the woman’s last menstrual period (LMP) here, or circle “unknown”.

3.2: Date of birth: Record the date of the birth here, whether live or stillborn.

3.3: Gestational age: Enter in weeks and days at the time of birth (live or stillbirth), using the LMP.

Choose gestational age to record in this order:

1. If there is a gestational age based on early ultrasound, enter this.
2. If there is no gestational age based on early ultrasound, enter the estimated gestational age according to woman’s recollection of her LMP.
3) If there is no gestational age estimate either based on ultrasound or the woman’s recollection, circle “unknown” (DO NOT enter gestational age based on late ultrasound or estimated by size at delivery).

3.3.1: Method of determination: Circle the method by which this gestational age was calculated. Additionally, circle “sure” or “unsure” for the LMP dates, depending on the woman’s stated level of certainty. If the woman’s certainty is not stated, or if another method was used, write this in the “other, specify” box.

3.4: Place of delivery: Circle to indicate the place. If delivery was at a facility, enter the facility’s name on this line.

3.5: Attendant at delivery:
- Circle “midwife” if delivery was attended by a trained midwife.
- Circle “nurse” if delivery was attended by a nurse with midwifery skills.
- Circle “doctor” if delivery was attended by a physician.
- If the delivery was attended but none of the provided options fit, write in the type of attendant in the “other” box (e.g. traditional birth attendant, community health worker, relative).
- Circle “no one” if no one other than the woman was present at the delivery.
- Circle “unknown” if delivery attendance is not known.

3.6: Mode of delivery: Circle to indicate the appropriate information for the fetus or neonate being discussed.
- “CVD” for cephalic vaginal (or normal) delivery
- “assisted vaginal delivery” if vacuum and/or forceps were used
- “caesarean” if indicated
- “other” if indicated, and describe
- “unknown” if this information is not available.

More than one answer can be chosen, as appropriate.

3.7: Sex of baby: Circle “male”, “female” or “unknown” as indicated.

3.8: Birth weight: Record the total birth weight, and circle the appropriate category of birth weight, or “unknown” if birth weight is not available. The acronyms stand for:
- LBW: Low birth weight (1500–2499 g)
- VLBW: Very low birth weight (1000–1499 g)
- ELBW: Extremely low birth weight (< 1000 g)

**Section 4: Details of the death**

This section is only applicable in the case of death. If the baby was discharged alive, this section will not be completed.

4.1 and 4.2: Record the date of death and time of death.
4.3: Type of death: Circle to indicate the appropriate category based on the following definitions.

- “Neonatal death” is the death of a baby born alive but who died within the first 28 days of life.
- “Intrapartum stillbirth” is the death of a fetus who was alive at the onset of labour but who died before delivery. This can be determined by the presence of fetal heart sounds (fetal heart tones) on admission or prior to delivery, or by appearance of a “fresh” stillbirth (intact skin and fetus on delivery).
- “Antepartum stillbirth” is the death of a fetus before the onset of labour. This can be determined by “macerated” appearance of the fetus upon delivery, in combination with absence of fetal heart sounds on admission.
  - Absence of fetal heart sounds on admission does not necessarily indicate an antepartum stillbirth, if the woman was admitted with labour already in progress.
  - Presence of fetal heart sounds on admission of a labouring woman does exclude the possibility of an antepartum stillbirth.
- “Stillbirth, unknown timing” should be circled if it is not possible to tell the time of death of the fetus.

**Abbreviations:** CVD: cephalic vaginal delivery; ELBW: extremely low birth weight; HAART: highly active antiretroviral therapy; HIV: human immunodeficiency virus; LBW: low birth weight; LMP: last menstrual period; NVP: nevirapine prophylaxis; SB: stillbirth; VLBW: very low birth weight
Annex 4. Approaches for classifying modifiable factors

A modifiable factor is something that may have prevented the death if a different course of action had been taken.

Many modifiable factors are due to missed opportunities within the health system. These represent potential for positive change. Documenting these modifiable factors is a very important priority of perinatal death review (also known as “perinatal mortality audit”).

Modifiable factors are often discussed in terms of delays in care and in levels of system failure. Modifiable factors are often analysed using a root cause analysis, including fishbone diagrams.

Participants in the perinatal death review should work together to highlight the critical delays and avoidable factors that can be targeted by interventions. It is particularly helpful to ask the question: What could actually be done to prevent a critical delay or avoidable factor?

Instructions, part 1: Three delays model

The “three delays” model describes three types of delays in getting adequate care:

**Delay 1:** Delay in the decision to seek care. For example, a woman may labour at home for too long because she and/or her family are afraid to come for care, are concerned about the cost of care, or do not recognize developing problems. Participants in the perinatal death review meeting should write down any type 1 delays they can identify on the Stillbirth and Neonatal Death Case Review Form (Annex 1a).

**Delay 2:** Delay in reaching care. For example, a labouring woman may not be able to find or afford expedient transportation to a health-care facility. The perinatal death review meeting participants should write down any type 2 delays they can identify on the Stillbirth and Neonatal Death Case Review Form (Annex 1a).

**Delay 3:** Delay in receiving adequate care. For example, a labouring woman may arrive at a hospital without any clinicians available to provide care to her, or transfer between lower- and higher-level facilities may take too long to provide effective care and prevent stillbirth. Participants in the perinatal death review meeting should write down any type 3 delays they can identify on the Stillbirth and Neonatal Death Case Review Form (Annex 1a).
Instructions, part 2: Patient–provider–administration model

Discussion of modifiable factors in terms of levels of system failure may be helpful to guide interventions. Typically three levels are discussed:

1. **Family level**: Did the family of a victim of neonatal death not understand when to seek care for their infant? Should families in their community be targeted with an educational campaign or provided with resources to help them get to care sooner? Family-level modifiable factors can be recorded on the bottom of the Stillbirth and Neonatal Death Case Review Form (Annex 1a), to help develop the comments and the root cause analysis.

2. **Administrative level**: Was transfer between lower- and higher-level facilities inhibited by administrative barriers? Was there a stock-out of any needed medicines or equipment? Administrative-level modifiable factors can be recorded on the bottom of the Stillbirth and Neonatal Death Case Review Form (Annex 1a), to help develop the comments and the root cause analysis.

3. **Provider level**: Was a health-care provider unable to give adequate resuscitation? Are there needs for additional training or resources for providers? Provider-level modifiable factors can be recorded on the bottom of the Stillbirth and Neonatal Death Case Review Form (Annex 1a), to help develop the comments and the root cause analysis.

For example, if a baby dies of congenital syphilis, and the mother did not attend antenatal care, then the modifiable factor would most likely have been related to family- or patient-level factors. However, if the mother attended the antenatal clinic but the health worker failed to screen her for syphilis or failed to collect the result and treat her, then the avoidable factor would have been provider related. Finally, if the mother attended antenatal clinic, and the health worker wanted to screen her for syphilis but either transport or the facilities to perform the test were not available, then the modifiable factor would have been administration related.

Some modifiable factors can be clearly identified as being the cause of a death, while other avoidable factors may have contributed to the death more distally. Therefore, avoidable factors can be further divided into “probable” and “possible” factors.

Only when the specific avoidable factor or missed opportunity has been identified can steps be taken to prevent similar deaths in the future. If it is not clear why the care was substandard, it is very difficult to solve the problem. Identifying modifiable factors is an important step in improving care.

**Instructions, part 3: Root cause analysis**

A root cause analysis helps to identify all of the problems that led to or contributed to an event. In this case, the event is the stillbirth or neonatal death under review. This analysis may help facilitate the formulation of integrated strategies and recommendations.
There are multiple tools available for completing a root cause analysis. One of the most helpful is called an Ishikawa diagram, which is also known as a “fishbone” diagram, because a completed diagram can look like the skeleton of a fish (see Figure A4–1).

Steps for a group to complete a root cause analysis through a fishbone diagram:

**Step 1: Record the event at the head**

The first step is to identify the problem or event – for example, a death with a specific cause, such as an intrapartum-related perinatal death in a full-term baby. Write this problem in a box on the far right-hand side of a large sheet of paper as the “head” of the fish, to represent the event that is under investigation for contributing problems and factors, and then draw a line across the paper horizontally from the box as the “spine” of the fish.

**Step 2: Brainstorm contributing factors**

Next, draw lines as “bones” off the spine of the fish with a box at the end of each line/bone in which to write down the contributing factors. The group then attempts to identify the problems and factors that led to the perinatal death. These may be problems at different levels of the health systems, or system building blocks such as staffing, equipment, information, etc. Identifying the contributing factors is typically done through open brainstorming, with every person in the group contributing out loud everything that they can think of that contributed to the occurrence of this death. Alternatively, instead of contributing out loud, groups may choose to have participants write down what they think the contributing factors to the death were and then submit them anonymously to a discussion leader who can read them out loud.

![Figure A4–1. Fishbone diagram](image-url)
The National Health Service (NHS) of England has developed a list of potential contributing factors which is provided to participants in its National Patient Safety Agency to assist them when brainstorming circumstances around adverse patient events, in the course of completing fishbone diagrams. These factors include:

- Team factors: role congruence, leadership, team cultural factors, team support factors;
- Organizational and strategic factors: organizational structure, organizational priorities, and culture of safety;
- Communication factors: verbal, written, non-verbal, and communication between management and staff;
- Working condition factors: administrative, design of physical environment, environment, staffing, workload, hours, and time;
- Task factors: guidelines, procedures, protocols, decision aids, task design;
- Equipment and resources: displays, integrity, positioning, usability;
- Individual staff factors: physical issues, psychological issues, social issues, personality, cognitive factors;
- Education and training factors: competence, supervision, availability, accessibility, appropriateness;
- Patient factors: clinical condition, physical factors, social factors, psychological factors, interpersonal relationships.

**Step 3: Record the contributing factors at the end of the bones**

After brainstorming, the next step is to write down each contributing factor in a box at the end of a bone leading to the head of the fish (the event).

*Steps 4 through 6 are best performed one contributing factor – or one “bone” – at a time, until each step has been completed for each bone before moving on to step 7.*

**Step 4: Brainstorm contributing causes within each bone**

The next step is to repeat the brainstorming process with each of the bones (each of the contributing factors), to identify possible contributing causes. What problems or factors contributed to that specific problem or factor written at the end of the bone?

**Step 5: Record contributing causes on the veins**

Again after this round of brainstorming, the next step is to write down these possible contributing problems or contributing causes as shorter lines or “veins” coming off each bone of the diagram.

**Step 6: Brainstorm contributing subcauses on the subveins**

For each contributing cause that is large or complex, it may be best to break it down into sub-causes, working from proximal to distal causes below. Therefore, further brainstorming is undertaken for each of the contributing problems or causes written on the veins.

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9 The list of contributing factors is adapted from Root cause analysis investigation tools: contributory factors classification framework, NHS National Patient Safety Agency, 2009 (http://www.nrls.npsa.nhs.uk/resources/?entryid45=75605, accessed 25 July 2016). This contributing factors list is not meant to be comprehensive, but to assist brainstorming.
What problems or factors (subcauses) contributed to the specific contributing problem or cause? These subcauses – as well as any additional problems or factors that contributed to their occurrence – are entered onto the fishbone diagram as the “subveins” coming off each vein or cause line.

**Step 7: Create action targets and develop actionable solutions**

By this stage of the root cause analysis exercise, the fishbone diagram should show many possible causes, problems and factors that likely contributed to the perinatal death (see Figure A4–1). From here, the team should be able to develop actionable solutions. There may be many problems and solutions that can be explored, but teams may choose to focus on gaps that are actionable within their sphere of influence in the short term, while advocating for more long-term systemic change.

To be most effective, a perinatal death review meeting can take this fishbone diagram one step further and circle the contributing causes and subcauses that will be targeted with action. These items are called action targets. Only causes and subcauses that can be addressed by participants in the perinatal death review may be designated as action targets. For example, “poverty” may be listed as a contributing factor on one of the bones. Causes written on veins for that bone may include “lack of income”, “family poverty” and “cost of health care”. Subveins for “cost of health care” may include “delivery fees”, “hospital debt” and “cost of gloves”. Of all these causes and subcauses, participants in the perinatal death review should only circle those things that they believe they can address through intervention. For example, “cost of gloves” may be circled as an action target if there is a programme or nongovernmental organization that may be approached for free gloves. Alternatively, “delivery fees” may even be circled as an action target if one of the participants is an administrator with the power to reduce or eliminate those fees. In contrast, “lack of income” should never be circled, because the perinatal death review participants have no way to intervene in that particular issue. To provide an even more extreme example, “poverty” itself should never be circled as an action target: this would unfortunately be unrealistic.

**Step 8: Create action spears**

The perinatal death review meeting participants can then add arrows or “action spears” to the fishbone diagram that point to these action target circles and specify on the end of these spears:

1. who will take the action
2. what action will be taken
3. when will the action be taken.

These action spears represent the power to prevent future perinatal deaths.
Annex 5. Setting up a mortality audit steering committee

The role of a steering committee in mortality audit is to organize and oversee the review process and, when it is time to act on the findings, help develop and implement the recommendations. The primary purpose of mortality audit is action, and without the support of key stakeholders, recommendations cannot be turned into actions. Key stakeholders are the people who have the responsibility and authority to achieve actions. These actions can include community- or facility-based interventions, the development and introduction of guidelines, improving access to services or health system reform. Thus, the importance of the support of local community leaders, facility directors, or national or state government entities for such audits cannot be overemphasized. Also, to ensure sustainability, since many good programmes come to an end when project funding ends for new initiatives, governments and other key stakeholders need to be involved from the beginning of the facility-based death review process, informed of progress and, as appropriate, invited to attend meetings or sit on steering committees.

Steering committee members for the facility-based death reviews (also known as “mortality audit”) should have an interest in neonatal and maternal health. The committee should include a diverse group of members, as appropriate. Members may include representatives from the district health office, the facility administration, the departments of neonatology/paediatrics, obstetrics, midwifery/nursing, anaesthesia, pathology, pharmacy and statistics, as well as a community liaison.

The key roles of the steering committee are to:

- help initiate the case review and mortality audit process and decide on the approach and its scope;
- oversee data collection, analysis and case selection for review meetings, including assigning responsibility for this task if not included in existing job descriptions;
- develop a schedule for the audit meetings, invite participants and ensure adequate facilitation;
- assist with dissemination of recommendations and advocate for their implementation.

At the national level, a stillbirth and neonatal mortality audit steering committee would have similar composition and roles as described above, but would likely be led by the national ministry of health, with official representation from health professional associations, and with more opportunity for diversity of membership, including epidemiologists, staff of nongovernmental organizations, development partners and high-level policy-makers.
Annex 6. Sample mortality audit meeting code of practice declaration

To foster an environment of collaboration rather than blame, it might be helpful if a written code of practice is established by the mortality audit (also known as “death review”) steering team, and agreed through discussion with facility staff and management. For the written code of practice, use of wording specific to each team is encouraged, but a suggested short text is provided below, which can be signed by each individual before each review meeting.

An attendance sheet could also be signed at the end of the meeting, so that those who were there to sign in at both the beginning and end of the meeting can be credited for staying and participating throughout the meeting.

**Code of practice**

To show respect for the babies and families we are responsible for looking after, we, the staff of [name of facility], agree to respect the rules of good conduct during meetings where cases of deaths that have occurred in our facility are reviewed. We understand and appreciate that the results of these meetings will not result in punitive measures. The rules of our stillbirth and neonatal mortality audit meetings include:

- arrive on time to the audit meetings;
- participate actively in discussions;
- respect everyone’s ideas and ways of expressing them;
- accept discussion and disagreement without resorting to verbal abuse;
- respect the confidentiality of the discussions that take place during the meetings;
- agree not to hide useful information or falsify information that could provide insight into the case(s) under review; and
- try as much as possible (recognizing that it is not easy) to accept that your own actions can be questioned.

Signed: _____________________________  Date: ________________
Signed: _____________________________  Date: ________________
Signed: _____________________________  Date: ________________
Signed: _____________________________  Date: ________________
Signed: _____________________________  Date: ________________
Signed: _____________________________  Date: ________________

[98] MAKING EVERY BABY COUNT: AUDIT AND REVIEW OF STILLBIRTHS AND NEONATAL DEATHS
Annex 7: Sample calculations for reporting

This form provides dummy data and formulas for calculating simple indicators that can be used to complete the Meeting Minutes and Action Items Form found in Annex 8.

| Facility name: |
| Period under review: |

<table>
<thead>
<tr>
<th>Numbers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Number of deliveries</td>
<td>1000</td>
</tr>
<tr>
<td><strong>B</strong> Number of live births</td>
<td>880</td>
</tr>
<tr>
<td><strong>C</strong> Number of stillbirths*</td>
<td>20</td>
</tr>
<tr>
<td><strong>D</strong> Number of intrapartum stillbirths</td>
<td>12</td>
</tr>
<tr>
<td><strong>E</strong> Number of antepartum stillbirths</td>
<td>8</td>
</tr>
<tr>
<td><strong>F</strong> Early neonatal deaths (1–7 days)</td>
<td>14</td>
</tr>
<tr>
<td><strong>G</strong> Neonatal deaths (1–28 days)</td>
<td>18</td>
</tr>
<tr>
<td><strong>H</strong> Maternal deaths</td>
<td>2</td>
</tr>
<tr>
<td><strong>I</strong> Number of caesarean section deliveries</td>
<td>150</td>
</tr>
<tr>
<td><strong>J</strong> Number of assisted deliveries</td>
<td>100</td>
</tr>
<tr>
<td><strong>K</strong> Number of babies born weighing &lt; 2500 g</td>
<td>200</td>
</tr>
<tr>
<td><strong>L</strong> Number of babies born &lt; 37 weeks gestational age</td>
<td>140</td>
</tr>
</tbody>
</table>

*specify definition in use at the health-care facility

<table>
<thead>
<tr>
<th>Rates</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth rate</td>
<td>((C/A)\times1000)</td>
</tr>
<tr>
<td>Percentage of stillbirths that are antepartum</td>
<td>((D/C)\times100)</td>
</tr>
<tr>
<td>Early neonatal mortality rate</td>
<td>((F/B)\times1000)</td>
</tr>
<tr>
<td>Perinatal mortality rate</td>
<td>(((C+F)/A)\times1000)</td>
</tr>
<tr>
<td>Neonatal mortality rate</td>
<td>((G/B)\times1000)</td>
</tr>
<tr>
<td>Maternal mortality ratio</td>
<td>((H/B)\times100 000)</td>
</tr>
<tr>
<td>Caesarean section rate (all births)</td>
<td>((I/A)\times100)</td>
</tr>
<tr>
<td>Assisted delivery rate (all births)</td>
<td>((J/A)\times100)</td>
</tr>
<tr>
<td>Low birth weight rate (live births)</td>
<td>((K/B)\times100)</td>
</tr>
<tr>
<td>Preterm rate (live births)</td>
<td>((L/B)\times100)</td>
</tr>
</tbody>
</table>
### Annex 8: Stillbirth and Neonatal Mortality Audit – Meeting Minutes and Action Items Form

### Annex 8a: Stillbirth and Neonatal Mortality Audit – Meeting Minutes and Action Items Form

| Institution: | __________________________________________________________________________ |
| Date of meeting: | ________________ | Start time: | ____________ | End time: | ____________ |
| Chairperson: | __________________________________________________________________________ |
| Month and year being reviewed: | __________________________________________________________________________ |

#### Statistics:
- Number of women delivered: ________
- Number of babies born: ________
- Preterm birth rate (< 37 weeks): ________%
- Low birth weight rate (< 2500 g): ________%
- Caesarean section rate: ________%
- Assisted delivery rate: ________%
- Antepartum stillbirth rate: ________
- Intrapartum stillbirth rate: ________
- Neonatal mortality rate: ________

#### Cases discussed

**Main causes of antepartum stillbirths:**
1. __________________________________________________________________________
2. __________________________________________________________________________
3. __________________________________________________________________________

**Main causes of intrapartum stillbirths:**
1. __________________________________________________________________________
2. __________________________________________________________________________
3. __________________________________________________________________________
Main causes of neonatal deaths:
1. 
2. 
3. 

Modifiable factors identified:
1. 
2. 
3. 

Action plans

<table>
<thead>
<tr>
<th>Modifiable factor identified</th>
<th>Specific actions to address modifiable factor</th>
<th>Responsible person</th>
<th>Time frame</th>
<th>Follow-up (this section to be completed at the next meeting)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Date of next meeting: ____________________________________________

Date minutes ratified: ____________________________________________

Proposed by: __________________________  Seconded by: __________________________

Chairperson’s signature: __________________________________________
Annex 8b. Guidance for completing the Stillbirth and Neonatal Mortality Audit – Meeting Minutes and Action Items Form

Steps for minute-taking at perinatal mortality audit meetings (also known as perinatal death review meetings):

1. Use this form to capture the minutes, which should be accompanied by the code of practice declaration signed before each meeting (see Annex 6) and the attendance register signed at the end of each meeting.

2. The meeting chairperson is responsible for ensuring that the minutes are taken, and that the form is filled in at the end of the meeting. Do not leave the filling of the form for a later time. For the minutes to be a functional document, the filling of the form needs to be part of the meeting process.

3. The statistics can be filled in on the form during preparations in advance of the meeting. If more extensive statistics are presented at the meeting, it is optional to attach a copy of the presentation as an addendum to the minutes.

4. Enter a one-line summary about each case presented. For example: “Case X.N., No. 45368, intrapartum stillbirth 2.5 kg, ruptured uterus”. It is not necessary to include a full case report. If requested, case presentations can be attached as an addendum to the minutes.

5. The chairperson should allocate at least 5 minutes at the end of the meeting to summarize the key problems that have been identified during the meeting, based on the presentation of statistics or the cases discussed, or both.

6. Based on these problems, action plans can be drawn up, as outlined on the table on the second page of the form. The task list should be clearly allocated and agreed upon at the meeting.

7. At the end of the meeting, the chairperson should ensure that the minutes form is fully complete, either on paper or electronically. Only the follow-up section of the table should be left blank.

8. Within 72 hours of the meeting, paper-based minutes should be typed up and stored electronically. This should not be a long task if the format of the template is adhered to. The typed minutes should be verified by the chairperson, and then circulated as draft minutes by email to all members on the attendance list for the meeting, other interested stakeholders and anyone with responsibility for one of the tasks in the action plan. The distribution of the draft minutes should be completed within a week of the date of the meeting.

9. At the following perinatal mortality audit meeting, the chairperson should allocate some time for reviewing the draft minutes of the previous meeting, preferably at the start of the meeting. If a task has not been completed, this should be noted in the follow-up column and the task can be carried over into the action plans table for the current meeting. Once the follow-up column from the minutes of the previous meeting has been filled in, those final minutes can be ratified, with a proposer and a seconder.

10. The meeting can then proceed with new statistics and/or case presentations.
Annex 9. Steps for establishing a mortality audit for stillbirths and neonatal deaths

Mortality audit (also known as “death review”) is a process to document the medical causes of each death and the contributing systemic failures across many cases, to identify solutions and to take action.

It is not a solution in itself.

It is a systematic way of improving quality of care by collecting and analysing data, linking solutions to identified problems, and ensuring accountability for changes to improve care.

1. Identify perinatal deaths
2. Collect information
3. Analyse results
4. Recommend solutions
5. Implement recommendations
6. Evaluate and refine
Steps

1. Understand the steps of the perinatal mortality audit cycle and underlying principles.
2. Establish or strengthen any local, regional or national stillbirth and neonatal mortality audit steering committee to oversee the process.
3. Ensure confidentiality and a legal and ethical framework.
4. Identify data and map all existing data and services.
5. Plan data collection:
   i. Obtain permission and engage the local community in the review process.
   ii. Set up the mortality audit steering committee.
   iii. Plan how you will identify cases.
   iv. Decide how to select a subset of identified cases for detailed review.
   v. Decide which data to collect on each case.
   vi. Pilot-test and refine data collection instruments.
   vii. Plan review of cases – who will do it and how.
   viii. Plan data analysis.
   ix. Educate and sensitize health-care staff.
   x. Set ground rules for review meetings.
6. Implement the system:
   i. Identify cases.
   ii. Collect the data.
   iii. Supervise data collectors.
   iv. Prepare data for review.
   v. Hold mortality audit meeting to review data.
   vi. Analyse the results.
   vii. Use findings to create a list of possible actions (during the review meeting).
   viii. Develop, prioritize and disseminate recommendations.
   ix. Forward data, case notes and recommendations to the next review level.
   x. Publish the results.
   xi. Evaluate and improve the system.
7. Assess the achievements of the perinatal mortality audit cycle, and expand and improve linkages.
Annex 10: Verbal and social autopsy tool for stillbirth and neonatal death audits in the community

Verbal and Social Autopsy Form
Stillbirths and Neonatal Deaths (1–28 days)

*Adapted for audit purposes from the 2014 WHO Verbal Autopsy Instrument*¹⁰,¹¹

*Instructions to interviewer:* Introduce yourself and explain the purpose of your visit. Ask to speak to the mother or to another adult caregiver who was present during the illness that led to the death. If this is not possible, arrange a time to revisit the household when the mother or caregiver will be home. Before interviewing the person, explain to him/her that participation in the interview is voluntary; s/he can refuse to answer any question and s/he can stop the interview at any time. Explain to him/her that the information provided is only for research purposes and will be confidential. *Leave the signed top page (copy of informed consent) with the interviewee.*


¹¹ The adaptation of the WHO 2014 Verbal Autopsy Instrument has been expanded for audit purposes with questions on social factors and questions specific to the perinatal period.
Informed Consent Form for verbal autopsy (VA) interviews (for stillbirths and decedents 1–28 days)

Hello. My name is ________________ and I am working with ________________ (AGENCY) a partner of the Ministry of Health. We are conducting a survey in this district that asks about health issues of newborn babies.

I am asking you to take part in this survey because I am trying to learn more about stillbirths and the causes of death among newborn babies. We are asking all households in this district that reported a stillbirth or death to a newborn baby since ________________ to participate in this survey. The government and its stakeholders have been improving access to health care and the provision of health services in this district. The information that you provide will help us understand health challenges faced by newborns.

I am visiting you today because we were informed about the death of (your baby). I am here now to ask you about the circumstances that led to his/her death. This information will help the government and its stakeholders to understand better ways through which they can improve neonatal health services and help us know whether the improvements in health care planned for your district are helping. The interview will take between 30 and 45 minutes to complete. Whatever information you provide will be kept strictly confidential and will not be shown to other persons.

Participation in this interview is voluntary, so if we should come to any question you don’t want to answer, just let me know and I will go to the next question; or you can stop the interview at any time. You should be aware that your answers about the deceased may say something about your own health. However, we hope that you will participate in this survey since your views are important. The information that you provide is strictly confidential. At this time, do you want to ask me anything about the information we are collecting or the survey?

May I begin the interview now?

☐ No, consent for participation not given  
Interviewer signature: ______________________________________

☐ Yes, consent for participation given  
Interviewer signature: ______________________________________

☐ Yes, consent for participation given  
Respondent signature: ______________________________________

OR Respondent thumb print: _______________________________

Date _______________________________

If you have any questions about this survey, please contact:
Name (Principal investigator)  
Institutional affiliation  
Telephone

If you ever have questions about your rights or ethics as a participant in this study, please contact:
Name (Principal investigator)  
Institutional affiliation  
Telephone
INFORMED CONSENT FORM (INTERVIEWER COPY)

Informed Consent Form for verbal autopsy (VA) interviews (for stillbirths and decedents 1–28 days)

Hello. My name is ____________________ and I am working with ____________________ (AGENCY) a partner of the Ministry of Health. We are conducting a survey in this district that asks about health issues of newborn babies.

I am asking you to take part in this survey because I am trying to learn more about the causes of death among stillbirths and newborn babies. We are asking all households in this district that reported a stillbirth or death to a newborn baby since __________ to participate in this survey. The Government and its stakeholders have been improving access to health care and the provision of health services in this district. The information that you provide will help us understand health challenges faced by newborns.

I am visiting you today because we were informed about the death of your baby. I am here now to ask you about the circumstances that led to his/her death. This information will help the government and its stakeholders to understand better ways through which they can improve neonatal health services and help us know whether the improvements in health care planned for your district are helping. The interview will take between 30 and 45 minutes to complete. Whatever information you provide will be kept strictly confidential and will not be shown to other persons.

Participation in this interview is voluntary, so if we should come to any question you don’t want to answer, just let me know and I will go to the next question; or you can stop the interview at any time. You should be aware that your answers about the deceased may say something about your own health. However, we hope that you will participate in this survey since your views are important. The information that you provide is strictly confidential. At this time, do you want to ask me anything about the information we are collecting or the survey?

May I begin the interview now?

☐ No, consent for participation not given  Interviewer signature: ________________________________

☐ Yes, consent for participation given  Interviewer signature: ________________________________

☐ Yes, consent for participation given  Respondent signature: ________________________________

OR Respondent thumb print: [ ]

Date ________________________________

If you have any questions about this survey, please contact:
Name (Principal investigator)
Institutional affiliation
Telephone

If you ever have questions about your rights or ethics as a participant in this study, please contact:
Name (Principal investigator)
Institutional affiliation
Telephone

SIGNATURE OF VA SUPERVISOR: ________________________________  VA SUPERVISOR CODE: [ ]
## SECTION 1. INTERVIEW AND DEMOGRAPHIC INFORMATION

### SECTION 1.1 INTERVIEWER VISITS

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>FINAL VISIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>DATE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INTERVIEWER'S NAME</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RESULT*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* RESULT CODES:
- 1 COMPLETED
- 2 NOT AT HOME
- 3 POSTPONED
- 4 REFUSED
- 5 PARTLY COMPLETED
- 6 NO APPROPRIATE RESPONDENT FOUND
- 7 OTHER (SPECIFY) _______________________________

## SECTION 1.2 ADDITIONAL DEMOGRAPHIC INFORMATION

(PLEASE USE CORRECT SPELLING FROM LIST)

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>TOTAL NUMBER OF VISITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISTRICT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEALTH SUBDISTRICT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUBCOUNTY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARISH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VILLAGE/LOCALITY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOUSEHOLD NUMBER (HHN)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAME OF DECEASED BABY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAME OF THE BABY'S MOTHER</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAME OF HOUSEHOLD HEAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

WHAT IS THE PRIMARY LANGUAGE OF THE INTERVIEW? ENGLISH _______________________________ 1
OTHER (SPECIFY) _______________________________ 2
## SECTION 2. BASIC INFORMATION ABOUT THE RESPONDENT

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 RECORD THE TIME AT THE START OF THE INTERVIEW</td>
<td>HOURS [ ] AND [ ] MINUTES</td>
</tr>
<tr>
<td>2.2 What is your name? RECORD THE NAME OF THE RESPONDENT</td>
<td>NAME</td>
</tr>
<tr>
<td>2.3 What is your relationship to the deceased baby? RECORD THE RELATIONSHIP OF THE MAIN RESPONDENT TO THE DECEASED BABY</td>
<td>MOTHER ............................................................... 1 → 3.1</td>
</tr>
<tr>
<td></td>
<td>FATHER ....................................................................... 2</td>
</tr>
<tr>
<td></td>
<td>SIBLING .................................................................... 3</td>
</tr>
<tr>
<td></td>
<td>OTHER RELATIVE ............................................................... 4</td>
</tr>
<tr>
<td></td>
<td>(SPECIFY)</td>
</tr>
<tr>
<td></td>
<td>NEIGHBOUR .................................................................. 5</td>
</tr>
<tr>
<td></td>
<td>FAMILY FRIEND ............................................................. 6</td>
</tr>
<tr>
<td></td>
<td>OTHER ...................................................................... 7</td>
</tr>
<tr>
<td></td>
<td>(SPECIFY)</td>
</tr>
<tr>
<td>2.4 Is the mother of the deceased alive?</td>
<td>YES ........................................................................ 1 → 2.8</td>
</tr>
<tr>
<td></td>
<td>NO .......................................................................... 2</td>
</tr>
<tr>
<td></td>
<td>DON’T KNOW ........................................................................ 8</td>
</tr>
<tr>
<td></td>
<td>REFUSE ....................................................................... 9</td>
</tr>
<tr>
<td>2.5 Did she die during or after delivery?</td>
<td>DURING DELIVERY ............................................................ 1 → 2.8</td>
</tr>
<tr>
<td></td>
<td>AFTER DELIVERY ........................................................... 2</td>
</tr>
<tr>
<td></td>
<td>DON’T KNOW ........................................................................ 8</td>
</tr>
<tr>
<td>2.6 How long after delivery did the mother die? ENTER TIME INTERVAL IN MINUTES OR HOURS OR DAYS</td>
<td>MINUTES ........................................ 1 [ ] [ ]</td>
</tr>
<tr>
<td></td>
<td>OR HOURS ............................................ 2 [ ] [ ]</td>
</tr>
<tr>
<td></td>
<td>OR DAYS ................................................... 3</td>
</tr>
<tr>
<td></td>
<td>2 OR MORE MONTHS ................................................ 777</td>
</tr>
<tr>
<td></td>
<td>DON’T KNOW ........................................................................ 998</td>
</tr>
<tr>
<td>2.7 What do you think was the primary cause of the mother’s death?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>2.8 Did you live with the deceased baby in the period leading to his/her death?</td>
<td>YES ........................................................................ 1</td>
</tr>
<tr>
<td></td>
<td>NO .......................................................................... 2</td>
</tr>
<tr>
<td></td>
<td>DON’T KNOW ........................................................................ 8</td>
</tr>
<tr>
<td></td>
<td>REFUSE ....................................................................... 9</td>
</tr>
</tbody>
</table>
### SECTION 3. INFORMATION ON THE DECEASED AND DATE/PLACE OF DEATH

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Was the baby named?</td>
<td>YES .................................................................................................1</td>
<td>→3.3</td>
</tr>
<tr>
<td></td>
<td>NO .................................................................................................2</td>
<td>→3.3</td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW ..................................................................................8</td>
<td>→3.3</td>
</tr>
<tr>
<td>3.2 What was the name of the baby who died?</td>
<td>NAME</td>
<td>RECORD THE NAME OF THE BABY AND USE THROUGHOUT THE INTERVIEW</td>
</tr>
<tr>
<td>3.3 What was the sex of the baby?</td>
<td>FEMALE ............................................................................................1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MALE ...............................................................................................2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UNDETERMINED ..................................................................................3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW ...................................................................................8</td>
<td></td>
</tr>
<tr>
<td>3.4 In what day, month and year was the baby born?</td>
<td>DAY .................................................................................................1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MONTH ..............................................................................................2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>YEAR ..............................................................................................3</td>
<td></td>
</tr>
<tr>
<td>3.5 In what day, month and year did the baby die?</td>
<td>DAY .................................................................................................1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MONTH ..............................................................................................2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>YEAR ..............................................................................................3</td>
<td></td>
</tr>
<tr>
<td>3.6 How old was the baby when he/she died?</td>
<td>MINUTES .........................................................................................1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR HOURS .......................................................................................2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR DAYS .........................................................................................3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW ...................................................................................998</td>
<td></td>
</tr>
<tr>
<td>3.7 INTERVIEWER, CHECK AGE AT DEATH (PROBE IF THE BABY DIED BEFORE OR AFTER 28 COMPLETED DAYS OF LIFE)</td>
<td>1. AGE BETWEEN 1 AND 28 DAYS ..................................................1</td>
<td>END</td>
</tr>
<tr>
<td></td>
<td>2. AGE 28 DAYS OR MORE ..................................................................2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. DON'T KNOW ................................................................................8</td>
<td></td>
</tr>
<tr>
<td>3.8 Was the baby a resident in this village, or was he/she brought home for illness or burial?</td>
<td>RESIDENT IN THE VILLAGE ...............................................................1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HOME COMING SICK ...........................................................................2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BODY BROUGHT HOME FOR BURIAL .....................................................3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW ...................................................................................8</td>
<td></td>
</tr>
<tr>
<td>3.9 Where did the baby die?</td>
<td>OWN HOME ..........................................................................................01</td>
<td>→3.9.2</td>
</tr>
<tr>
<td></td>
<td>TBA'S WORK AREA/HOME .....................................................................02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ENROUTE TO HOSPITAL/HEALTH FACILITY ..........................................03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PUBLIC SECTOR HEALTH CARE ................................................................</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GOVERNMENT HOSPITAL .......................................................................04</td>
<td></td>
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<td></td>
<td>GOVERNMENT HEALTH CENTRE ................................................................05</td>
<td></td>
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<tr>
<td></td>
<td>OTHER PUBLIC SECTOR (SPECIFY) .....................................................06</td>
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</tr>
<tr>
<td></td>
<td>PRIVATE SECTOR HEALTH CARE ..........................................................</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PRIVATE HOSPITAL/CLINIC ..................................................................07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OTHER PRIVATE SECTOR (SPECIFY) .....................................................08</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OTHER (SPECIFY) ...............................................................................10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW ...................................................................................98</td>
<td></td>
</tr>
<tr>
<td></td>
<td>REFUSE ............................................................................................99</td>
<td></td>
</tr>
<tr>
<td>3.9.1 What was the name of the health-care facility where the baby died?</td>
<td>NAME :</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.9.2 Was the baby taken to any (other) health-care facility for treatment prior to his/her death?

<table>
<thead>
<tr>
<th>Response</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>1</td>
</tr>
<tr>
<td>NO</td>
<td>2</td>
</tr>
<tr>
<td>DON’T KNOW</td>
<td>8</td>
</tr>
<tr>
<td>REFUSE</td>
<td>9</td>
</tr>
</tbody>
</table>

3.9.3 What was the name of the health-care facilities where he/she received treatment?

REVIEW LIST PROVIDED

PROBE: “ANY OTHER FACILITY?”

<table>
<thead>
<tr>
<th>Name</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NAME: ______________________</td>
<td></td>
</tr>
<tr>
<td>NAME: ______________________</td>
<td></td>
</tr>
<tr>
<td>NAME: ______________________</td>
<td></td>
</tr>
</tbody>
</table>

TBA: traditional birth attendant

RESPONDENT’S ACCOUNT OF ILLNESS/EVENTS LEADING TO DEATH

Instructions to interviewer: Allow the respondent to tell you about the illness in his or her own words. Do not prompt except for asking whether there was anything else after the respondent finishes. Keep prompting until the respondent says there was nothing else. While recording, underline any unfamiliar terms.

ASK THE RESPONDENT:

Could you tell me about the illness that led to the baby’s death?

PROBE FOR:

Recognition in the home – first symptoms recognized, other symptoms, when did the family realize it was severe, who recognized the first symptoms and the severity of the symptoms.

Timing – how long did it take from first symptoms to become severe.

Actions taken in the home and outside the home – how long after first symptom(s) and severe symptom(s) was any action taken, what actions, was there any treatment given, what treatment, who made the decision to seek or not to seek care, reason for this action, if care outside the home was not sought – why?

Transport: Include the time spent from making the decision for seeking care outside the home to getting transport, type of transportation used to reach the first level of care and any potential referrals, time spent during transport, any delays that may have occurred before reaching care.

Provider behaviour, if care was sought outside the home – advice given, treatment given, how long did it take to receive the care after reaching health-care services, complete referral history, timing of referral, time spent on travel to and between facilities, reasons for not going or delaying referral, referral experience.

ASK THE RESPONDENT:

Do you feel the death could have been avoided somehow? Please explain:

PROBE FOR: What could have been done at the household level? What could have been done to improve access to health care outside the house? What could have been done to improve care after reaching a health-care facility? What could have been done to improve referral to higher levels of care? etc.

____________________________________________________________________________________________________________
____________________________________________________________________________________________________________
____________________________________________________________________________________________________________
____________________________________________________________________________________________________________
____________________________________________________________________________________________________________
____________________________________________________________________________________________________________
____________________________________________________________________________________________________________
**ASK THE RESPONDENT:** What do you think was the primary or basic cause of death?

**OR** Based on our conversation, what would you say is the primary cause of death?

---

**PRIMARY CAUSE OF DEATH ACCORDING TO RESPONDENT**

---

**ASK THE RESPONDENT:** In addition to this primary cause, do you think there are any additional or secondary causes of death?

**OR** Based on our conversation, what would you say are the secondary causes of death?

---

**SECONDARY CAUSE OF DEATH ACCORDING TO RESPONDENT**
### SECTION 4. PREGNANCY HISTORY AND CARE

I would like to ask you some questions concerning the mother and symptoms that the deceased had/showed at birth and shortly after. Some of these questions may not appear to be directly related to the baby’s death. Please bear with me and answer all the questions. They will help us to get a clear picture of all possible symptoms that the deceased had.

**IF THE RESPONDENT IS THE MOTHER, ADJUST LANGUAGE TO REFLECT THAT BY ADDRESSING THE WOMAN.**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1 What was the age of the mother at the time the baby died?</td>
<td>YEARS .........................................................................................................</td>
</tr>
<tr>
<td></td>
<td>DON’T KNOW ............................................................................................</td>
</tr>
<tr>
<td>4.1.1 What was her occupation – that is, what kind of work did the mother mainly do?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>.............................................................................................................</td>
</tr>
<tr>
<td>4.1.2 What was the highest level and year (step/grade) of formal education the mother attended?</td>
<td>Level Years</td>
</tr>
<tr>
<td></td>
<td>NONE .................................................................................0 0</td>
</tr>
<tr>
<td></td>
<td>PRIMARY ........................................................................1 1</td>
</tr>
<tr>
<td></td>
<td>SECONDARY ..................................................................2 2</td>
</tr>
<tr>
<td></td>
<td>TERTIARY ......................................................................3 3</td>
</tr>
<tr>
<td></td>
<td>DON’T KNOW ........................................................................8 8</td>
</tr>
<tr>
<td></td>
<td>REFUSE .............................................................................9 9</td>
</tr>
<tr>
<td>4.2 Did the mother receive any antenatal care during the pregnancy?</td>
<td>YES .................................................................................................1 1</td>
</tr>
<tr>
<td></td>
<td>NO .............................................................................................2 2</td>
</tr>
<tr>
<td></td>
<td>DON’T KNOW ...............................................................................8 8</td>
</tr>
<tr>
<td>4.3 How many antenatal visits did the woman have during the pregnancy?</td>
<td>VISITS ...........................................................................................</td>
</tr>
<tr>
<td></td>
<td>AT LEAST 4 ........................................................................77 77</td>
</tr>
<tr>
<td></td>
<td>DON’T KNOW ...............................................................................98 98</td>
</tr>
<tr>
<td>4.4 How many weeks or months pregnant was the woman at her first antenatal visit?</td>
<td>WEEKS OR MONTHS</td>
</tr>
<tr>
<td></td>
<td>WEEKS ..................................................................................1 1</td>
</tr>
<tr>
<td></td>
<td>OR ............................................................................................</td>
</tr>
<tr>
<td></td>
<td>MONTHS ............................................................................2 2</td>
</tr>
<tr>
<td></td>
<td>DON’T KNOW ........................................................................98 98</td>
</tr>
<tr>
<td>4.4.1 When the woman became pregnant with this pregnancy, was she using any form of family planning?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NO METHOD ...........................................................................0 0</td>
</tr>
<tr>
<td></td>
<td>LACTATIONAL AMENORRHOEA METHOD ...........................................0 1</td>
</tr>
<tr>
<td></td>
<td>RHYTHM METHOD ................................................................0 2</td>
</tr>
<tr>
<td></td>
<td>WITHDRAWAL ...........................................................................0 3</td>
</tr>
<tr>
<td></td>
<td>PILL ........................................................................................0 4</td>
</tr>
<tr>
<td></td>
<td>IUD ..........................................................................................0 5</td>
</tr>
<tr>
<td></td>
<td>INJECTABLES ..............................................................................0 6</td>
</tr>
<tr>
<td></td>
<td>IMPLANTS ..............................................................................0 7</td>
</tr>
<tr>
<td></td>
<td>CONDOM ..................................................................................0 8</td>
</tr>
<tr>
<td></td>
<td>FEMALE CONDOM .....................................................................0 9</td>
</tr>
<tr>
<td></td>
<td>DIAPHRAGM .............................................................................10 10</td>
</tr>
<tr>
<td></td>
<td>FOAM/JELLY ..........................................................................11 11</td>
</tr>
<tr>
<td></td>
<td>OTHER MODERN (SPECIFY) .........................................................12 12</td>
</tr>
<tr>
<td></td>
<td>OTHER TRADITIONAL (SPECIFY) ....................................................13 13</td>
</tr>
<tr>
<td></td>
<td>DON’T KNOW ...............................................................................98 98</td>
</tr>
</tbody>
</table>
4.4.2 Before the woman became pregnant with this pregnancy, how many times per week was she drinking alcoholic beverages?

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 TIMES OR MORE /ALMOST DAILY</td>
<td>1</td>
</tr>
<tr>
<td>1–3 TIMES</td>
<td>2</td>
</tr>
<tr>
<td>LESS THAN ONCE PER WEEK</td>
<td>3</td>
</tr>
<tr>
<td>NEVER</td>
<td>4</td>
</tr>
</tbody>
</table>

4.4.3 How many times per week was she drinking alcoholic beverages during pregnancy?

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 TIMES OR MORE /ALMOST DAILY</td>
<td>1</td>
</tr>
<tr>
<td>1–3 TIMES</td>
<td>2</td>
</tr>
<tr>
<td>LESS THAN ONCE PER WEEK</td>
<td>3</td>
</tr>
<tr>
<td>NEVER</td>
<td>4</td>
</tr>
</tbody>
</table>

4.5 Did the baby’s mother receive any tetanus vaccination during the pregnancy?

<table>
<thead>
<tr>
<th>Response</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>1</td>
</tr>
<tr>
<td>NO</td>
<td>2</td>
</tr>
<tr>
<td>DON'T KNOW</td>
<td>8</td>
</tr>
</tbody>
</table>

4.5.1 How many doses?

<table>
<thead>
<tr>
<th>Number of Doses</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>98</td>
</tr>
</tbody>
</table>

4.6 How many times per week was she drinking alcoholic beverages during pregnancy?

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 TIMES OR MORE /ALMOST DAILY</td>
<td>1</td>
</tr>
<tr>
<td>1–3 TIMES</td>
<td>2</td>
</tr>
<tr>
<td>LESS THAN ONCE PER WEEK</td>
<td>3</td>
</tr>
<tr>
<td>NEVER</td>
<td>4</td>
</tr>
</tbody>
</table>

4.6.1 Did the mother receive IPTp (IPTp-SP, Fansidar or equivalent) for malaria prevention during the pregnancy?

<table>
<thead>
<tr>
<th>Response</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>1</td>
</tr>
<tr>
<td>NO</td>
<td>2</td>
</tr>
<tr>
<td>DON'T KNOW</td>
<td>8</td>
</tr>
</tbody>
</table>

4.7 Did the mother take iron supplements?

<table>
<thead>
<tr>
<th>Response</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>1</td>
</tr>
<tr>
<td>NO</td>
<td>2</td>
</tr>
<tr>
<td>DON'T KNOW</td>
<td>8</td>
</tr>
</tbody>
</table>

4.7.1 Did the mother take folic acid?

<table>
<thead>
<tr>
<th>Response</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>1</td>
</tr>
<tr>
<td>NO</td>
<td>2</td>
</tr>
<tr>
<td>DON'T KNOW</td>
<td>8</td>
</tr>
</tbody>
</table>

4.8 Did the mother take deworming tablets?

<table>
<thead>
<tr>
<th>Response</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>1</td>
</tr>
<tr>
<td>NO</td>
<td>2</td>
</tr>
<tr>
<td>DON'T KNOW</td>
<td>8</td>
</tr>
</tbody>
</table>

4.9 Did the mother sleep under a bed net during the pregnancy?

<table>
<thead>
<tr>
<th>Response</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>1</td>
</tr>
<tr>
<td>NO</td>
<td>2</td>
</tr>
<tr>
<td>DON'T KNOW</td>
<td>8</td>
</tr>
</tbody>
</table>

4.10 Was the mother ever tested for HIV/AIDS?

<table>
<thead>
<tr>
<th>Response</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>1</td>
</tr>
<tr>
<td>NO</td>
<td>2</td>
</tr>
<tr>
<td>DON'T KNOW</td>
<td>8</td>
</tr>
</tbody>
</table>

4.11 Was she HIV-positive or HIV-negative?

<table>
<thead>
<tr>
<th>Response</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>POSITIVE</td>
<td>1</td>
</tr>
<tr>
<td>NEGATIVE</td>
<td>2</td>
</tr>
<tr>
<td>DON'T KNOW</td>
<td>8</td>
</tr>
</tbody>
</table>

4.12 How long ago had she been diagnosed as HIV-positive?

<table>
<thead>
<tr>
<th>Time</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>WEEKS AGO</td>
<td>1</td>
</tr>
<tr>
<td>OR MOWNTHS AGO</td>
<td>2</td>
</tr>
<tr>
<td>OR YEARS AGO</td>
<td>3</td>
</tr>
<tr>
<td>DON'T KNOW</td>
<td>998</td>
</tr>
</tbody>
</table>

4.13 At the time of delivery, was she taking ARVs or Septrin for HIV or was she not taking HIV treatment?

<table>
<thead>
<tr>
<th>Response</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARVS</td>
<td>1</td>
</tr>
<tr>
<td>ARVS + SEPTRIN</td>
<td>2</td>
</tr>
<tr>
<td>SEPTRIN</td>
<td>3</td>
</tr>
<tr>
<td>NOT TAKING TREATMENT</td>
<td>4</td>
</tr>
<tr>
<td>DON'T KNOW</td>
<td>8</td>
</tr>
<tr>
<td>REFUSE</td>
<td>9</td>
</tr>
</tbody>
</table>
### 4.14 How long has she been taking ARVs for HIV?

- **Weeks**
- **Month**
- **Year**
- **Don't know**

IF LESS THAN 1 YEAR, NOTE NUMBER OF MONTHS; IF GREATER THAN 12 MONTHS, NOTE NUMBER OF YEARS

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>DON'T KNOW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

During the pregnancy was the mother told by a health-care provider that she suffers from any of the following known illnesses: READ ALL OPTIONS:

1. **High Blood Pressure**
2. **Heart Disease**
3. **Diabetes**
4. **Epilepsy/Convulsion**
5. **Malnutrition**
6. **Malaria**
7. **TB**
8. **Anaemia**
9. **Sickle Cell Anaemia**
10. **Syphilis**
11. **Rubella**
12. **Other Sexually Transmitted Infections (excluding HIV)**
13. **Did she suffer from any other medically diagnosed illness? (specify illness)**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>DON'T KNOW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

During the last 3 months of pregnancy but before labour, did the mother have any of the following symptoms: READ ALL OPTIONS:

1. **Heavy Vaginal Bleeding**
2. **Foul Smelly Vaginal Discharge**
3. **Swelling of Fingers, Face, Legs**
4. **Headache**
5. **Blurred Vision**
6. **Convulsion**
7. **Fever**
8. **Severe Abdominal Pain that was not labour pain**
9. **Pallor and Shortness of Breath (both present)**
10. **Yellow Discolouration of the Eyes**
11. **Did she suffer from any other illness? (specify illness)**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>DON'T KNOW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

It is common for women during and after pregnancy to feel down or depressed.

During the last 3 months of pregnancy but before labour, how often did (you – if mother is the respondent; or the mother – if other respondent) have little interest or pleasure in doing things?

- **Not at all**
- **Several weeks**
- **More than half of the time (of 3 months)**
- **Nearly every day**
- **Don't know**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>DON'T KNOW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Footnotes

115 MAKING EVERY BABY COUNT: AUDIT AND REVIEW OF STILLBIRTHS AND NEONATAL DEATHS
### 4.16.2 During the last 3 months of pregnancy but before labour, how often were (you – if mother is the respondent; or the mother – if other respondent) down, depressed or hopeless?

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>1</td>
</tr>
<tr>
<td>Several weeks</td>
<td>2</td>
</tr>
<tr>
<td>More than half of the time (of 3 months)</td>
<td>3</td>
</tr>
<tr>
<td>Nearly every day</td>
<td>4</td>
</tr>
<tr>
<td>Don't know</td>
<td>8</td>
</tr>
</tbody>
</table>

### 4.17 How many births, including stillbirths, did the mother have **before** this baby?

**Count all babies born alive or dead at or after 7 months of pregnancy; do not count the birth of the baby who died**

<table>
<thead>
<tr>
<th>Number of births</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Don't know</td>
<td>98</td>
</tr>
</tbody>
</table>

### 4.18 How many of these previous births were stillbirths?

**Born dead after 7 months of pregnancy**

<table>
<thead>
<tr>
<th>Number of stillbirths</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Don't know</td>
<td>98</td>
</tr>
</tbody>
</table>

### 4.19 Now, let's talk about the birth of the baby who died. How many weeks or months was the mother pregnant when the baby was born?

**Try to record in weeks, whenever possible**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Don't know</td>
<td>998</td>
</tr>
</tbody>
</table>

### 4.20 Was the baby born before expected?

<table>
<thead>
<tr>
<th>Was the baby born before expected?</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Don't know</td>
<td>8</td>
</tr>
</tbody>
</table>

### 4.20.1 How many days, weeks or months was the baby born before the expected date of delivery?

**Enter in days or weeks or months**

<table>
<thead>
<tr>
<th>Days</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Don't know</td>
<td>998</td>
</tr>
</tbody>
</table>

### 4.21 Was the baby a single or multiple birth?

<table>
<thead>
<tr>
<th>Type of birth</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singleton</td>
<td>1</td>
</tr>
<tr>
<td>Twin</td>
<td>2</td>
</tr>
<tr>
<td>Triplet or more</td>
<td>3</td>
</tr>
<tr>
<td>Don't know</td>
<td>8</td>
</tr>
</tbody>
</table>

### 4.21.1 What was the birth order of the baby that died, in the case of a multiple birth?

<table>
<thead>
<tr>
<th>Birth order</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>1</td>
</tr>
<tr>
<td>Second</td>
<td>2</td>
</tr>
<tr>
<td>Third</td>
<td>3</td>
</tr>
<tr>
<td>Other (Specify)</td>
<td>4</td>
</tr>
<tr>
<td>Don't know</td>
<td>8</td>
</tr>
</tbody>
</table>

### 4.21.2 Before the birth of this baby (babies, if twin delivery), when did the woman have her previous pregnancy (dd/mm/yyyy)?

**Record “98” if don’t know day or month**

<table>
<thead>
<tr>
<th>Day</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Don’t know</td>
<td>998</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Month</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Don't know</td>
<td>998</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Don’t know</td>
<td>9998</td>
</tr>
</tbody>
</table>

### 4.21.3 What was the outcome of the last pregnancy before this baby?

**Circle “7” if the baby who died was the first pregnancy**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single live birth</td>
<td>1</td>
</tr>
<tr>
<td>Multiple birth (all alive)</td>
<td>2</td>
</tr>
<tr>
<td>Multiple birth (one alive)</td>
<td>3</td>
</tr>
<tr>
<td>Multiple birth (all dead)</td>
<td>4</td>
</tr>
<tr>
<td>Single stillbirth</td>
<td>5</td>
</tr>
<tr>
<td>Abortion</td>
<td>6</td>
</tr>
<tr>
<td>No previous pregnancy</td>
<td>7</td>
</tr>
<tr>
<td>Don't know</td>
<td>8</td>
</tr>
</tbody>
</table>
## SECTION 5. DELIVERY HISTORY

### 5.1 Where was the baby born?

<table>
<thead>
<tr>
<th>Option</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>OWN HOME</td>
<td>01</td>
</tr>
<tr>
<td>TBA’S WORK AREA/HOME</td>
<td>02</td>
</tr>
<tr>
<td>ENROUTE TO HOSPITAL/HEALTH FACILITY</td>
<td>03</td>
</tr>
<tr>
<td>PUBLIC SECTOR HEALTH CARE</td>
<td></td>
</tr>
<tr>
<td>GOVERNMENT HOSPITAL</td>
<td>04</td>
</tr>
<tr>
<td>GOVERNMENT HEALTH CENTRE</td>
<td>05</td>
</tr>
<tr>
<td>OTHER PUBLIC SECTOR (SPECIFY)</td>
<td>06</td>
</tr>
<tr>
<td>PRIVATE SECTOR HEALTH CARE</td>
<td></td>
</tr>
<tr>
<td>PRIVATE HOSPITAL/CLINIC</td>
<td>07</td>
</tr>
<tr>
<td>OTHER PRIVATE SECTOR (SPECIFY)</td>
<td>08</td>
</tr>
<tr>
<td>OTHER (SPECIFY)</td>
<td>77</td>
</tr>
<tr>
<td>DON’T KNOW</td>
<td>98</td>
</tr>
</tbody>
</table>

### 5.1.1 How soon after labour started did she receive assistance with labour and delivery?

- **HOURS**
  - Did not receive assistance: 20
- Induction of labour for fetal death: 55
- Induction of labour/postdate baby: 66
- No labour, planned C-section: 77
- Don’t know: 98

### 5.2 Who assisted the delivery?

<table>
<thead>
<tr>
<th>Role</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor</td>
<td>1</td>
</tr>
<tr>
<td>Clinical officer/medical assistant</td>
<td>2</td>
</tr>
<tr>
<td>Nurse</td>
<td>3</td>
</tr>
<tr>
<td>Midwife</td>
<td>4</td>
</tr>
<tr>
<td>Traditional birth attendant</td>
<td>5</td>
</tr>
<tr>
<td>Relative</td>
<td>6</td>
</tr>
<tr>
<td>Mother by herself</td>
<td>7</td>
</tr>
<tr>
<td>Other (specify)</td>
<td>8</td>
</tr>
<tr>
<td>Don’t know</td>
<td>9</td>
</tr>
</tbody>
</table>

### 5.3 How many hours or days was she in labour before delivery?

- **HOURS**
  - More than 24 hours: 777
- Don’t know: 998

### 5.3.1 Was the mother given any medication during labour to stimulate contractions?

- Yes (specify): 1
- No: 2
- Don’t know: 8

### 5.3.2 Do you know whether the mother used local herbs during pregnancy, labour and delivery, or after delivery (in relation to this last pregnancy)?

- During pregnancy but before labour: 1
- During labour and delivery: 2
- After delivery: 3
- During pregnancy and labour/delivery: 4
- Don’t know: 8

### 5.4 When did the water break?

- Before labour started: 1
- During labour: 2
- Don’t know: 8

⇒ 5.7
<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
</table>
| 5.5 How many hours or days passed between her water breaking and birth? | **HOURS** ............................................................................. 1  
**OR**  
**DAYS** ............................................................................. 2  
**IF LESS THAN 1 HOUR, RECORD “00” IN HOURS**  
**IF RESPONDENT DOESN’T KNOW, ASK IF THE WATER BROKE > 24 HOURS BEFORE DELIVERY.** |
| 5.5.1 What colour was the water?                                         | **CLEAR** ............................................................................... 1  
**YELLOW/GREEN** .................................................................... 2  
**GREEN/BROWN** ..................................................................... 3  
**DARK RED** ............................................................................ 4  
**BRIGHT RED** ......................................................................... 5  
**DON’T KNOW** ......................................................................... 8  |
| 5.6 Was the water foul smelling?                                         | **YES** ................................................................................. 1  
**NO** ...................................................................................... 2  
**DON’T KNOW** ......................................................................... 8  |
| 5.7 Was there excessive bleeding before, during or after delivery?      | **NO** .................................................................................... 1  
**BEFORE DELIVERY** ................................................................ 2  
**DURING DELIVERY** ................................................................ 3  
**AFTER DELIVERY** .................................................................. 4  
**BOTH BEFORE AND AFTER** .................................................... 5  
**DON’T KNOW** ......................................................................... 8  |
| 5.8 Did she have convulsions before, during or after delivery?          | **NO** .................................................................................... 1  
**BEFORE DELIVERY** ................................................................ 2  
**DURING DELIVERY** ................................................................ 3  
**AFTER DELIVERY** .................................................................. 4  
**BOTH BEFORE AND AFTER** .................................................... 5  
**DON’T KNOW** ......................................................................... 8  |
| 5.9 Did she have fever before, during or after delivery?                | **NO** .................................................................................... 1  
**BEFORE DELIVERY** ................................................................ 2  
**DURING DELIVERY** ................................................................ 3  
**AFTER DELIVERY** .................................................................. 4  
**BOTH BEFORE AND AFTER** .................................................... 5  
**DON’T KNOW** ......................................................................... 8  |
| 5.10 Did the baby stop moving in the womb?                               | **YES** ................................................................................. 1  
**NO** ...................................................................................... 2  
**DON’T KNOW** ......................................................................... 8   |
| 5.10.1 When did the baby stop moving in the womb?                       | **BEFORE LABOUR STARTED** .................................................... 1  
**DURING LABOUR** .................................................................... 2  
**DON’T KNOW** ......................................................................... 8  |
| 5.11 Did a birth attendant listen for fetal heart sounds during labour with an electric device (Doppler) or cone-shaped stethoscope placed on the abdomen? | **YES, DOPPLER** ................................................................. 1  
**YES, STETHOSCOPE** ........................................................... 2  
**NO** ...................................................................................... 3  
**DON’T KNOW** ......................................................................... 8  |
| 5.11.1 Were fetal heart sounds present?                                 | **YES** ................................................................................. 1  
**NO** ...................................................................................... 2  
**DON’T KNOW** ......................................................................... 8  |
| 5.11.2 Was an ultrasound scan done just before labour started or during labour? | **JUST BEFORE LABOUR STARTED** ............................................ 1  
**DURING LABOUR** .................................................................... 2  
**NEITHER JUST BEFORE NOR DURING LABOUR** ............................ 3  
**DON’T KNOW** ......................................................................... 8  |
<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.11.3 Did the scan show any fetal heart beats?</td>
<td>YES 1, NO 2, DON'T KNOW 8</td>
</tr>
<tr>
<td>5.12 What type of delivery was it?</td>
<td>NORMAL VAGINAL DELIVERY 0, FORCEPS/VACUUM 1, CAESAREAN SECTION 2, ASSISTED BREECH DELIVERY 3, OTHER (SPECIFY) 4, DON'T KNOW 8</td>
</tr>
<tr>
<td>5.12.1 After the baby was delivered, was any injection given to the mother?</td>
<td>YES 1, NO 2, DON'T KNOW 8</td>
</tr>
<tr>
<td>5.13 Which part of the baby came first?</td>
<td>HEAD 1, BOTTOM 2, FEET 3, ARM/HAND 4, CORD 5, OTHER (SPECIFY) 6, DON'T KNOW 8</td>
</tr>
<tr>
<td>5.14 Did the umbilical cord come out before the baby was born?</td>
<td>YES 1, NO 2, DON'T KNOW 8</td>
</tr>
<tr>
<td>5.15 Was the cord wrapped more than once around the neck of the baby?</td>
<td>YES 1, NO 2, DON'T KNOW 8</td>
</tr>
<tr>
<td>5.15.1 Was there a cord knot?</td>
<td>YES 1, NO 2, DON'T KNOW 8</td>
</tr>
<tr>
<td>5.15.2 What colour was the cord?</td>
<td>NORMAL WHITE/GREY COLOR 1, RED/BROWN 2, GREEN/YELLOW 3, OTHER (SPECIFY) 7, DON'T KNOW 8</td>
</tr>
<tr>
<td>5.16 Was the placenta different from the normal red/blue in colour, soft in consistency, circular normal placenta?</td>
<td>YES (SPECIFY) 1, NO 2, MOTHER DIED WITH PLACENTA INSIDE HER 3, DON'T KNOW 8</td>
</tr>
<tr>
<td>5.16.1 Was the placenta foul smelling?</td>
<td>YES 1, NO 2, DON'T KNOW 8</td>
</tr>
<tr>
<td>5.17 What was the birth weight in grams?</td>
<td>IF ANSWERED IN KILOGRAMS, MULTIPLY BY 1000 AND RECORD IN GRAMS</td>
</tr>
<tr>
<td>5.18 Would you say the baby’s size at birth was smaller than normal, normal or bigger than normal?</td>
<td>SMALLER THAN NORMAL 1, NORMAL 2, BIGGER THAN NORMAL 3, DON'T KNOW 8</td>
</tr>
<tr>
<td>Question</td>
<td>Option 1</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>5.19 On what surface did the mother deliver?</td>
<td>LABOUR BED</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW</td>
</tr>
<tr>
<td>5.20 Did the birth attendant wash his/her hands before examining the mother?</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>5.21 Did the birth attendant use gloves?</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>5.22 Was anything applied to the umbilical cord stump after birth?</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>5.22.1 What was applied to the umbilical cord stump after birth?</td>
<td>CLORHEXIDINE</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW</td>
</tr>
<tr>
<td>5.23 What tool was used for cutting the cord?</td>
<td>NEW RAZOR BLADE</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW</td>
</tr>
<tr>
<td>5.24 What material was used for tying the cord?</td>
<td>CLEAN PIECE OF THREAD</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW</td>
</tr>
<tr>
<td>5.25 Were there any bruises or signs of injury on the baby’s body after birth?</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>5.25.1 Where were the injury marks?</td>
<td>SPECIFY</td>
</tr>
<tr>
<td>5.26 Was there any sign of paralysis?</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>5.27 Did the baby have any major malformation at birth?</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Question</td>
<td>Options</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>5.27.1 What kind of malformation did the baby have?</td>
<td>SWELLING/DEFECT ON THE BACK ..................................................................................1</td>
</tr>
<tr>
<td></td>
<td>VERY LARGE HEAD .........................................................................................................2</td>
</tr>
<tr>
<td></td>
<td>VERY SMALL HEAD ..........................................................................................................3</td>
</tr>
<tr>
<td></td>
<td>DEFECT OF LIP AND/OR PALATE ....................................................................................4</td>
</tr>
<tr>
<td></td>
<td>EXTRA FINGER/TOES .........................................................................................................5</td>
</tr>
<tr>
<td></td>
<td>INTESTINES PROTRUDING THROUGH ABDOMEN ......................................................................6</td>
</tr>
<tr>
<td></td>
<td>OTHER (SPECIFY) ............................................................................................................7</td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW ................................................................................................................8</td>
</tr>
<tr>
<td>5.28 What was the colour of the baby at birth?</td>
<td>NORMAL/PINK ................................................................................................................1</td>
</tr>
<tr>
<td></td>
<td>PALE ALL OVER ...............................................................................................................2</td>
</tr>
<tr>
<td></td>
<td>BLUE ALL OVER ................................................................................................................3</td>
</tr>
<tr>
<td></td>
<td>PALE/BLUE HANDS AND FEET ............................................................................................4</td>
</tr>
<tr>
<td></td>
<td>OTHER (SPECIFY) ............................................................................................................7</td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW ................................................................................................................8</td>
</tr>
<tr>
<td>5.28.1 Was there any green/brown material or substance on the baby's skin?</td>
<td>YES ................................................................................................................................1</td>
</tr>
<tr>
<td></td>
<td>NO ................................................................................................................................2</td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW ...................................................................................................................8</td>
</tr>
<tr>
<td>5.28.2 Were the baby's hands or feet swollen?</td>
<td>YES ................................................................................................................................1</td>
</tr>
<tr>
<td></td>
<td>NO ................................................................................................................................2</td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW ...................................................................................................................8</td>
</tr>
<tr>
<td>5.29 Did the baby ever cry after birth, even a little?</td>
<td>YES ................................................................................................................................1</td>
</tr>
<tr>
<td></td>
<td>NO ................................................................................................................................2</td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW ...................................................................................................................8</td>
</tr>
<tr>
<td>5.30 How many minutes after birth did the baby first cry?</td>
<td>LESS THAN ONE MINUTE .....................................................................................................77</td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW ..................................................................................................................98</td>
</tr>
<tr>
<td>5.30.1 Did the baby stop being able to cry?</td>
<td>YES ................................................................................................................................1</td>
</tr>
<tr>
<td></td>
<td>NO ................................................................................................................................2</td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW ...................................................................................................................8</td>
</tr>
<tr>
<td>5.30.2 How long before death did the baby stop crying?</td>
<td>MINUTES ........................................................................................................................1</td>
</tr>
<tr>
<td></td>
<td>OR HOURS ......................................................................................................................2</td>
</tr>
<tr>
<td></td>
<td>OR DAYS ........................................................................................................................3</td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW ..................................................................................................................998</td>
</tr>
<tr>
<td>5.31 Did the baby breathe after birth, even a little?</td>
<td>YES ................................................................................................................................1</td>
</tr>
<tr>
<td></td>
<td>NO ................................................................................................................................2</td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW ...................................................................................................................8</td>
</tr>
<tr>
<td>PROBE FOR PRESENCE OF ANY CHEST MOVEMENT; CIRCLE &quot;YES&quot; EVEN IF ONLY SMALL OR IRREGULAR MOVEMENTS WERE PRESENT</td>
<td></td>
</tr>
<tr>
<td>5.32 Was the baby given assistance to breathe?</td>
<td>YES NO DON'T KNOW</td>
</tr>
<tr>
<td></td>
<td>STIMULATION ....................................................................................................................1</td>
</tr>
<tr>
<td></td>
<td>RUBBING THE BACK ...........................................................................................................1</td>
</tr>
<tr>
<td></td>
<td>BAG AND MASK ..................................................................................................................1</td>
</tr>
<tr>
<td></td>
<td>SUCTION ............................................................................................................................1</td>
</tr>
<tr>
<td></td>
<td>INTUBATION ......................................................................................................................1</td>
</tr>
<tr>
<td></td>
<td>STIMULATION ....................................................................................................................2</td>
</tr>
<tr>
<td></td>
<td>RUBBING THE BACK ...........................................................................................................2</td>
</tr>
<tr>
<td></td>
<td>BAG AND MASK ..................................................................................................................2</td>
</tr>
<tr>
<td></td>
<td>SUCTION ............................................................................................................................2</td>
</tr>
<tr>
<td></td>
<td>INTUBATION ......................................................................................................................2</td>
</tr>
<tr>
<td></td>
<td>STIMULATION ....................................................................................................................8</td>
</tr>
<tr>
<td></td>
<td>RUBBING THE BACK ...........................................................................................................8</td>
</tr>
<tr>
<td></td>
<td>BAG AND MASK ..................................................................................................................8</td>
</tr>
<tr>
<td></td>
<td>SUCTION ............................................................................................................................8</td>
</tr>
<tr>
<td></td>
<td>INTUBATION ......................................................................................................................8</td>
</tr>
<tr>
<td>5.32.1 Was the baby given any oxygen?</td>
<td>YES ................................................................................................................................1</td>
</tr>
<tr>
<td></td>
<td>NO ................................................................................................................................2</td>
</tr>
<tr>
<td></td>
<td>DON'T KNOW ...................................................................................................................8</td>
</tr>
<tr>
<td>5.33</td>
<td>Did the baby ever move, even a little?</td>
</tr>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>5.33.1</td>
<td>Were the arms and legs limp, or did they have some flexing?</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
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<tr>
<td>5.33.2</td>
<td>Did the baby have any heartbeats?</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tr>
<tr>
<td>5.34</td>
<td>CHECK QUESTIONS 5.29, 5.31, 5.33 AND 5.33.2: IF ALL ARE “NO”, CONTINUE</td>
</tr>
<tr>
<td>5.35</td>
<td>If the baby did not cry, breathe or move, and had no heartbeats, was he/she born dead?</td>
</tr>
<tr>
<td></td>
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<tr>
<td>5.36</td>
<td>Was the baby macerated; that is, skin peeling or showing signs of decay?</td>
</tr>
<tr>
<td></td>
<td>ASK ONLY IF THE BABY WAS BORN DEAD</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>5.37</td>
<td>Was the baby ever breastfed?</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>5.38</td>
<td>How soon after birth was breastfeeding initiated?</td>
</tr>
<tr>
<td></td>
<td>IF LESS THAN 1 HOUR, RECORD “00” IN HOURS</td>
</tr>
<tr>
<td>5.39</td>
<td>Was the breastfeeding exclusive?</td>
</tr>
<tr>
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<tr>
<td>5.40</td>
<td>Were any other feeds administered before breast-milk flow started?</td>
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<tr>
<td>5.40.1</td>
<td>Was the baby dried immediately after birth?</td>
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<td></td>
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<tr>
<td>5.40.2</td>
<td>Was the baby kept warm immediately after birth?</td>
</tr>
<tr>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>5.41</td>
<td>How was the baby kept warm on the first day after birth?</td>
</tr>
<tr>
<td></td>
<td>MULTIPLE ANSWERS ARE ALLOWED; READ ALL OPTIONS</td>
</tr>
<tr>
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<tr>
<td>5.42</td>
<td>How was the baby cleaned on the first day after birth?</td>
</tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Question</td>
<td>Options</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>5.43 How many hours or days after birth was the baby examined by a health worker?</td>
<td>HOURS: 1 OR DAYS: 2</td>
</tr>
<tr>
<td>5.44 Was the baby ever admitted to the neonatal intensive care unit?</td>
<td>YES: 1 NO: 2 DON’T KNOW: 8</td>
</tr>
<tr>
<td>5.45 How soon after birth was the baby discharged?</td>
<td>HOURS: 1 OR DAYS: 2</td>
</tr>
<tr>
<td>5.46 Did the mother receive any counselling by a health worker before discharge?</td>
<td>YES: 1 NO: 2 DON’T KNOW: 8</td>
</tr>
<tr>
<td>5.47 What was the mother counselled on?</td>
<td>BREAST FEEDING: 1 IMMUNIZATION: 1 POST-NATAL CARE ATTENDANCE: 1 DANGER SIGNS: 1 FAMILY PLANNING: 1 OTHER (SPECIFY): 1</td>
</tr>
<tr>
<td>5.48 Was the mother given vitamin A just before or after delivery?</td>
<td>YES: 1 NO: 2 DON’T KNOW: 8</td>
</tr>
<tr>
<td>5.49 Was the baby given any of the following vaccines in the first week of life?</td>
<td>BCG (TB): 1 OPV (POLIO): 1 HEPATITIS B: 1</td>
</tr>
<tr>
<td>5.50 Did the baby sleep under a bed net?</td>
<td>YES: 1 NO: 2 DON’T KNOW: 8</td>
</tr>
</tbody>
</table>
### SECTION 6. NEONATAL ILLNESS HISTORY

<table>
<thead>
<tr>
<th>Section</th>
<th>Question</th>
<th>Answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1</td>
<td>How old was the baby when the fatal illness started?</td>
<td>HOURS ......................................................1  OR  DAYS ......................................................2  DON'T KNOW ..........................................998</td>
</tr>
<tr>
<td>6.2</td>
<td>Was the baby ever able to suckle or bottle-feed?</td>
<td>YES ......................................................1  NO ......................................................2  DON'T KNOW ..........................................8</td>
</tr>
<tr>
<td>6.3</td>
<td>Did the baby stop suckling or bottle-feeding?</td>
<td>YES ......................................................1  NO ......................................................2  DON'T KNOW ..........................................8</td>
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<tr>
<td>6.3.1</td>
<td>How many days after birth did the baby stop suckling or bottle-feeding?</td>
<td>DAYS ......................................................  IF LESS THAN 1 DAY, RECORD “00” IN DAYS DON'T KNOW ..........................................98</td>
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<tr>
<td>6.4</td>
<td>Did the baby have a fever?</td>
<td>YES ......................................................1  NO ......................................................2  DON'T KNOW ..........................................8</td>
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<tr>
<td>6.4.1</td>
<td>How many hours or days after birth did the fever start?</td>
<td>HOURS ......................................................1  OR  DAYS ......................................................2  DON'T KNOW ..........................................998</td>
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<tr>
<td>6.4.2</td>
<td>How many hours/days did the fever last?</td>
<td>HOURS ......................................................1  OR  DAYS ......................................................2  DON'T KNOW ..........................................998</td>
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<tr>
<td>6.5</td>
<td>Did the baby’s body feel cold when touched?</td>
<td>YES ......................................................1  NO ......................................................2  DON'T KNOW ..........................................8</td>
</tr>
<tr>
<td>6.5.1</td>
<td>How many hours or days after birth did the baby become cold to the touch?</td>
<td>HOURS ......................................................1  OR  DAYS ......................................................2  DON'T KNOW ..........................................998</td>
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<tr>
<td>6.6</td>
<td>Did the baby have a cough?</td>
<td>YES ......................................................1  NO ......................................................2  DON'T KNOW ..........................................8</td>
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<td>6.6.1</td>
<td>How many days after birth did the baby start to cough?</td>
<td>DAYS ......................................................  IF LESS THAN 1 DAY, RECORD “00” IN DAYS DON'T KNOW ..........................................98</td>
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<tr>
<td>6.7</td>
<td>Did the baby have fast breathing?</td>
<td>YES ......................................................1  NO ......................................................2  DON'T KNOW ..........................................8</td>
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<tr>
<td>6.7.1</td>
<td>How many hours or days after birth did the baby start breathing fast?</td>
<td>HOURS ......................................................1  OR  DAYS ......................................................2  DON'T KNOW ..........................................998</td>
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<td>Section</td>
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<td>---------</td>
<td>--------------------------------------------------------------------------</td>
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<td>6.7.2</td>
<td>For how many days did the fast breathing last?</td>
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<td></td>
<td>DAYS ....................................................................................................</td>
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<td>DON'T KNOW ...................................................................................</td>
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<td></td>
<td>DON'T KNOW ...................................................................................</td>
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<tr>
<td>6.8</td>
<td>Did the baby have any difficulty in breathing?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>YES ...............................................................................................</td>
<td></td>
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<td></td>
<td>NO ...............................................................................................</td>
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<td></td>
<td>DON'T KNOW ...................................................................................</td>
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<tr>
<td>6.8.1</td>
<td>How many hours or days after birth did the baby start having difficulty in breathing?</td>
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<td>IF LESS THAN 1 DAY, RECORD “00” IN DAYS</td>
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<td></td>
<td>HOURS ............................................................................................</td>
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<td></td>
<td>OR</td>
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<td></td>
<td>DAYS ............................................................................................</td>
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<td>6.8.2</td>
<td>For how many days did the difficulty breathing last?</td>
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<td></td>
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<tr>
<td>6.9</td>
<td>Did the baby have indrawing of the chest?</td>
<td></td>
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<tr>
<td></td>
<td>YES ...............................................................................................</td>
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<tr>
<td></td>
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<td>6.10</td>
<td>Did the baby have noisy breathing (grunting or wheezing)?</td>
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<td>DEMONSTRATE WHEEZING</td>
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<td>NO ...............................................................................................</td>
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<tr>
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<td>DON'T KNOW ...................................................................................</td>
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<td>6.11</td>
<td>Did the baby have flaring of the nostrils?</td>
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<td>DEMONSTRATE FLARING OF THE NOSTRILS</td>
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<td>NO ...............................................................................................</td>
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<tr>
<td></td>
<td>DON'T KNOW ...................................................................................</td>
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<tr>
<td>6.12</td>
<td>Did the baby have convulsions?</td>
<td></td>
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<tr>
<td></td>
<td>YES ...............................................................................................</td>
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<td>6.12.1</td>
<td>How many hours/days after birth did the convulsions start?</td>
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<td>ENTER IN HOURS OR DAYS</td>
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<td>OR</td>
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<td></td>
<td>DAYS ............................................................................................</td>
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<td></td>
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<tr>
<td>6.13</td>
<td>Did the baby’s body become stiff and arched backwards?</td>
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</tr>
<tr>
<td></td>
<td>YES ...............................................................................................</td>
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<td>DON'T KNOW ...................................................................................</td>
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<tr>
<td>6.14</td>
<td>Did the baby become unresponsive or unconscious?</td>
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<tr>
<td></td>
<td>YES ...............................................................................................</td>
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<td>NO ...............................................................................................</td>
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<td>6.14.1</td>
<td>How many hours or days after birth did the baby become unresponsive or unconscious?</td>
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<td>ENTER IN HOURS OR DAYS</td>
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<td></td>
<td>HOURS ............................................................................................</td>
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<td>OR</td>
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<td>DAYS ............................................................................................</td>
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<td></td>
<td>DON'T KNOW ...................................................................................</td>
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<td>6.15</td>
<td>Did the baby become lethargic after a period of normal activity?</td>
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<td></td>
<td>YES ...............................................................................................</td>
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<td>NO ...............................................................................................</td>
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<td></td>
<td>DON'T KNOW ...................................................................................</td>
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<tr>
<td>6.16</td>
<td>During the illness that led to death, did the baby have sunken fontanelles?</td>
<td></td>
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<tr>
<td></td>
<td>YES ...............................................................................................</td>
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<td>NO ...............................................................................................</td>
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<td>DON'T KNOW ...................................................................................</td>
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<tr>
<td>6.16.1</td>
<td>During the illness that led to death, did the baby have a bulging or raised fontanelle?</td>
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</tr>
<tr>
<td></td>
<td>YES ...............................................................................................</td>
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<td>NO ...............................................................................................</td>
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<td></td>
<td>DON'T KNOW ...................................................................................</td>
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</tr>
<tr>
<td>Question</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>6.17 Did the baby have a swollen stomach (abdomen)?</td>
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<tr>
<td>6.17.1 How many days after birth did the baby develop a swollen stomach?</td>
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<td></td>
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<tr>
<td><em>IF LESS THAN 1 DAY, RECORD &quot;00&quot; IN DAYS</em></td>
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<tr>
<td>6.18 Did the baby vomit?</td>
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<tr>
<td>6.18.1 How many days after birth did vomiting start?</td>
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<tr>
<td><em>IF LESS THAN 1 DAY, RECORD &quot;00&quot; IN DAYS</em></td>
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<tr>
<td>6.18.2 When the vomiting was most severe, how many times did the baby vomit in a day?</td>
<td></td>
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<tr>
<td>6.18.3 Did the baby vomit blood?</td>
<td></td>
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</tr>
<tr>
<td>6.19 Did the baby have diarrhoea (more frequent or more liquid stools than usual)?</td>
<td></td>
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<tr>
<td>6.19.1 How many days after birth did the baby have diarrhoea?</td>
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<td></td>
</tr>
<tr>
<td><em>IF LESS THAN 1 DAY, RECORD &quot;00&quot; IN DAYS</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.19.2 On the day when the diarrhoea was most severe, how many times did he/she pass stools in a day?</td>
<td></td>
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</tr>
<tr>
<td>6.20 At any time during the final illness was there blood in the stool?</td>
<td></td>
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</tr>
<tr>
<td>6.21 Did the baby have redness around, or drainage from, the umbilical cord stump?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.22 During the illness that led to death, did the baby have a skin rash?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.22.1 During the illness that led to death, did the baby have skin ulcer(s) or pits?</td>
<td></td>
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</tr>
<tr>
<td>6.23 Did the baby have yellow palms or soles?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.23.1 How many days after birth did the yellow palms or soles begin?</td>
<td></td>
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<tr>
<td><em>IF LESS THAN 1 DAY, RECORD &quot;00&quot; IN DAYS</em></td>
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<tr>
<td>6.23.2 For how many days did the baby have yellow palms or soles?</td>
<td></td>
<td></td>
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<tr>
<td><em>IF LESS THAN 1 DAY, RECORD &quot;00&quot; IN DAYS</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.23.3 Did the baby have yellow discoloration of the eyes?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 6.24 | During the illness that led to death, did the baby bleed from anywhere? | YES .................................................................1  
NO .................................................................2  
DON’T KNOW .....................................................8 |
| 6.25 | After birth, was the baby growing normally? | YES .................................................................1  
NO .................................................................2  
DON’T KNOW .....................................................8 |
| 6.26 | Did the baby appear to be healthy and then just die suddenly? | YES .................................................................1  
NO .................................................................2  
DON’T KNOW .....................................................8 |
| 6.27 | LIST SYMPTOMS IN CHRONOLOGICAL ORDER AND RECORD AT HOW MANY DAYS AFTER BIRTH WAS THE ONSET OF EACH SYMPTOM. THE DAY WHEN BIRTH OCCURED IS DAY “0”. PROBE THE SEQUENCE OF OCCURENCE OF EACH SYMPTOM ALREADY MENTIONED IN SECTION 6. | SYMPTOM |
|  | 1: ...................................................................................... |
|  | 2: ...................................................................................... |
|  | 3: ...................................................................................... |
|  | 4: ...................................................................................... |
|  | 5: ...................................................................................... |
| 6.28 | How long after the first symptom was recognized did the baby die? ENTER IN HOURS OR DAYS | HOURS ......................................................1  
OR  DAYS .........................................................2  
DON’T KNOW .....................................................998 |
### SECTION 7. HISTORY OF INJURIES/ACCIDENTS

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>YES</th>
<th>NO</th>
<th>DON'T KNOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1</td>
<td>Did the baby die from an injury or accident?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.1.1</td>
<td>What kind of injury or accident?</td>
<td></td>
<td></td>
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<tr>
<td>7.1.2</td>
<td>Was the injury or accident inflicted by someone else?</td>
<td></td>
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<tr>
<td>7.2</td>
<td>Did the baby suffer from any animal/insect bite that led to her/his death?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.2.1</td>
<td>What kind of animal/insect?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **7.1**: Did the baby die from an injury or accident?
  - YES: 1
  - NO: 2
  - DON'T KNOW: 8

- **7.1.1**: What kind of injury or accident?
  - ROAD TRAFFIC ACCIDENT: 1
  - FALL: 2
  - DROWNING: 3
  - POISONING: 4
  - BURNS: 5
  - VIOLENCE/ASSAULT (HOMICIDE/ABUSE): 6
  - OTHER (SPECIFY): 7

- **7.1.2**: Was the injury or accident inflicted by someone else?
  - YES: 1
  - NO: 2
  - DON'T KNOW: 8

- **7.2**: Did the baby suffer from any animal/insect bite that led to her/his death?
  - YES: 1
  - NO: 2
  - DON'T KNOW: 8

- **7.2.1**: What kind of animal/insect?
  - DOG: 1
  - SNAKE: 2
  - INSECT: 3
  - OTHER (SPECIFY): 7
  - DON'T KNOW: 8
### SECTION 8. TREATMENT AND HEALTH SERVICE USE FOR THE FINAL ILLNESS

| 8.1 Did the baby receive any treatment before s/he died? | YES ................................................................................1 | \(\rightarrow\) 8.3 |
| | NO ................................................................................2 |
| | DON’T KNOW ........................................................................8 | \(\rightarrow\) 8.3 |
| 8.2 Why did the baby not receive any treatment? | \(\rightarrow\) 9.1 |
| 8.3 How was the baby treated at home? | \(\rightarrow\) 9.1 |
| | WITH DRUGS ........................................................................1 |
| | WITH HERBS .........................................................................2 | \(\rightarrow\) 8.5 |
| | NO HOME TREATMENT ..........................................................3 | \(\rightarrow\) 8.6 |
| | OTHER (SPECIFY) ..............................................................7 | \(\rightarrow\) 8.5 |
| | DON’T KNOW ........................................................................8 | \(\rightarrow\) 8.6 |
| 8.4 What type of treatment was given to the baby at home? | YES NO DON’T KNOW |
| | MALARIA DRUG (SPECIFY) .........................................................1 2 8 |
| | SEPTRIN ...............................................................................1 2 8 |
| | OTHER ANTIBIOTIC (SPECIFY) .................................................1 2 8 |
| | PARACETAMOL .......................................................................1 2 8 |
| | ORS .......................................................................................1 2 8 |
| | ARVs ......................................................................................1 2 8 |
| | OTHER (SPECIFY) ...............................................................1 2 8 |
| 8.5 How many hours or days after onset of the illness that led to death was care initialized at home? | HOURS ...............................................................................1 | \(\rightarrow\) 8.3 |
| | OR .........................................................................................2 | \(\rightarrow\) 8.3 |
| | DAYS ......................................................................................2 | \(\rightarrow\) 8.3 |
| | DON’T KNOW .........................................................................998 |
| 8.5.1 As far as you know, was anyone aware that the baby needed medical help before the baby died? | YES ................................................................................1 | \(\rightarrow\) 8.6 |
| | NO .........................................................................................2 | \(\rightarrow\) 8.6 |
| | DON’T KNOW .........................................................................8 | \(\rightarrow\) 8.6 |
| 8.5.2 How long before the baby’s death was the illness or health problem recognized? | HOURS ...............................................................................1 | \(\rightarrow\) 8.8 |
| | OR .........................................................................................2 | \(\rightarrow\) 8.8 |
| | DAYS ......................................................................................2 | \(\rightarrow\) 8.8 |
| | DON’T KNOW .........................................................................998 |
| 8.6 Was the baby brought outside the home for care during the illness that led to death? | YES ................................................................................1 | \(\rightarrow\) 8.8 |
| | NO .........................................................................................2 | \(\rightarrow\) 8.8 |
| | DON’T KNOW .........................................................................8 | \(\rightarrow\) 9.1 |
### 8.7 What were the reasons the baby was not taken to care outside the home?
**CIRCLE ALL MENTIONED**
**PROBE: Any other reason?**

<table>
<thead>
<tr>
<th>Reason</th>
<th>MENTIONED</th>
<th>NOT MENTIONED</th>
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</thead>
<tbody>
<tr>
<td>BABY DIED SUDDENLY</td>
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<td>2</td>
</tr>
<tr>
<td>DID NOT RECOGNIZE HOW SERIOUS ILLNESS WAS</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>DID NOT KNOW WHERE TO GO</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>HAD NO ONE TO TAKE CARE OF OTHER CHILDREN</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>TRANSPORT WAS NOT AVAILABLE</td>
<td>1</td>
<td>2</td>
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<tr>
<td>TRANSPORT WAS TOO EXPENSIVE</td>
<td>1</td>
<td>2</td>
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<tr>
<td>FAMILY LACKED MONEY FOR HEALTH CARE</td>
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<td>2</td>
</tr>
<tr>
<td>HEALTH FACILITY IS TOO FAR AWAY</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>DID NOT TRUST QUALITY OF HEALTH CARE</td>
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<td>2</td>
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<td>STAFF MAY BLAME MOTHER FOR HOME DELIVERY</td>
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<tr>
<td>PROVIDER REFUSE TO WAKE DURING THE NIGHT</td>
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<tr>
<td>FEAR TO BE SCOLDED OR SHOUTED AT BY THE STAFF</td>
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<td>2</td>
</tr>
<tr>
<td>OTHER (SPECIFY)</td>
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<td>2</td>
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</tbody>
</table>

### 8.8 How many hours or days after onset of the illness that led to death was treatment initiated outside the home?
**ENTER IN HOURS OR DAYS**

<table>
<thead>
<tr>
<th>Time Unit</th>
<th>MENTIONED</th>
<th>NOT MENTIONED</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOURS</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAYS</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

### 8.9 At what place was treatment sought?
**CIRCLE ALL THAT APPLY**
**PROBE: Anywhere else?**
**INCLUDE ALL PLACES THAT WERE VISITED WHILE SEEKING CARE FOR THE ILLNESS THAT LED TO DEATH**

<table>
<thead>
<tr>
<th>Place Name</th>
<th>YES</th>
<th>NO</th>
<th>DON'T KNOW</th>
<th>998</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOSPITAL</td>
<td>1</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>HEALTH CENTRE</td>
<td>1</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>PRIVATE CLINIC</td>
<td>1</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>DRUG SHOP/PHARMACY</td>
<td>1</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>TRADITIONAL HEALER</td>
<td>1</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>OTHER (SPECIFY)</td>
<td>1</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>DON'T KNOW</td>
<td>1</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

### 8.10 List care sought in chronological order, starting with the first place where care was sought; use codes below for the level that best describes the place
**RECORD THE MAIN PROVIDER AT EACH PLACE (USE CODES LISTED BELOW)**
**RECORD THE NUMBER OF DAYS AFTER ILLNESS STARTED AT THE TIME OF VISITING EACH PLACE**

<table>
<thead>
<tr>
<th>Place Name</th>
<th>Level</th>
<th>Provider</th>
<th>When?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Codes for Level

1. Hospital  
2. Health Centre IV  
3. Health Centre III/II  
4. Private Clinic  
5. TBA Place  
6. Traditional Healer Place  
7. Pharmacy  
8. Church  
9. Other

### Codes for Type of Provider

1. Doctor  
2. Nurse/Midwife  
3. TBA  
4. Traditional Healer  
5. Pharmacy, Drug Seller, Store  
6. Religious Leader  
7. Other

#### 8.11 What kind of treatment was given to the baby outside the home?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Yes</th>
<th>No</th>
<th>Don't Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORS</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>ARVS</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>SEPTRIN</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Other Antibiotic (Specify)</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Blood Transfusion</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>IV Fluid</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Oxygen</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>NG Tube Feeding</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Surgery</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>No Treatment</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Other (Specify)</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

#### 8.12 Did a health worker tell you or anyone the cause of the baby's death?

<table>
<thead>
<tr>
<th>Response</th>
<th>Yes</th>
<th>No</th>
<th>Don't Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>DON'T KNOW</td>
<td></td>
<td></td>
<td>8</td>
</tr>
</tbody>
</table>

#### 8.13 What did the health worker say?

________________________________________

#### 8.14 What means of transportation were used to get the baby to the first place of care?

**Circle “1” for all that apply**

<table>
<thead>
<tr>
<th>Transportation</th>
<th>Yes</th>
<th>No</th>
<th>Don't Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private Car</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Bicycle</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Motorcycle</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Taxi</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>On Foot</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Other (Specify)</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>DON'T KNOW</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

#### 8.15 How much total transportation time did it take to reach the first place of care?

**Enter in minutes or hours or days**

- **Minutes**: 1 □ □
- **Hours**: 2 □ □
- **Days**: 3 □ □
- **DON'T KNOW**: 998

#### 8.15.1 Did you have difficulties when you sought help care for the baby at the facility?

<table>
<thead>
<tr>
<th>Response</th>
<th>Yes</th>
<th>No</th>
<th>Don't Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>DON'T KNOW</td>
<td></td>
<td></td>
<td>8</td>
</tr>
</tbody>
</table>
### 8.15.2 What difficulties did you have when you sought health care for the baby at the facility?

*Circle “1” for each difficulty had when they sought health care at the place of care.*

<table>
<thead>
<tr>
<th>Mentions</th>
<th>Not Mentioned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not have difficulty being given care</td>
<td>1 2</td>
</tr>
<tr>
<td>Had been turned away</td>
<td>1 2</td>
</tr>
<tr>
<td>Waited long to be seen</td>
<td>1 2</td>
</tr>
<tr>
<td>Lack of qualified staff</td>
<td>1 2</td>
</tr>
<tr>
<td>Lack of equipment</td>
<td>1 2</td>
</tr>
<tr>
<td>Lack of supplies</td>
<td>1 2</td>
</tr>
<tr>
<td>Lack of medication</td>
<td>1 2</td>
</tr>
<tr>
<td>No electricity</td>
<td>1 2</td>
</tr>
<tr>
<td>Treated poorly/disrespected</td>
<td>1 2</td>
</tr>
<tr>
<td>Treatment not available, too complex</td>
<td>1 2</td>
</tr>
<tr>
<td>Delayed referral for better care</td>
<td>1 2</td>
</tr>
<tr>
<td>Cost/denied treatment for fees</td>
<td>1 2</td>
</tr>
<tr>
<td>Other (specify)</td>
<td>1 2</td>
</tr>
<tr>
<td>Died without being given care</td>
<td>1 2</td>
</tr>
</tbody>
</table>

### 8.16 How much time passed between when the baby arrived at the first place of care and treatment was given?

*Enter in minutes or hours.*

<table>
<thead>
<tr>
<th>Minutes</th>
<th>Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

- No care received: 777
- Don’t know: 998

### 8.17 Was the baby ever referred/transferred to another place of care during the final illness?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

→ 8.23

### 8.18 Where was the baby referred or transferred?

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Health Centre</th>
<th>Private Clinic</th>
<th>Drug Shop</th>
<th>Traditional Healer</th>
<th>Other (Specify)</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

### 8.19 What was the reason for the referral/transfer?

<table>
<thead>
<tr>
<th>Lack of equipment</th>
<th>For better care</th>
<th>Lack of blood</th>
<th>Lack of drugs</th>
<th>Lack of oxygen</th>
<th>Other (Specify)</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

### 8.20 Did the baby reach the place where he/she was referred/transferred?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

→ 8.22
<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
<th>DON'T KNOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.21 What means of transportation were used to get the baby to the place of referral/transfer?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRIVATE CAR</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>BICYCLE</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>MOTORCYCLE</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>TAXI</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>ON FOOT</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>OTHER (SPECIFY)</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>DON'T KNOW</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

| 8.23 Why did the baby not reach the place of referral/transfer?        |      |    |            |
| BABY DIED BEFORE REACHING PLACE OF REFERRAL                           | 1   |    |            |
| FAMILY THOUGHT IT WASN'T NECESSARY                                    | 2   |    |            |
| FAMILY HOPED/WAITED FOR IMPROVEMENT                                   | 3   |    |            |
| LACK OF MONEY                                                         | 4   |    |            |
| LACK OF TRANSPORT                                                     | 5   |    |            |
| OTHER (SPECIFY)                                                       | 6   |    |            |
| DON'T KNOW                                                             | 8   |    |            |

<p>| 8.23 Altogether, how much did you pay for transport during the illness that led to death? |
| NO COST                                                                 | UGS |
| DON'T KNOW                                                              |     |
| 8.24 Altogether, how much did you pay for treatment and other costs related to care of the baby (including fees for admission, consultation, lab tests, consumables, etc.)? |
| NO COST                                                                 | UGS |
| DON'T KNOW                                                              |     |
| 8.25 Altogether, how much did you pay for other costs (including accommodation, feeding, etc.)? |
| NO COST                                                                 | UGS |
| DON'T KNOW                                                              |     |</p>
<table>
<thead>
<tr>
<th>Section 9: Data Abtracted From Records</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.1 Do you have a death certificate for the deceased?</td>
</tr>
<tr>
<td>YES ................................................................. 1 → 9.2</td>
</tr>
<tr>
<td>NO ................................................................. 2 → 9.2</td>
</tr>
<tr>
<td>DON'T KNOW ....................................................... 8 → 9.2</td>
</tr>
</tbody>
</table>

| 9.1.1 Can I see the death certificate? |
| COPY THE DAY, MONTH AND YEAR OF DEATH FROM THE DEATH CERTIFICATE |
| DAY | MONTH | YEAR |

| 9.2 Do you have an immunization card for the baby? |
| YES ................................................................. 1 → 9.3 |
| NO ................................................................. 2 → 9.3 |
| DON'T KNOW ....................................................... 8 → 9.3 |

| 9.2.1 ASK TO SEE THE IMMUNIZATION CARD AND RECORD THE DATE OF BCG AND OPV1; USE CODE “98” FOR MISSING INFORMATION |
| BCG |
| DAY | MONTH | YEAR |
| OPV1 |
| DAY | MONTH | YEAR |
| DON'T KNOW ....................................................... 98 |

| 9.3 RECORD THE CAUSE OF DEATH FROM THE POST-MORTEM RESULTS |

| 9.4 RECORD THE CAUSE OF DEATH FROM THE BURIAL PERMIT |

| 9.5 RECORD RELEVANT INFORMATION FROM THE MCH/ANC CARD |

<p>| 9.6 RECORD RELEVANT INFORMATION FROM THE HOSPITAL PRESCRIPTION FORM/TREATMENT CARDS |</p>
<table>
<thead>
<tr>
<th>9.7</th>
<th>RECORD RELEVANT INFORMATION FROM HOSPITAL DISCHARGE FORMS, INCLUDING DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RECORD THE DATE OF THE MOST RECENT (LAST VISIT); THE LAST BUT ONE VISIT (SECOND TO LAST); THE DATE OF THE LAST NOTE IN THE HEALTH RECORDS; RECORD THE WEIGHT IN GRAMS AT THE LAST VISIT; RECORD THE WEIGHT IN GRAMS AT THE SECOND TO LAST VISIT IF ANSWERED IN KILOGRAMS MULTIPLY BY 1000</td>
</tr>
<tr>
<td></td>
<td>LAST VISIT ........................................... [ ] [ ] GRAMS</td>
</tr>
<tr>
<td></td>
<td>DON’T KNOW ............................................. 9998</td>
</tr>
<tr>
<td></td>
<td>SECOND TO LAST VISIT ..................... [ ] [ ] GRAMS</td>
</tr>
<tr>
<td></td>
<td>DON’T KNOW ............................................. 9998</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9.8</th>
<th>RECORD RELEVANT INFORMATION FROM OTHER HOSPITAL DOCUMENTS</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>9.9</th>
<th>RECORD RELEVANT INFORMATION FROM LABORATORY RESULTS</th>
</tr>
</thead>
</table>

**END OF INTERVIEW**

**THANK RESPONDENT FOR THEIR COOPERATION**

**RECORD THE TIME AT THE END OF THE INTERVIEW**

<table>
<thead>
<tr>
<th></th>
<th>HOURS [ ] AND [ ] MINUTES</th>
</tr>
</thead>
</table>

Date: [ ] [ ] [ ]

DAY MONTH YEAR

Interviewer comments and observations:

______________________________________________________________________________________________________________________

______________________________________________________________________________________________________________________

______________________________________________________________________________________________________________________

______________________________________________________________________________________________________________________

______________________________________________________________________________________________________________________

______________________________________________________________________________________________________________________

______________________________________________________________________________________________________________________

______________________________________________________________________________________________________________________
VA Supervisor comments and observations:

______________________________________________________________________________________________________________________
______________________________________________________________________________________________________________________
______________________________________________________________________________________________________________________
______________________________________________________________________________________________________________________
______________________________________________________________________________________________________________________

Signature of the Supervisor
Maternal and Neonatal Death Review (MNDR): A Useful Approach to Identifying Appropriate and Effective Maternal and Neonatal Health Initiatives in Bangladesh

AUTHORS: Animesh Biswas, Fazlur Rahman, Abdul Halim, Charl Eriksson, Koustuv Dalal

KEYWORDS: Maternal and Neonatal Health, Death Review, Primary Healthcare, Bangladesh


ABSTRACT: Objectives: To identify the effects of Maternal and Neonatal Death Review (MNDR) in terms of improving maternal and neonatal health at the community level in Bangladesh. Methods: Both quantitative and qualitative methods were undertaken for collecting data in Kashipur Union, Bangladesh. Death notifications from households, subsequent data collections from a focus-group discussion (FGD), a group discussion (GD) and in-depth interviews (IDIs) were obtained using structured tools and guidelines. Results: A total of four maternal deaths, 21 neonatal deaths and 15 still births were reported in the MNDR death notification system at Kashipur Union in 2010. Data were presented to local programme managers, who took various initiatives including awareness programmes, pregnancy registration, antenatal care, birth planning, and also the revitalization of a community clinic. The coverage of antenatal care, delivery in clinics, postnatal care and referral of complications increased through the active participation of the community. Community healthcare providers, care recipients and members of the community expressed satisfaction with the quality of maternal and neonatal services. In the preceding two years, maternal and neonatal deaths substantially reduced in Kashipur (in 2011 maternal death = 1,
neonatal death = 20, still birth = 8; in 2012 maternal death = 1, neonatal death = 8, still birth = 13). Conclusions: The MNDR system successfully delivered notification of all maternal and neonatal deaths in the defined area and collected information for the formulation and implementation of specific interventions, which resulted in visible and tangible changes in care-seeking and client satisfaction.
Report of the Final validation assessment of maternal and neonatal tetanus elimination (MNTE) in Somali Region, Ethiopia 28-30 June 2017

Background
Ethiopia (figure 1) began accelerated MNTE efforts in 1999. Zones were selected following an in-depth review of the risk factors for maternal and neonatal tetanus (MNT) using the high-risk approach. Over 14 million women of reproductive age (WRA) in 59 high-risk zones were immunized during 3 rounds of tetanus toxoid (TT) Supplementary Immunization Activities (SIAs) between 1999 and 2009. In April 2011, the validation survey concluded that the whole country except the Somali region has been validated for MNT. The mission recommended additional activities for Somali region. To date over 15 million WRA have been vaccinated against tetanus during TT SIAs in the high risk zones.

Figure 1: Administrative map of Ethiopia

The Somali region implemented recommended supplementary immunization activities and in December 2015 the validation assessment mission to Somali region recommended to a) implement one extra round of TT SIAs for women of reproductive age in the five zones where the last round took place in 2012: Afder, Fafan, Liban, Shabale and Siti, and b) conduct a post-campaign coverage survey to confirm if 80% of the women have been reached during this corrective round.

The Somali region completed implementation of recommended corrective round in 2016 followed by post campaign assessment survey. The administrative as well as survey data revealed more than 85% coverage in each zone and hence, the Ministry of Health requested WHO to conduct the validation assessment.

MNTE validation assessment in Somali Region
Note; this may be considered as continuation of 2015 validation mission report December 2015.

The objectives of this MNTE validation assessment were:
• To assess the MNTE status in Somali Region
• To assess the implementation and performance of the 2015 recommendations on specific strategic activities of MNT elimination in Somali Region
• To conclude on the status of MNTE for Somali Region and, by extension, the whole of Ethiopia
• To review the readyness of the country in sustaining MNTE and recommend the way forward

Assessment Methodology
In continuation of the 2015 MNTE validation assessment findings of Somali Region and the subsequent recommendations, the assessment team conducted in-depth review of reported data for routine immunization and reproductive health indicators and achievements of recommended corrective TT SIAs. Additional guidance was also obtained by reviewing set of documents (annex 2) and key informants’ interviews jointly with the Ministry of Health, WHO and UNICEF country teams. List of document and key informants are in annex 1.
Figure 2: Spreadsheet for district data analysis

Data review findings
The data compiled in the district data spreadsheet (figure 2) was used for the desk review. Although seven cases of neonatal tetanus have been reported in the last three years from Somali region, and five out of seven in 2016, still the NT rate remained at maximum of 0.2 per 1000 live births for only one zone, well below elimination threshold level of 1 per 1000 LB in every zone. However, because there was only 61% completeness of surveillance data and NT cases are usually underreported, and the quality of NT surveillance did not meet WHO criteria for reliability in spite of progress made, surveillance alone cannot be used to determine the elimination status of MNT in Somali Region.

There is improvement in availability of reproductive health data by woreda and zone, as compared to by region only in 2015. From administrative data, skilled birth attendance has more than doubled in 2016 at 38% as compared to 17% in 2015, but with broader range between 14% and 119%. Significant contributions has been attributed to growing number of Community Health Workers (CHWs).

ANC1 coverage in 2016 ranges between 36% and 117%, with the average more than doubling at 73% when compared to 2015 average of 31%. Low TT2+ and PAB coverage in 2016 might indicate missed tetanus vaccination opportunities at ANC platform or poor recording and reporting.

There are big fluctuations among coverage results of tetanus Protection at Birth (PAB), routine DTP1, DTP3, ANC and SBA coverage for the same zones for 2014, 2015 and 2016. The reported zonal DTP3 coverage results ranges between 32% and 88%, but there is evidence of low completeness of reports. The country is using tetanus PAB rather than TT2+ and in Somali region the PAB coverage in 2016 ranges between 19% and 68%. But mostly two valid TT doses in previous pregnancy are taken as PAB – slight divergence from WHO guidelines. These gaps may be a reason for under reporting of immunization coverage.

TT SIAs coverage of 3 rounds conducted between 2010 and 2015 is above 80% in all zones, except the third dose in Siti, Afder, Fafan and Liban. As a recommendation of 2015 assessment mission, the corrective round conducted in 5 zones during 2016 had more than 95% coverage in every zone, dually verified through independent LQAS surveys. The surveys concluded that only one out of 31 randomly selected woredas (Keberibeyah 78.9%) failed the accepted (80%) coverage in the last TT SIAs. The maps in figure 3 below show outcome of SIAs in Somali region.
Strengths, weaknesses and opportunities

Somali region with the challenges of insecurity, access, 85% pastoralist communities, predominately rural setting and limited health infrastructure with all these compounded by drought since 2015 and acute watery diarrhoea (AWD) outbreak. It is currently considered as one of the developing regions in the country. In addition the region has been responding to confirmed Wild Polio Virus outbreak due to importation from 2014 with repeated Polio SIAs that was contained, and outbreak of measles that was responded to. Despite all the challenges the region has made significant progress in health system strengthening, emergency response and improvement in access to previously insecure areas.

**Strengths:**

- Improving leadership, governance and commitment of federal and regional governments substantiated by various innovative initiatives and funding opportunities during last few years has made tremendous improvement in human resources, financial access, service delivery, supply and logistics, and health information.
- Overall the security situation has improved in 2017 and all zones are accessible.
- Creation of more zones / woredas with increase in health infrastructure has proved effective in reaching scattered populations.
- Deployment of additional human resource and partner support have contributed to improvement in routine immunization services and surveillance (Zonal TA from WHO (20) and UNICEF (9 for C4D and one for Emergency)) since 2014.
- Presence of HEWs in health workforce in all Kebeles is an added advantage but the quality and availability of human resource and the cultural norms is still one of the barriers to overcome.
- Periodic Intensification of Routine Immunization (PIRI), Child Health Days (CHDs), measles SIAs and drought emergency response are being used as opportunities for catch-up to vaccinate defaulters of routine immunization (mothers and children).
- The use of ‘Family folder’ for recording vital information of mother, father and children is widely used in urban and agrarian settings. This record is in paper form, but is to be digitalized.

**Weakness:**

- Hospital delivery is almost negligible and skilled birth attendance is below recommended 70% threshold in 6 of the 9 zones of Somali Region
- Larger pool of un-immunized in 4 out of 9 zones of Somali region; Degehabour, Gode Afder and Fafan/Somali region. Massive missed immunization opportunities at ANC platform
- Timeliness and completeness of data is low, leading to delay in response/action.
Opportunities

- Reproductive Health Innovative Fund (RHIF) has made significant contributions in the past 2 years with a focus on improving reproductive and child health services in Somali Region. Equity Package Fund is an opportunity to boost MNCH and immunization human resource and infrastructure, and improving logistics, water and sanitation facilities. The initiatives for RED/REC microplanning will improve number of out-reach immunization sessions including delivery of tetanus toxoid containing vaccines (TTCV).
- Engagement of TBAs with reproductive health services to educate on clean and safe delivery and linkages with HEW and health facilities.
- HEW number, skills and scope is being increased from 2 to 3 per 5,000 population that will be able to deliver a package of 18 health interventions instead of the current 16 interventions.
- Establishing school health services as third leg of services of primary health care will be an opportunity for reaching adolescent population with package of immunization services (Td booster and HPV)
- The use of ‘Family folder’ for recording vital information is being digitalized, and that will also capture pastoral communities and will make it a real time for evidence based decision making.
- Maternal Death Surveillance & Response / Perinatal Death Surveillance & Response are operational in one region (pilot) that is being expanded to include neonatal deaths (up to 30 days) with extension to other regions including Somali region.
- NT is among the 21 priority notifiable disease conditions in IDSR. Most of the notified NT cases are investigated by Woreda Surveillance Officers complemented by WHO surveillance staff. JRF reported 18 cases each in 2015 and 2016 that matches with HMIS. NT cases from home delivery may not be reported as the community surveillance structure is just being established. There is limited NT case response due to limited coordination between PHEM and EPI. Completeness of surveillance reporting for Somali Region remained low at 61%.
- DHIS-2 will be replacing HMIS in July 2017 with online submission facilities that will increase accuracy making it real time information for decision making.

Conclusion:

Based on the review of the risk indicators’ performance, all Zones of Somali Region have status compatible with MNTE and, by extension, the whole of Ethiopia has achieved MNTE

Recommendations:

- Sustain tetanus protection level above 80% in every zone especially in zones that achieved elimination through SIAs
  - Three zones in Somali region (Jarar, Korahe, Nogob/Fik) that were inaccessible in 2014-2016 have less than 30% TT2+/PAB coverage, with status quo will need catch-up immunization in 2020.
- In line with SAGE recommendations,
  - Implement the sustainability plan of action-2014 including switching from TT to Td.
  - Joint Review of national MNT risk status end of every year to guide response action
  - Address discrepancies between reported and assessed coverages
- Sustain and strengthen partnerships for improving MNCH and HSS; RHIF, Equity Package Fund, HSTP, RED/REC microplanning initiative, etc.
- Implement school health programme to open opportunities for adolescent health interventions i.e. Td boosters, HPV vaccination, VAS, deworming, etc
- Make TT vaccination available in fixed facilities and in out-reach ANC clinics to minimize missed opportunities.
• Continue prioritizing maternal and infant catch-up immunization in PIRI, CHDs, Drought Emergency Response
• Ensure regular coordination meetings between PPD/HMIS/PHEM and EPI, to improve flow of data

* * * * *
Annex 1. List of Participants for MNTE validation June, 28-30/2017

<table>
<thead>
<tr>
<th>SN</th>
<th>Name</th>
<th>Position</th>
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<tbody>
<tr>
<td>1</td>
<td>Dr Ephrem Tekle</td>
<td>MCH director</td>
<td>FMOH</td>
<td><a href="mailto:mchdirector.fmoh@gmail.com">mchdirector.fmoh@gmail.com</a></td>
</tr>
<tr>
<td>2</td>
<td>Mrs Liya wondwossen</td>
<td>EPI team leader ,assistant mch director</td>
<td>FMOH</td>
<td><a href="mailto:epicordinator.mch@gmail.com">epicordinator.mch@gmail.com</a></td>
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<tr>
<td>3</td>
<td>Mrs Seralem Genet</td>
<td>EPI Officer</td>
<td>FMOH</td>
<td><a href="mailto:Epiexpert5.mch@gmail.com">Epiexpert5.mch@gmail.com</a></td>
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<td>4</td>
<td>Mr Mikias Alayu</td>
<td>VPD surveillance officer</td>
<td>EPHI</td>
<td><a href="mailto:Mikiasalayu7@gmail.com">Mikiasalayu7@gmail.com</a></td>
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<tr>
<td>5</td>
<td>Mr Mehadi Abdi</td>
<td>EPI officer</td>
<td>Eth. Somali</td>
<td><a href="mailto:mabdisimeter@yahoo.com">mabdisimeter@yahoo.com</a></td>
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<tr>
<td>6</td>
<td>Meskerem Abebaw</td>
<td></td>
<td>FMOH</td>
<td><a href="mailto:meskeremabebawtt@gmail.com">meskeremabebawtt@gmail.com</a></td>
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<tr>
<td>7</td>
<td>Dr Assefu lemlem</td>
<td>Immunization officer</td>
<td>WHO</td>
<td><a href="mailto:asseful@who.int">asseful@who.int</a></td>
</tr>
<tr>
<td>8</td>
<td>Dr Aysheshem Adem</td>
<td>Surveillance officer</td>
<td>WHO</td>
<td><a href="mailto:aysheshema@who.int">aysheshema@who.int</a></td>
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<tr>
<td>9</td>
<td>Mr Fasil Teshager</td>
<td>Data manager</td>
<td>WHO</td>
<td><a href="mailto:teshagerf@who.int">teshagerf@who.int</a></td>
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<tr>
<td>10</td>
<td>Dr Thomas Kerengera</td>
<td>Routine Immunization . Acting team leader</td>
<td>WHO</td>
<td><a href="mailto:karengerat@who.int">karengerat@who.int</a></td>
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<tr>
<td>11</td>
<td>Dr Ricardo Marisa</td>
<td>Health Specialist</td>
<td>UNICEF</td>
<td><a href="mailto:mvricardo@unicef.org">mvricardo@unicef.org</a></td>
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<tr>
<td>12</td>
<td>Ms Almaz Merdikios</td>
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<td>UNICEF</td>
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List of Evaluation Team

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<tr>
<td>1</td>
<td>Dr Francois Gasse</td>
<td>consultant</td>
<td>WHO</td>
<td><a href="mailto:francois.gasse@gmail.co">francois.gasse@gmail.co</a></td>
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<td>2</td>
<td>Dr Ahmadian Yakubu</td>
<td>Senior Health Specialist</td>
<td>WHO HQ</td>
<td><a href="mailto:yakuba@who.int">yakuba@who.int</a></td>
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<td>3</td>
<td>Dr Messeret Shibeshi</td>
<td>Accelerated Immunization &amp; Medical Epidemiologist</td>
<td>WHO/ISTESA</td>
<td><a href="mailto:asheleum@who.int">asheleum@who.int</a></td>
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<td>4</td>
<td>Dr Azhar Abid Raza</td>
<td>Maternal and Adolescent Immunization specialist</td>
<td>UNICEF HQ</td>
<td><a href="mailto:aaraza@unicef.org">aaraza@unicef.org</a></td>
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## Annex 2. List of documents reviewed

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| 1         | Admin reports of 5 zones of Somali Regional Health bureau | - Administrative TT SIA report of Fafan & Siti zone by woreda (Phase I)  
- Administrative TT SIA report of Afder, Liben and Shebelle zones by woreda (Phase II) |
| 2         | Agenda | Agenda of MNTE assessment |
| 3         | Best practices documented | - Best practices documented during corrective campaign in 5 zones |
| 4         | JRF 2014-2016 | - JRF data by year - 2014, 2015 and 2016 |
| 5         | MNTE validation report | - 2015 MNTE validation report of Somali region (word) & PPT for debriefing |
| 6         | MNTE risk assessment spread sheet (data sets of EPI, Maternal health & Sur indicators) | 2017 Master MNTE risk assessment data set  
2011 Master MNTE Risk assessment data set & report on assessment of MNTE |
| 7         | MNTE sustaining guideline , 2014 Ethiopia | SUSTAIN MATERNAL AND NEONATAL TETANUS In Ethiopia, Federal Ministry Health of Ethiopia 2014 |
| 8         | National adolescent and youth strategy | NATIONAL ADOLESCENT AND YOUTH HEALTH STRATEGY (2016-2020), FMOH |
| 9         | National communication strategy | National Health promotion and communication strategy (2016-2020), FMOH |
| 10        | National school health programme | - SCHOOL HEALTH PROGRAM FRAME Work , March 2017  
- school health service package for costing |
| 11        | NNT surveillance | - IDSR case based reporting form  
- IDSR Core indicators  
- NNT risk assessment tool  
- Manual for Neonatal Tetanus Surveillance  
- NNT detailed form for additional information  
Standard case definition Ethiopia |
| 12        | Post TT SIA converge Survey report | - Post TT SIA converge Survey report  
- Post TT SIA coverage Survey findings dissemination work shop doc. |
| 13        | Somali HMIS and surveillance reports | - PHEM IDSR data 2014-2016  
- HMIS HF and HR data  
- HMIS Maternal health Data  
- HMIS Health system indicators data |
| 14        | Status of implementation of Recommendations | - Status of implementation of Recommendations from Last MNTE validation |
| 15        | TT SIA data Ethiopia 1999-2016 | - TT SIA data 1999-2016 by year of campaign and coverage |
| 16        | Strategy for revitalizing Health Extension program in pastoralist areas | - June 2017 version |
| 17        | Health Sector Transformation plan (October 2015 version) | The FMoH Ethiopia, 2015/16 - 2019/20  
- (2008-2012 EFY) |
Summary of the characteristics and key findings from LQA-CS surveys conducted from 2000 to 2019

(Data sources: WER and mission reports)

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<th>Number of Districts</th>
<th>Sample Size</th>
<th>Set-up as single or double sampling</th>
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<th>TTCV2+ PW (card &amp; history)</th>
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<td>Pass</td>
<td>48%</td>
<td>Mission report</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Equatorial Guinea</td>
<td>2016</td>
<td>1</td>
<td>2350</td>
<td>Single</td>
<td>0</td>
<td>Pass</td>
<td>68%</td>
<td>WER 16/06/2017</td>
<td></td>
</tr>
<tr>
<td>41</td>
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<td>2015</td>
<td>3</td>
<td>2560</td>
<td>Double</td>
<td>0</td>
<td>Pass</td>
<td>90%</td>
<td>Mission report</td>
<td></td>
</tr>
<tr>
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<td>2015</td>
<td>1</td>
<td>1750</td>
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<td>0</td>
<td>Pass</td>
<td>87%</td>
<td>Mission report</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>Mauritania</td>
<td>2015</td>
<td>2</td>
<td>1450</td>
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<td>0</td>
<td>Pass</td>
<td>58%</td>
<td>Mission report</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>Niger</td>
<td>2016</td>
<td>1</td>
<td>2350</td>
<td>Single</td>
<td>2</td>
<td>Pass</td>
<td>59%</td>
<td>Mission report</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>Haiti</td>
<td>2016</td>
<td>1</td>
<td>2300</td>
<td>Single</td>
<td>0</td>
<td>Pass</td>
<td>53%</td>
<td>Mission report</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>Kenya</td>
<td>2018</td>
<td>1</td>
<td>2690</td>
<td>Double</td>
<td>1</td>
<td>Pass</td>
<td>83%</td>
<td>Mission report</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Chad</td>
<td>2019</td>
<td>1</td>
<td>1600</td>
<td>Single</td>
<td>0</td>
<td>Pass</td>
<td>37%</td>
<td>WER 28/06/2019</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>DRC</td>
<td>2019</td>
<td>2</td>
<td>1610</td>
<td>Single</td>
<td>0</td>
<td>Pass</td>
<td>60%</td>
<td>WER 01/11/2019</td>
<td></td>
</tr>
</tbody>
</table>

India (AP)
<table>
<thead>
<tr>
<th>S/N</th>
<th>Country</th>
<th>Survey Year</th>
<th>Number of Districts</th>
<th>Sample Size</th>
<th>Set-up as single or double sampling</th>
<th>NT deaths</th>
<th>Pass/Fail</th>
<th>TTCV2+ PW (card &amp; history)</th>
<th>Deliveries with qualified assistance (in &amp; out HF)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>India (AP)</td>
<td>2003</td>
<td>1</td>
<td>2029</td>
<td>Single</td>
<td>0</td>
<td>Pass</td>
<td>66%</td>
<td>64%</td>
<td>WER 06/08/2004</td>
</tr>
<tr>
<td>51</td>
<td>India (Haryana)</td>
<td>2006</td>
<td>1</td>
<td>1413</td>
<td>Single</td>
<td>0</td>
<td>Pass</td>
<td>68%</td>
<td>59%</td>
<td>WER 27/04/2007</td>
</tr>
<tr>
<td>52</td>
<td>India (Karnataka)</td>
<td>2006</td>
<td>1</td>
<td>993</td>
<td>Double</td>
<td>0</td>
<td>Pass</td>
<td>81%</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>India (Maharashtra)</td>
<td>2006</td>
<td>1</td>
<td>1987</td>
<td>Single</td>
<td>2</td>
<td>Pass</td>
<td>74%</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>India (Tamil Nadu)</td>
<td>2006</td>
<td>1</td>
<td>1009</td>
<td>Double</td>
<td>0</td>
<td>Pass</td>
<td>84%</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>India (West Bengal)</td>
<td>2006</td>
<td>1</td>
<td>1003</td>
<td>Double</td>
<td>0</td>
<td>Pass</td>
<td>96%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>India (West Bengal)</td>
<td>2006</td>
<td>1</td>
<td>2075</td>
<td>Single</td>
<td>0</td>
<td>Pass</td>
<td>85%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>India (Chandigarh, Goa, Punjab, Sikkim)</td>
<td>2008</td>
<td>4</td>
<td>Chandigarh = 1408; Goa = 1460; Punjab = 1988; Sikkim = 1401</td>
<td>Single</td>
<td>0 for all four districts</td>
<td>Pass for all four districts</td>
<td>Chand = 92%; Goa = 91%; Punjab = 88%; Sikkim = 81%</td>
<td>Chand = 77%; Goa = 100%; Punjab = 56%; Sikkim = 76%</td>
<td>WER 21/05/2008</td>
</tr>
<tr>
<td>58</td>
<td>India (Gujarat Himachal Pradesh)</td>
<td>2008</td>
<td>2</td>
<td>Gujarath = 1970 Himachal Pradesh = 1409</td>
<td>Single</td>
<td>0 for both districts</td>
<td>Pass in Gujarath Inconclusiv e for Himachal Pradesh</td>
<td>Gujarath = 78% Himachal Pradesh = 58%</td>
<td>Gujarath = 73% Himachal Pradesh = 39%</td>
<td>WER 27/07/2010</td>
</tr>
<tr>
<td>59</td>
<td>India (Delhi, Mizoram, Odisha, Uttarakhand)</td>
<td>2013</td>
<td>4</td>
<td>Delhi = 3000; Mizoram = 1375; Odisha = 1400; Uttarakhand = 3000</td>
<td>Delhi &amp; Uttarakhand – Double; Mizoram &amp; Odisha – Single</td>
<td>0 for all four districts</td>
<td>Pass in Delhi, Mizoram and Uttarak Fail in Odisha</td>
<td>Delhi = 87% Mizoram = 91% Odisha = 55% Uttarakhand = 44%</td>
<td>Delhi = 90% Mizoram = 75% Odisha = 43% Uttarakhand = 59%</td>
<td>WER 02/05/2014</td>
</tr>
<tr>
<td>60</td>
<td>**India (Jammu/Kashmir))</td>
<td>2014</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Pass for all four</td>
<td>Dardra &amp; Nagar Haveli = 97%; Jammu/Kashmir = 94%; Meghalaya = 83%; Nagaland = 87%</td>
<td>Dardra &amp; Nagar Haveli = 96%; Jammu/Kashmir = 79%; Meghalaya = 59%; Nagaland = 67%</td>
<td>Mission report</td>
</tr>
<tr>
<td>61</td>
<td>India (Assam, Bihar, Pradesh)</td>
<td>2014</td>
<td>4</td>
<td>30 x 7 cross-sectional survey in all four</td>
<td>Double for all four</td>
<td>0 for all four districts</td>
<td>Pass for all four</td>
<td>Assam = 95% Bihar = 96% Chhattisgarh = 91% Uttar Pradesh = 77%</td>
<td>Assam = 56% Bihar = 57% Chhattisgarh = 71% Uttar Pradesh = 61%</td>
<td>WER 30/10/2015</td>
</tr>
<tr>
<td>62</td>
<td>Indonesia</td>
<td>2010</td>
<td>1</td>
<td>3000</td>
<td>Double</td>
<td>2</td>
<td>Pass</td>
<td>78%</td>
<td>52%</td>
<td>WER 26/11/2010</td>
</tr>
<tr>
<td>63</td>
<td>Indonesia (Sumatera)</td>
<td>2010</td>
<td>1</td>
<td>1450</td>
<td>Single</td>
<td>0</td>
<td>Pass</td>
<td>91%</td>
<td>72%</td>
<td>Mission report</td>
</tr>
<tr>
<td>64</td>
<td>Indonesia (part?)</td>
<td>2011</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Pass</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>Indonesia (part?)</td>
<td>2016</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Pass</td>
<td>NA</td>
<td>NA</td>
<td>WER 24/06/2016</td>
</tr>
<tr>
<td>66</td>
<td>***Indonesia (part?)</td>
<td>2016</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Pass</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

**Indonesia**

62 Indonesia (Bali, Java) 2010 1 3000 Double 2 Pass 78% 52% WER 26/11/2010
64 Indonesia (Sumatera) 2010 1 1450 Single 0 Pass 91% 72% Mission report
65 Indonesia (part?) 2011 NA NA NA NA NA NA NA NA NA

**Ethiopia**
<table>
<thead>
<tr>
<th>S/N</th>
<th>Country</th>
<th>Survey Year</th>
<th>Number of Districts</th>
<th>Sample Size</th>
<th>Set-up as single or double sampling</th>
<th>NT deaths</th>
<th>Pass / Fail</th>
<th>TTCV2+ PW (card &amp; history)</th>
<th>Deliveries with qualified assistance (in &amp; out HF)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td>Ethiopia (all regions except Somali)</td>
<td>2011</td>
<td>1</td>
<td>1364</td>
<td>Single</td>
<td>0</td>
<td>Pass</td>
<td>44%</td>
<td>40%</td>
<td>Mission report</td>
</tr>
<tr>
<td>68</td>
<td>* Ethiopia (Somali regions)</td>
<td>2017</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Mission report</td>
</tr>
<tr>
<td>69</td>
<td>Pakistan (Punjab)</td>
<td>2016</td>
<td>2</td>
<td>2740</td>
<td>Double</td>
<td>0</td>
<td>Pass</td>
<td>97%</td>
<td>74%</td>
<td>WER 20/01/2017</td>
</tr>
<tr>
<td>70</td>
<td>Nigeria (southeast zone)</td>
<td>2017</td>
<td>1</td>
<td>1430</td>
<td>Double</td>
<td>0</td>
<td>Pass</td>
<td>95%</td>
<td>79%</td>
<td>Mission report</td>
</tr>
<tr>
<td>71</td>
<td>Nigeria (southwest zone)</td>
<td>2019</td>
<td>2</td>
<td>1710</td>
<td>Single</td>
<td>0</td>
<td>Pass</td>
<td>75%</td>
<td>61%</td>
<td>WER 02/10/2020</td>
</tr>
<tr>
<td>72</td>
<td>Mali (southern regions)</td>
<td>2018</td>
<td>3</td>
<td>2026</td>
<td>Double</td>
<td>0</td>
<td>Pass</td>
<td>71%</td>
<td>56%</td>
<td>WER 01/08/2020</td>
</tr>
</tbody>
</table>

*Desk review of documents as opposed to LQA-CS
**30 x 7 cross-sectional survey
****RCA

[https://www.who.int/wer/2020/en/](https://www.who.int/wer/2020/en/)
Validation of Maternal and Neonatal Tetanus Elimination

including a guide to the use of Lot Quality Assurance – Cluster Sample Surveys to assess neonatal tetanus mortality
Validation of Maternal and Neonatal Tetanus Elimination

including a guide to the use of Lot Quality Assurance – Cluster Sample Surveys to assess neonatal tetanus mortality
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ABBREVIATIONS

ANC  antenatal care
BCG  Bacillus Calmette-Guérin
CBAW  childbearing-aged woman
CBR  crude birth rate
CS  cluster sample
DTP  diphtheria–tetanus–pertussis vaccine
HH  household
LB  live birth
LQA  lot quality assurance
MNT  maternal and neonatal tetanus
MO  medical officer
MOH  ministry of health
ND  neonatal death
NGO  nongovernmental organization
NT  neonatal tetanus
NMR  neonatal mortality rate
NTMR  neonatal tetanus mortality rate
PAB  protection at birth
PPS  probability proportionate to size
QA  quality assurance
SIAs  supplemental immunization activities
TBA  traditional birth attendant
Td  tetanus–diphtheria toxoid vaccine (adult formulation)
TT  tetanus toxoid vaccine; in this manual, “TT” also signifies either TT or Td
TT2+  2 or more TT doses at the time of the last pregnancy
UNFPA  United Nations Population Fund
UNICEF  United Nations Children’s Fund
WHO  World Health Organization
INTRODUCTION

In the 1980s, community-based surveys demonstrated that neonatal tetanus (NT) was one of the principle causes of global neonatal mortality, resulting in an estimated 770,000 deaths per year. In response to the recognition of this high NT burden, the 1989 World Health Assembly called for global NT elimination.

Neonatal tetanus elimination was defined as a neonatal tetanus mortality rate of less than 1 case per 1000 live births in every district. The principal strategies adopted for NT elimination were:

• routine and supplemental immunization with tetanus toxoid-containing vaccine (TT or Td)\(^1\)
• clean delivery and cord care
• effective surveillance to identify areas where NT persists and to monitor elimination progress

By 2000, 104 developing countries had achieved NT elimination; estimated NT cases had declined to 238,000 annually. UNICEF, UNFPA and WHO reaffirmed their commitment to NT elimination in that year, adding maternal tetanus to the elimination goal (MNT elimination) and creating a revised strategic plan.\(^2\)

To accelerate MNT elimination, the revised plan recommended the high-risk approach: women of childbearing age living in high-risk districts, or in high risk areas within districts, are immunized with 2 or 3 doses of TT through supplemental immunization activities (SIAs – i.e., community-wide campaigns). TT SIAs supplement the three strategies listed above, all of which continue to form the basis for achieving and sustaining MNT elimination.

Since the 2000 revitalization of the MNT Elimination Initiative, 34 countries, 18 of 35 Indian states, 29 of 34 Indonesian provinces and Ethiopia excluding the restive Somali Region have validated MNT elimination,\(^3\) and many others are close to being able to demonstrate elimination.

The purpose of this guide is to describe the recommended process for assessing and validating MNT elimination in countries believed to have achieved that goal.

The companion Statistical Supplement to the Guide for Validation of Maternal and Neonatal Tetanus Elimination (“Statistical Supplement”) describes in detail the statistical underpinnings of the recommended survey methods.

---

1 In this manual, the abbreviation TT represents either single antigen tetanus toxoid vaccine or adult formulation tetanus-diphtheria vaccine (Td).
3 Count as of December 2013.
1. Assessing MNT Elimination
1. ASSESSING MNT ELIMINATION

When a country believes it has eliminated MNT, it can proceed to validation of that claim, following the steps outlined in this guide. In most instances, WHO participates in the validation exercises to ensure adherence to recommended methods, and consistency of results among countries achieving elimination.

Definition of MNT Elimination: less than 1 NT case per 1000 live births in every district

1.1 REVIEW OF DISTRICT-LEVEL DATA

Countries can consider claiming MNT elimination when district-level indicator data suggest that NT has fallen below the threshold of 1 NT case per 1000 live births in all districts.

The first step in evaluating whether elimination has been achieved is a formal review of district-level data. There are 3 possible outcomes of this review:

1. The data clearly support elimination; elimination can be declared

2. The data clearly indicate that elimination has not been achieved (or is highly unlikely). Additional measures required to achieve elimination are then identified.

3. Elimination appears likely, but some doubt remains. Districts with data that lead to uncertainty, or are suggestive of continued NT risk, are identified for additional evaluation, including possible field visits or surveys.

The data review process

The district data review evaluates the core indicators: reported NT cases and incidence per 1000 live births, clean delivery coverage and TT2+ coverage, and supplemental indicators such as SIA TT coverage, ANC coverage, infant DPT coverage, and various socioeconomic indices. Typically administrative data are used, but when survey data are available, especially for TT2+, PAB, and DPT3, they should be included, even if available only at the provincial level.

The process is individualized for each country based on the indicators available, the quality of the indicator data, and the knowledge and insight of national and local representatives of the country under review.

A spreadsheet with a row for each district and columns for each core and supplemental indicator for the 2-3 most recent years must be prepared in advance. A template is available
from WHO/HQ (see example in Annex 1). At a minimum, the following variables should be included for each district, if available:

<table>
<thead>
<tr>
<th>Core</th>
<th>Supplemental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported NT cases</td>
<td>PAB</td>
</tr>
<tr>
<td>Number of Live Births (LBs)</td>
<td>SIA TT coverage (TT1, TT2, TT3)</td>
</tr>
<tr>
<td>Reported NT rate/1000 LBs</td>
<td>ANC Coverage (1 visit minimum)</td>
</tr>
<tr>
<td>Quality of surveillance (zero reporting,</td>
<td>DPT1 and DPT3 coverage</td>
</tr>
<tr>
<td>number and distribution of reporting sites, completeness and timeliness of reporting)</td>
<td></td>
</tr>
<tr>
<td>Clean Delivery Rate</td>
<td>DPT3-DPT1 dropout rate</td>
</tr>
<tr>
<td>TT2+ coverage</td>
<td>Urban vs. rural status</td>
</tr>
</tbody>
</table>

Other indicators used for the review have included: measles vaccine and/or BCG coverage, trained TBA coverage, women's literacy, human development indicators (life expectancy, adult literacy, gross school enrollment, population living in poverty), and health service access indicators (population per health center, health centers/km², difficulty of terrain). The most current district-level population estimates, including annual numbers of births, numbers of pregnant women and women of childbearing age, should be included in the spreadsheet, if available.

Once the spreadsheet has been prepared, a team of national and international staff including representatives of the MOH, WHO, UNICEF and, if appropriate, local NGOs, should review the data district-by-district. Ideally, the meeting should take place in-country with all team members present and an accurate district-level map at hand. If that is not feasible, the review can be conducted by telephone and e-mail.

The following is a summary of the major considerations involved in the data review:

### 1.1.1 The core indicators

#### 1.1.1.1 Reported incidence of NT and review of the surveillance system

Most countries where NT continues to be a problem do not have uniform nationwide surveillance or vital event registration with medical certification of the cause(s) of death. Unreliable routine surveillance is most likely to be found in districts with higher risk for NT. Such districts may have active NT surveillance in district hospitals; however, if their reported NT rates are low, an evaluation of the sensitivity and reliability of the surveillance system is necessary before they can be accepted.
While a comprehensive evaluation of a surveillance system cannot be undertaken by the NT assessment team, the following parameters should be considered when evaluating the quality of surveillance data:

- The presence of an adequate number of reporting sites, with representative distribution
- Mandatory negative (or “zero”) reporting.
- Completeness of reporting of at least 80%
- Annual reviews of hospital records and/or of active NT surveillance
- Active community surveillance in rural areas with limited health facility access to ensure that neonatal deaths are detected, reported and investigated to rule out NT

Because MNT elimination is defined as less than 1 NT case per 1000 LBs in every district, any district with a reported NT rate above 1 per 1000 live births, particularly in more than 1 year, has not met the definition of elimination and must be given close attention. The details of reported NT cases in such a district, or any district with a suspiciously high number of NT cases should be requested and reviewed to rule out misdiagnoses. Surveillance data for several years should be evaluated.

Because NT surveillance is frequently unreliable, reported NT rates must be interpreted with caution.

Effective evaluation of surveillance systems and data from a distance is very difficult. Reports of no NT cases can hide significant on-going NT. For that reason, surveillance data alone cannot be used to make a decision about the likelihood of MNT elimination - all available indicators must be considered.

1.1.1.2 Percentage of births with clean delivery

The indicator, “clean delivery” is usually defined as a delivery assisted by a medically trained health worker (physician, nurse, or midwife). Some countries define clean deliveries as those occurring in health facilities. For the data review, the nationally-accepted definition can be used, as long as it is clearly specified and used consistently for all districts.

Most developing countries have some type of hygienic delivery and/or safe motherhood promotion that includes providing clean delivery information to pregnant women, training traditional birth attendants (TBAs), and/or distributing safe delivery kits. These efforts can reduce NT incidence substantially, even if many deliveries still take place at home without medically trained attendants.

Districts with clean delivery coverage of at least 70% are generally likely to have achieved MNT elimination. This is both because the majority of deliveries occur in hygienic
conditions and because clean delivery concepts are likely to have reached subpopulations with limited access to professional care when clean delivery coverage is high.

However, in districts with clean delivery coverage below 70%, especially those with large rural, dislocated or slum populations, home deliveries may continue to take place under non-sterile conditions, and application of potentially infectious traditional substances to the umbilical stump may still be common. Such districts should be carefully evaluated as elimination may not yet have been achieved.

1.1.1.3 Percentage of pregnant women immunized with TT

Immunization of childbearing-aged women (CBAW) with tetanus toxoid (TT) provides maternal anti-tetanus antibodies, which are transferred from the mother to the developing fetus during pregnancy, thereby protecting infants against tetanus during the first several months of life. Because tetanus immunity wanes with time, women must receive a series of doses during their reproductive years to maintain protection (Table 1).

<table>
<thead>
<tr>
<th>TT or Td Dose</th>
<th>Optimal Dosing Interval</th>
<th>Minimum Acceptable Dosing Interval</th>
<th>Estimated Duration of protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>At first contact or as early as possible in pregnancy</td>
<td>At first contact or as early as possible in pregnancy</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>6-8 weeks after TT1*</td>
<td>At least 4 weeks after TT1</td>
<td>1-3 years</td>
</tr>
<tr>
<td>3</td>
<td>6-12 months after TT2*</td>
<td>At least 6 months after TT2 or during subsequent pregnancy</td>
<td>At least 5 years</td>
</tr>
<tr>
<td>4</td>
<td>5 years after TT3*</td>
<td>At least one year after TT3 or during subsequent pregnancy</td>
<td>At least 10 years</td>
</tr>
<tr>
<td>5</td>
<td>10 years after TT4*</td>
<td>At least one year after TT4 or during subsequent pregnancy</td>
<td>All childbearing age years; possibly longer</td>
</tr>
</tbody>
</table>

*optimally given at least several weeks before due date if administered during pregnancy

If a high proportion of pregnant or childbearing-aged women in a district have received enough TT to ensure protection, MNT most likely has been eliminated.

The standard indicator to measure TT coverage, “TT2+”, is the proportion of pregnant women who received their second or higher TT dose during pregnancy in a given year. This indicator is based on district administrative data that tend to underestimate the true level of protection in mothers and their newborns. The reasons why administrative estimates of TT2+ coverage may not reflect actual protection include:
• Pregnant women already may have received 5 TT doses before their last pregnancy, and therefore do not need additional TT doses. However, the administrative computation of TT2+ will count them as pregnant women who did not receive TT. This problem is most common in countries with longstanding, well-functioning immunization systems.
• If TT immunization records for pregnant women are unavailable, health workers may re-start the TT series in every pregnancy. A single dose is reported as TT1, while in reality it might represent a third (or higher) dose. The actual protection again would not be captured by the TT2+ indicator.
• In areas where TT SIAs have been performed, the supplemental doses are not included in the routine TT2+ count.
• As young women who received DTP in infancy enter their childbearing years, they require fewer TT boosters to achieve protection, a fact not captured by “TT2+”. Similarly, booster doses given later in childhood or adolescence are not reflected in TT2+.

The indicator “Protection at Birth (PAB)” is used by some countries to complement TT2+. PAB is the proportion of children protected against NT at the time of birth based on their mothers’ complete TT immunization history. PAB is often registered at the DTP1 contact. If PAB data are available, they should be included in the district review.

### 1.1.2 Supplemental indicators

When high quality data are available for the reported NT rate, clean delivery coverage, and TT2+/PAB coverage, assessment of MNT elimination is straightforward. However, more commonly, data are incomplete or unreliable. Additional information on “supplemental indicators” are used to create a series of data which, when taken together, help complete the picture of whether each district is likely to have eliminated MNT, and to identify districts which are still at relatively high risk for NT.

The most frequently used supplemental indicators are:
• The proportion of pregnant women having made at least one visit for antenatal care (may complement data on clean delivery)
• DPT1 coverage (indicates access to immunization services and may indicate access to other health care)
• DPT3 coverage (may indicate a well-managed immunization program and complements TT2+ coverage estimates)
• DTP1 to DTP3 drop-out rate (calculated as: [(DTP1– DTP3) / DPT1] x 100%; also provides an indication of the management of immunization services)
• The proportion of women in the district having received 2 or 3 doses of TT during SIAs - only for districts with SIAs
• Urban or rural status of a district; difficulty of terrain
As mentioned above, other indicators used for the review have included: measles vaccine and/or BCG coverage, trained TBA coverage, women’s literacy, % population living in poverty and other Human Development Indicators, and health service access indicators such as population per health center and health centers/km². The choice of supplemental indicators is country-specific and depends on data availability and reliability. Supplemental indicator data for each district should be incorporated into the data review spreadsheet (Annex 1).

1.1.3 Supplemental Data
In addition to core and supplemental indicator data, other helpful information may be available for the district review. Examples are reports of surveys of coverage or serological status, neonatal death investigations, annual record reviews, etc. Such reports can be useful in evaluating the likely elimination status of the districts involved or the status of specific population subgroups.

The assessment team may also decide, if necessary, to carry out field visits to clarify uncertainties, for example: to better understand the NT reporting system, to discuss the limitations of the immunization program with health workers and women utilizing the health system, to explore the circumstances under which "clean deliveries" are performed, etc. Such additional information may resolve concerns about questionable data.

At the completion of the data review, the group should come to unanimous decisions about:

- **The likelihood that MNT is eliminated, given the available data**
  If the data and information indicate that MNT is likely eliminated, the reviewers should judge whether or not additional information is needed (e.g., field visits to resolve doubts and inconsistencies, and/or whether to conduct a survey to validate MNT elimination) if the data seem to show that MNT has not been eliminated, the actions necessary to achieve elimination should be determined (e.g., conduct SIAs in high risk areas, strengthen outreach services to increase routine immunization coverage, etc.)

- **The selection of the highest-risk district(s) for a survey**
  If MNT elimination is likely, a confirmatory survey is usually recommended. The assessment team must then select the district, or districts to be surveyed (selection methods are discussed below).

1.2 DISTRICT FIELD VISITS
When there are problematic data or program issues that leave the MNT elimination status of districts in doubt, field visits may be indicated. Examples of situations that might prompt field visits are: districts that report NT rates above 1 per 1000 LB; districts with very low or very high TT2+, or large TT2+ fluctuations over time; or large inconsistencies among the core and supplemental indicators.
Activities during field visits may include:

- Examination of reports of NT cases to see if there have been misdiagnoses, or if the cases belonged to other districts (e.g. referral cases)
- Review of the NT surveillance procedures, including if and how hospital record reviews are performed; if there is active/community-based surveillance and community sensitization in rural areas
- Review of registers, micro plans, vaccine stock records to assess whether TT2+ is over- or underestimated
- Interviews with a sample of childbearing aged women to get a rough idea of TT coverage, the frequency of missed opportunities for TT administration, typical delivery conditions, cord care practices, use of ANC services, and perceptions about service availability and reliability
- Discussions with local health workers and authorities, including hospital pediatric ward staff, to get an impression of the general state of health services in the area and to obtain any additional reports and information
- Review of earlier reports on district performance (surveys, service or surveillance evaluations, etc.)

At the end of a field visit, if the MNT elimination status of the district remains unclear, the assessment team should consider what else needs to be done. For example, a small coverage survey may help to determine TT2+ and/or clean delivery coverage.

Once all additional information has been collected, the assessment team should consider again whether it is likely that MNT elimination has been achieved, and if a confirmatory survey is required.

1.3 SELECTION OF DISTRICTS FOR THE SURVEY

(See also Section 1 of the Statistical Supplement)

If, after reviewing the district level data, the assessment team agrees that MNT is likely eliminated, but that the available data are not conclusive, the team may decide that a survey is required. Because surveys are labor-intensive and expensive, they should only be performed when little doubt remains that MNT elimination has been achieved.

The survey should be carried out in one or a few districts that are judged to be at highest risk for on-going NT compared with the other districts in the country. The basis for surveying only those districts at highest risk is the assumption that if NT has been eliminated in the highest risk districts, it is reasonable to assume that the disease also has been eliminated in districts at lower risk, i.e., in the rest of the country.
The spreadsheet prepared for the data review (Annex 1) also is used to select the survey district. A shortlist of districts with the weakest performance levels is created using the indicators which the assessment team thinks are most reliable for judging performance. This short list is then carefully reviewed by the team. The final district selection should depend not only on indicator performance levels, but also on local knowledge, “gut impressions”, and consideration of other public health, logistical and financial factors.

Normally, only one district is surveyed, however when the poorest performing districts have very small populations, the survey may combine several high-risk districts or encompass an entire province. More details can be found in the section "Sample Size Determination" below.
2. Planning a LQA–CS Survey
2.

PLANNING A LQA–CS SURVEY

Part 2 outlines the steps required for planning a survey to validate MNT elimination once the decision to perform a survey has been made and the district(s) to be surveyed has been selected. WHO-HQ will review the objectives, specific terms of reference, survey protocol and required preparations with the national core team of MOH, WHO and UNICEF representatives. The core team should agree on individual team member responsibilities and the activities timeline.

2.1 SURVEY PREPARATIONS – OVERVIEW & SUGGESTED TIMELINE

2.1.1 Preliminary planning

1. National team briefing on LQA-CS survey
   - Review summary of required preparations; assign responsibilities; adopt timeline (sample checklists in Annex 2; budget calculator in Annex 3)
   - WHO/HQ to ensure the team understands the tasks ahead and is prepared to complete them

2. Appoint a National Focal Point
   - Ideally an MOH representative who assumes overall responsibility for coordinating the survey

3. Notify the selected district(s) and obtain approval(s) for the survey
   - The district team leader(s) should be identified and briefed
   - Security conditions should be reviewed

4. Decide on dates for the survey (with district team leader(s))
   - Consider access, weather and local customs (religious events, seasonal migration, planting/harvesting times, etc.)
   - Notify WHO/HQ

2.1.2 Determine survey design, micro plan & budget

1. Determine sample size, cluster size and number of clusters (pp 13-15 & Annex 4)
   - Decide on a single or a double sample plan
   - Determine total sample size; calculate cluster size and number of clusters

2. Select cluster locations (pp. 16-17)
   - A list of district villages/wards with populations in hand is required
Planning a LQA–CS Survey

3. Prepare micro plan based on actual clusters to be surveyed.¹
   - Who, what, where, when, how - as prepared for SIAs and/or other surveys
   - Develop a micro plan with district representatives
   - The micro plan should be detailed and designed specifically for local conditions - staffing ratios and transport needs may vary depending on population density and terrain within the district(s).

4. Calculate budget based on the micro plan.
   - A rough budget calculator is available from WHO (see Annex 3 – modify as appropriate)
   - Prepare budget with input from district representatives (local costs may vary)
   - Include all anticipated expenses based on micro plan and past experience

5. Submit micro plan and budget request to WHO/HQ
   - Funds are available from WHO HQ for most surveys, but in some cases countries have contributed to the costs.

6. Provide district team(s) with final micro plan and timeline
   - (District-level checklist sample in Annex 2)

7. Identify the survey staff (see section on Roles & Responsibilities below)
   - WHO/HQ will identify the consultant(s)
   - The national team typically identifies the monitors
   - The district team(s) should identify supervisors, surveyors, local guides, and MOs with assistance from national team if needed

2.1.3 Training

1. National-level training for monitors
   - For national team, monitors (and supervisors if possible) who will conduct district training workshop(s)
   - Usually conducted by the WHO consultant in the capital city during the week before the survey; lasts 2-3 days
   - Follows standard training package available from WHO/HQ; must include a field-exercise

2. National team arrives in district(s)
   - Preferably 1-2 days before district workshop to review preparations and assist with final tasks

3. District training workshop for entire survey staff

¹ While early selection of clusters creates risks of falsification, it is impossible to do proper microplanning and budgeting without knowing where teams are going — this is of crucial significance for difficult-to-access areas. Microplanning could be done with trusted local informants (perhaps people who are not directly involved with the MNTE program or survey) or using general target areas that include the specific clusters but without naming the actual villages/wards.
Training conducted by monitors in the local language of the survey district(s)
- Usually held in the district capital just before the survey start; usually 2-3 days long
- Follows standard training packages for different staff roles; must include a field-exercise

2.2 DESIGNING THE COUNTRY-SPECIFIC SURVEY

The community-based survey method recommended in this manual uses a combination of lot quality assurance (LQA) and cluster sampling (CS) techniques to judge whether the neonatal tetanus mortality rate, or NTMR, is probably greater than 1 NT death/1000 live births or not.

The structural elements that must be determined for each specific survey are:
- Single vs. double sample plan
- Survey sample size – the total number of live births to be identified and surveyed
- Cluster size – the number of live births per cluster (sampling unit)
- Number of clusters – the total number of clusters to be surveyed
- Duration of survey – depends on sampling plan, average time required to complete clusters and staff availability

The following sections describe the LQA-CS survey and how to determine the structural elements required for each survey. See the Statistical Supplement for greater detail.

2.2.1 Background

The LQA-CS survey method is appropriate for selected populations in the final stage of MNT elimination when there is evidence suggesting that NT has been reduced to less than, case/1000 live births and only occurs sporadically (not in clusters). The method was developed because conventional surveys to measure low NTMRs require very large sample sizes - tens of thousands of live births. The LQA-CS method uses samples of 3000 live births or less, making surveys feasible and affordable in countries ready to demonstrate MNT elimination.

- The statistical basis and technical aspects of the LQA-CS methodology is described in detail elsewhere. The following summarize basic survey assumptions and structure.

The NT LQA-CS is a type of neonatal mortality survey in which identified neonatal deaths are investigated by verbal autopsy to determine if the death was caused by tetanus (see “Neonatal Death Investigations” below for the NT case definition).

Planning a LQA–CS Survey

While MNT elimination is defined as less than 1 NT case per 1000 live births, the survey measures NT deaths per 1000 live births. Because NT mortality is very high (>80%), especially in areas without intensive care medical facilities, the NT mortality rate is assumed to approximate NT incidence.³

The primary elements sampled are live births delivered during a 12-month eligibility period that ends at least 4 weeks before the start of the survey. The 4-week interval between the end of the eligibility period and the start of the survey is to ensure that the outcome for all eligible live births can be determined for the entire neonatal period.

- The LQA-CS survey assesses whether the NTMR in the survey area probably exceeds 1/1000 live births during the 12-month eligibility period, or not. It is not designed to provide a point estimate of the NTMR for the surveyed area.

The number of NT deaths detected during the survey is compared to a pre-determined maximum acceptance number of NT deaths that defines whether the district “passes” (NTMR probably does not exceed 1/1000) or “fails” (NTMR is probably greater than 1/1000). This pass/fail design comes from LQA methodology.⁴

The acceptance number is calculated to ensure that there is a high probability that a district given a “pass” did not have an actual NTMR greater than 1/1000 live births during the 12 month interval covered by the survey.

- A double sample procedure divides the total sample in two parts to be surveyed sequentially. The double sample plan has the advantage of allowing a decision to be made from the results of the first sample if the number of NT deaths detected is very low (0), or very high (more than the acceptance number). When results of the first sample fall in between, the second sample is needed (see “Survey Procedures – Overview” below).

When the second sample is required, a decision can be made before completing the second sample if the number of detected NT deaths surpasses the acceptance number (fail). Thus, a double sample plan can reduce the total sample size needed to reach a decision, and decrease the amount of field work and costs associated with the survey.

- The cluster selection method used for the LQA-CS survey is the same as that used for a standard 30 x 7 cluster survey for immunization coverage,⁵ except that more clusters are used. The larger number of clusters increases the representativeness of the sample and the precision of point estimates for variables other than NT mortality.

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⁴ LQA is a technique which originally was developed for quality control in manufacturing to ensure that lots (batches) of products do not have an unacceptable proportion of defective items.
• TT coverage, clean delivery coverage and cord care practices are measured during the survey as well.

### 2.2.2 Sample Size Determination

The survey sample size is determined by the population size of the survey district(s), and the sampling scheme chosen.

Originally, the surveys were designed as double sample surveys for populations with at least 30,000 births per year. In that case, the total sample size required is 3000 live births: 1000 live births in the first sample with an acceptance number of 0 NT deaths; 2000 live births in the second sample with a maximum acceptance number of 3 NT deaths.

Modifications to the original design were made to enable double sample surveys of smaller populations and use of single sample surveys. In 2012, the statistical basis and assumptions of the method were thoroughly reviewed. Recommended sample sizes were refined. Sample sizes and acceptance numbers were determined for single and double sample surveys for both large populations (at least 50,000 live births) and smaller ones, with similar probabilities of acceptance for all, thereby maintaining comparability among surveys.

See Annex 4 for a table that provides the required sample sizes for double or single sampling in populations with different numbers of annual live births.

Note: sample sizes were determined based on the assumptions that NT mortality is approximately 80% and that 90% of all NT deaths will be identified (see Statistical Supplement). If these assumptions are not appropriate for a given survey, the required sample sizes can be recalculated with the “LQASdesign” package written for the computer program R.\(^6\)

### Sample size for populations of less than 50,000 births per year, using a double sample plan

Annex 4 provides sample sizes and acceptance levels for surveys of populations with fewer than 50,000 live births per year. For example, a population with 15,000 live births requires 1340 live births for the first sample and 1220 live births for the second. NT can be considered eliminated if 0 NT deaths are found upon completion of the first sample, or if 2 or fewer NT deaths are identified in samples 1 and 2 combined.

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\(^6\) Contact Dr. Nasir Yusuf, Senior Health Specialist - Monitoring, MNTE & GVAP, for the necessary statistical package and instructions: yusufn@who.int
Sample size for single sample surveys

Adjusted sample sizes and acceptance levels for single sample surveys also can be found in Annex 4. For example, if a district has 30,000 live births, a single sample survey requires a sample size of 2470 live births. NT can be considered eliminated if 2 or fewer NT deaths are identified. In a district of 10,000 live births, the recommended single sample size is 1730 live births; NT is considered eliminated with 0 or 1 NT death.

Sample size for districts with very small populations

When districts have fewer than 3000 live births, two or more districts at high NT risk can be combined in the same survey to increase the total population size. The results will be interpretable only for the group of districts, not for each district separately. Strictly speaking, a pass for the combined districts does not validate MNT elimination at the district level, but this is considered an acceptable limitation. See also Section 1 of the Statistical Supplement.

Single versus double sample surveys

Double sample surveys are usually chosen when it is expected that NT elimination can be demonstrated with the first sample alone, that is, when a country is confident that NT has become so rare that it is likely that no NT deaths will be found in the first sample. In such cases, NT elimination status can be determined from the relatively small first sample of a double sample plan, or before finishing the survey of all second sample clusters. See also Section 2.4 of the Statistical Supplement.

Single sample plans are appropriate when logistics are too complicated and/or communications inadequate for a double sample plan. Double sample surveys are more complicated to organize because arrangements (transport, per diems, etc) must be made for both samples in advance, even if it is possible that only the first sample will be required. Communication among teams is critical in double sample surveys, as the decision to implement the second sample depends on timely receipt of all results from the first sample. In addition, results from second sample clusters must be monitored continuously to determine whether the number of identified neonatal deaths has exceeded the acceptance number, yielding a “fail” and allowing the survey to be terminated. Single sample surveys are thus indicated when logistics and communications infrastructures cannot support a double sample survey.

2.2.3 Determination of the size and number of clusters

Once the total sample size of live births required for the survey is determined, the cluster size and number of clusters can be calculated.
Ideally one cluster should be completed in 1 day or less. Thus the cluster size, or number of live births per cluster, is equal to the number of live births that can be surveyed in a day.

**To calculate the cluster size**, calculate the number of live births that can be surveyed in 1 day by multiplying:

- the average number of households that can be visited in 1 day
  
  by

- the average household size (*this gives the number of people that can be surveyed in 1 day*)
  
  by

- the crude birth rate or CBR (*this gives the number of live births surveyed in 1 day*)

\[
\text{Cluster size} = (\#\text{HHs}) \times (\text{HH size}) \times (\text{CBR})
\]

For example: if 100 households can be visited in 1 day, the average household size is 5.5, and the CBR is 0.036, the cluster size will be: 100*5.5*0.036 = 19.8, or 20 live births per cluster.

**To calculate the total number of clusters** required, divide the total sample size by the cluster size.

\[
\text{Number of clusters} = \frac{\text{sample size}}{\text{cluster size}}
\]

Continuing the example from above, if the total sample size is 3000 live births, the number of clusters required is: 3000/20 = 150. For a double sample survey, this total number of clusters is divided into those required for the first and second samples based on the respective sample sizes.

District specific data for average household size and crude birth rate should be used whenever possible. If district data are not available, provincial or national data are acceptable substitutes.

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A realistic estimate of the average number of households that can be visited in a day (or 2 days for especially hard-to-reach populations) is critical for determining realistic cluster sizes and therefore realistic workloads for survey teams.\(^7\)

District authorities should be consulted about past local experience with other surveys or door-to-door vaccination campaigns to determine an appropriate estimate.

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\(^7\) The estimated number of households that can be visited in one day is ONLY used to compute cluster size and number. Surveyors must visit households until they reach the pre-set number of live births for each cluster (20 in the example above), regardless of the number of households it takes to find the required number.
In districts with low population densities and/or difficult terrain, it may be necessary to complete clusters in more than 1 day. The cluster size and number of clusters should be calculated as above, but the days required to complete the clusters can be increased.

In districts with a wide range of conditions, some surveyors will be able to complete clusters in less than 1 day, while others will need more than 1 day. Allocation of survey staff should reflect differences in conditions (e.g., extra staff assigned to difficult areas, or more clusters assigned per surveyor in easy areas).

**The size of every cluster must be the same; the time to complete clusters can vary.**

### 2.2.4 Sample Size for TT2+, Clean Delivery and Cord Care Assessment

At least 250 mothers of eligible live births are asked about their TT immunization history, the circumstances of delivery and the application of traditional substances on the umbilical cord.\(^8\)

When a double sample plan is used, the first 5-8 mothers with an eligible live birth in each cluster of the first sample are asked the additional questions. The number of mothers surveyed per cluster depends on the number of clusters to be surveyed. In a single sample survey, usually only the first 3 mothers per cluster are asked the additional questions because the number of clusters is larger.

To calculate the number of mothers per cluster who will be asked the additional TT, clean delivery and cord care questions, divide the total number of mothers to be surveyed (250) by the number of clusters, and round up to the next whole number if necessary:

\[
\text{Mothers per cluster} = \frac{250}{\#\text{clusters}}
\]

For example, in a double sample survey, if there are 50 clusters in the first sample, the number of surveyed mothers per cluster would be: \(\frac{250}{50} = 5\) mothers per cluster.

For a single sample survey with 110 clusters, \(\frac{250}{110} = 2.5\) or 3 mothers per cluster.

**The number of mothers surveyed in each cluster must be the same; the total number must be 250 or more.**

### 2.2.5 Cluster selection

Once the number of clusters required for the survey is determined, the locations of the clusters are randomly selected from a list of the smallest population units available, e.g., villages, towns, and wards / census blocks of larger cities in the district(s) to be surveyed.

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\(^8\) The sample size recommended here (250) should provide estimates with narrower confidence intervals than the + 10% maximum assumed for a 30 x 7 cluster survey because a larger number of clusters are surveyed and coverage is usually higher than 50%. There is no advantage to increasing the number of mothers surveyed per cluster unless a subset analysis is desired (e.g., comparing coverage in different age groups) or greater precision is required.
A complete list of population units with current populations is essential.

Cluster selection is performed in the same manner as in the 30 x 7 cluster survey method, and like the 30 x 7 cluster survey, uses “probability proportionate to size” (PPS) so that all individuals in the population have an equal probability of being selected. The procedure is most easily performed with a computer spreadsheet program, although it can be done by hand if necessary. Refer to the example in Table 2 below.

1. The first step is to obtain a complete list of all villages and urban population units (wards, census blocks, etc.) with the best estimates of the population for each in a second column. An up-to-date list is essential and must be compiled if not available from district authorities.

2. Next, calculate the cumulative population for each community on the list and place it in a third column. This is done by adding the population of the first community on the list to the population of the second community – the sum is shown as the cumulative population of the second community. Continue by adding the population of the next community on the list to the cumulative population of the preceding community for each listed community. The cumulative population of the last community on the list should equal the total population for the district(s) to be surveyed.

3. Calculate the sampling interval by dividing the total population to be surveyed by the total number of clusters; round off the result to the nearest whole number. This sampling interval is the number used to systematically select clusters from the list. In Table 2, an example is shown in which 30 clusters will be sampled, the sampling interval is: 139,324/30 = 4644

4. Choose a random number to determine the starting point on the list. The number should be less than or equal to the sampling interval, and have the same number of digits. The random number can be obtained from a random number table or computer program, or from the serial number on a currency note. In the example, it is 3311.

5. Select the location of the clusters. The first cluster is the community on the list with a cumulative population that is equal to or more than the random number. Write “1” beside this community in a column for listing cluster numbers. As 3311 falls in the cumulative population of the first community on the list (11,627), the first cluster is located in the first community.

To select the location of the second cluster, add the sampling interval to the random number and find the community with a cumulative population that equals or exceeds that sum. Write “2” besides the community. In the example, 3311+4644 = 7955; 7955 also falls within the cumulative population of the first community.
The location of the rest of the clusters is determined in the same way - the community in which the cumulative population equals or exceeds the sum of the previous total plus the sampling interval is the next location of a cluster. This procedure is continued until all cluster locations are identified. (Note: it is possible that some large communities will have several clusters).

If the survey has a double sample plan, the final step is to allocate the selected cluster locations to the first and second samples. This is done by selecting the cluster locations for the first sample by one of the two methods described below. The remaining cluster locations will be used for the second sample if needed.

First, re-number all the selected cluster locations (from 1 to the total number).

**Method 1** - systematic allocation of clusters to first and second samples:
(This is the preferred method as the allocation will be PPS):

In the case of surveys in large districts, if the second sample size is twice the size of the first (e.g., \( n_1 = 1000; n_2 = 2000 \)), every third cluster location should be selected for the first sample.

- Select a random number from 1 to 3. The community with the cluster number equal to the random number is the first cluster location for the first sample. The second cluster location is that with the number equal to the random number plus three. Continue sequentially adding 3 (selecting every third cluster number) until all clusters for the first sample have been identified.
- The remaining cluster locations constitute the second sample.

**Method 2** - random allocation of clusters to first and second samples:
(for surveys in smaller districts when the size of the second sample is not a multiple of the first.)

- Generate random numbers between 1 and the total number of clusters in the survey. The quantity of random numbers required is the same as the number of clusters in the first sample.\(^9\)
- The communities with numbers corresponding to the random numbers will be the cluster locations for the first sample. The remaining cluster locations will be used for the second sample (if needed).

For example, if the total number of clusters is 168, and 60 are required for the first sample, then 60 random numbers between 1-168 (inclusive) are needed. The 60

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\(^9\) Epi Info 7 is a small, easy-to-use computer application that will generate a list of random numbers based on specifications entered into the program "random number list" found in EPITABLE. The software is freely available at: [http://www.cdc.gov/epiinfo](http://www.cdc.gov/epiinfo). Many other statistical software packages have similar programs.
communities with numbers corresponding to the random numbers will be the first sample; the rest are second sample clusters.

**Table 2. Example of systematic cluster location selection proportionate to community size**

<table>
<thead>
<tr>
<th>Column 1</th>
<th>Column 2</th>
<th>Column 3</th>
<th>Column 4</th>
<th>Column 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Community/Area</td>
<td>Population</td>
<td>Cumulative population</td>
<td>Cluster numbers</td>
</tr>
<tr>
<td>1</td>
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<td>11 637</td>
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<td>2 000</td>
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<td>8,9</td>
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<td>Arkaweet</td>
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<td>59 334</td>
<td>11,12,13</td>
</tr>
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<td>7</td>
<td>Helat Hasan</td>
<td>6 000</td>
<td>69 334</td>
<td>14,15</td>
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<td>Al Dubasin</td>
<td>3 363</td>
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<td>139 324</td>
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<tr>
<td></td>
<td>TOTAL</td>
<td>139 324</td>
<td></td>
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</tbody>
</table>

Sampling interval \( \frac{139,324}{30} = 4644 \)

Random number 3311

(Source: Immunization coverage cluster survey – Reference manual, WHO/IVB/04.23)
2.3 SURVEY STAFF – ROLES & RESPONSIBILITIES

The success and validity of the survey depends on the performance of the staff involved. Survey personnel should be chosen on the basis of their qualifications and willingness to participate. Roles and responsibilities must be clearly delineated.

The following summarizes the categories of survey personnel and their general duties.

Surveyors

- Usually 1 per cluster (often responsible for more than 1 cluster)
- Responsible for:
  - going house-to-house, interviewing residents
  - collecting survey data and completing survey forms
  - notifying supervisors/MOs when neonatal deaths are identified.
- Should be health care workers, public health staff or medical/nursing students with experience in communicating with families about the sensitive issues of pregnancy, childbirth and child deaths. Teachers may be acceptable alternatives if sufficient health workers are not available.
- Must know the local language and be familiar with local customs. Women surveyors are preferred because of the sensitive nature of some questions.
- Surveyors should NOT be assigned clusters in the areas where they normally live and/or work. If possible, surveyors should come from outside the survey district.
- Several back up surveyors should be hired and trained to cover for drop-outs.

Local guides

- 1 per surveyor (for a given cluster area)
- Responsible for introducing the surveyor / other survey personnel to community leaders and household residents, and helping the surveyors identify and navigate the cluster localities.
- Should be selected/approved by the village/ward head; preferably well-known to the community; often are auxiliary community health workers.

Supervisors

- Usually 1 for 3-5 surveyors; ideally able to visit all surveyors in the field each day. In areas with exceptionally scattered population and/or difficult terrain might be assigned to only 2 surveyors.
- Are preferably Medical Officers (doctors) who can conduct neonatal death investigations.
- Responsible for:
  - providing/arranging transport for surveyors to and from clusters.
supervising surveyors in the field to ensure that household selection and data collection are properly performed (daily if possible)

- Responsible for investigation of all neonatal deaths identified in the survey in their assigned areas, including completion of the neonatal death investigation form (Form 3)
- contacting MOs when neonatal deaths are identified (if supervisor is not an MO)
- reviewing data collection forms at the end of the day, tallying cluster results and checking Quality Assurance indicators (QA Section, p. 30), and informing monitors of results
- troubleshooting any problems that arise

• Usually recruited from district-level supervisory/senior staff; ideally from another district. Should NOT be assigned areas where they normally live/work.

Exceptionally, when there are no MOs available in the country, NDs could be investigated by paramedics or midwives, but to be verified by the monitors based on the clinical history.

Monitors

• Usually 3-5 per survey – more may be required for widely dispersed populations / difficult terrain.
• Responsible for:
  - district-level training of surveyors, supervisors and MOs
  - second level supervision during the survey, including visits to as many surveyors and supervisors in the field per day as possible
  - helping trouble-shoot any problems that arise
  - reviewing data with supervisors at the end of each day to ensure correct procedures are being followed
  - monitoring survey quality indicators, especially NDs; providing feedback to supervisors and surveyors
  - re-investigating and confirming any identified NT deaths in assigned area
  - assisting with data entry (optional – depends on circumstances)

• Usually national and provincial staff; may include district heads

International consultant

• 1 per survey (or more when several districts are covered)
• Responsible for:
  - acting as main technical advisor; ensuring adherence to global protocol
  - leading / participating in national training workshop; assisting with district training
  - serving as monitor during the survey
  - assisting with data entry & analysis
  - helping draft first survey report
Coordinators - “Core Team” for survey

- Usually consist of national-level team and the international consultant; often also serve as monitors. One national member serves as the overall survey coordinator and main contact with WHO/HQ
- Make ultimate decisions about survey outcome, the need to repeat portions of the survey if procedures are not followed, etc.
- Finalize survey report.

Data Manager

- 1 per survey (optional – data management may be performed by coordinators)
- Assists with data entry of cluster-level data and/or compiling data entered by monitors; might assist with district-level survey preparations and worksheets, and with monitoring.
- Usually a district IT staff member or data manager; may be provincial or national level

2.4 TRAINING

Good training ensures a well-executed survey.

When procedures are not followed correctly, survey results are invalid – survey staff must be retrained and the survey repeated.

An LQA-CS survey training kit is available from WHO/HQ. The kit contains:

- 2 sets of PowerPoint presentations designed for national-level monitors and supervisors training, and one for district-level surveyors training. Subjects covered include:
  - MNT elimination and the purpose of the survey
  - Survey staff roles and responsibilities
  - Survey procedures, including how to use the data collection forms
  - Survey quality issues and indicators
  - Understanding survey results
- A role-play board game that takes trainees through survey procedures and a range of situations they are likely to encounter.
- Instructions for a mandatory field exercise
- Sample workshop agendas, surveyor instructions and scripts, and survey forms (Annexes 7-10).

The materials should be adapted for the local setting and specific survey before use; slides, handouts and forms used by surveyors must be translated into the local language.
Training should be well-organized, practical and participatory to ensure that survey personnel are provided with all the preparation they need to conduct the survey properly and collect high quality data.

For the role-play game and field exercise, trainees should be divided into small groups. Organizing groups by survey assignments is preferred. (Surveyors, supervisors and monitors who will work together also should train together). At the end of the field exercise, all trainees should return for a large group discussion of encountered problems and questions.

At the end of the training, the following areas of understanding are critical:

- **Surveyors must be knowledgeable on:**
  - How to choose households and why no household can be skipped
  - How to find ALL eligible live births and ALL eligible neonatal deaths
  - How to complete Forms 1 and 2
  - How and when to contact their supervisors

- **Supervisors must be knowledgeable on:**
  - All survey materials
  - How to tally Forms 1 and 2 when clusters are completed
  - How to supervise effectively and monitor quality indicators
  - What to do if problems are identified
  - What is the NT case definition; what supplemental factors can be useful in diagnosing NT?
  - How to decide if a neonatal death was caused by NT
  - How to complete Form 3

- **Monitors must be knowledgeable on:**
  - All aspects of the survey including all surveyor, supervisor and monitor materials.
3. Survey Implementation
3. SURVEY IMPLEMENTATION

3.1 SURVEY PROCEDURES - OVERVIEW

Note: Supervisors and Monitors must all have independent transportation for optimal supervision and prompt investigation of neonatal deaths.

Start of survey day:
- Supervisors drop their surveyors at the assigned cluster sites.
- (When distances between clusters are large, supervisors may arrange for independent transportation for some of the surveyors assigned to them.)
- Surveyors meet the local guides; visit the head of the cluster area (village chief, head of ward, etc.) to explain the purpose of the survey and obtain permission to work in the area
- Monitors help ensure that survey personnel have transport and can begin work in a timely manner.

During the survey day:
- After the introduction to the cluster area head, surveyors select the first household of the cluster (see below) and proceed with interviews and data collection as described in section 2 and annex 6.
- If questions/problems arise, and when NDs are identified, surveyors contact their supervisors.
- Supervisors return to the clusters being covered by their surveyors to check the progress of the work, ensure that procedures are being followed properly (observe surveyors at work; recheck several houses), solve any problems that arise, and investigate identified neonatal deaths.
- Monitors visit clusters being covered by the groups of surveyors and supervisors assigned to them, independently checking the work and ensuring proper procedures are adhered to.
- Monitors (core team) should re-check neonatal deaths that are thought to be due to tetanus.
- Throughout the day, the number of identified neonatal deaths and neonatal tetanus deaths should be communicated to the survey coordinators so that progress of the survey can be monitored.
- A cluster is completed when the pre-set number of live births have been identified, regardless of the number of HH visited, or the number of ND identified.
End of survey day:

- Supervisors pick up their surveyors, review the data sheets and, with their group of surveyors, discuss any questions/problems that arose. When the clusters are completed, supervisors collect all forms and tally the cluster results.
- Monitors meet with (or talk by telephone) with their supervisors to learn of the day’s progress, noting the number of clusters completed, neonatal deaths identified and if any cases of NT have been found.
- Completed data forms should be collected and all quality assurance indicators checked as soon as possible (see QA Section, p. 30).
- Monitors meet with supervisors to review ND investigations at the end of the day, or as soon as possible.
- Monitors meet as a group each evening to review survey progress and discuss/resolve any problems that arose. This coordinating meeting also should include staff responsible for survey logistics.
- (When monitors are based in geographically dispersed areas, they may need to call in the progress of their teams to the head survey coordinator.)
- Surveyors and supervisors should be given feedback about survey progress (number of clusters completed, numbers of identified neonatal and NT deaths, etc.) at the end of each day or before starting work the following morning. Observed problems must be discussed and solutions be proposed.
- If major flaws in survey implementation have surfaced by the end of the first day, the survey may need to be stopped, and surveyors/supervisors retrained on Day 2, before restarting the survey.

Survey completion:

- **Single sample survey:** work proceeds as above until all clusters are completed.
- **Double sample survey:** work proceeds as above until all clusters in first sample are completed.

The results of the first sample will determine whether the second sample must be performed. After all clusters in the first sample have been completed:

- If no NT deaths are detected, NT elimination can be accepted (pass) without surveying the second sample. The survey can be stopped.
- If more than the maximum acceptance number of NT deaths is detected, NT elimination is rejected (fail); the second sample is unnecessary. The survey can be stopped.
- If any NT deaths have been identified, up to and including the maximum acceptance number, a decision about NT elimination cannot be made; the second sample of clusters must be started.
When the second sample of clusters is required, work continues in the same manner as described above. Identified neonatal deaths and neonatal tetanus deaths must be reported as soon as possible to the coordinators so that progress of the survey is continuously monitored.

- If the total number of identified NT deaths (both samples combined) remains less than the maximum acceptance number, all clusters in the second sample must be completed.

If the total number of identified NT deaths exceeds the maximum acceptance number at any time, the second sample can be stopped, even if not all clusters are completed.

3.2 SURVEY PROCEDURES - SPECIFICS

Essential definitions

• A household is defined as a group of people sharing the same kitchen.
• Eligible live births are those delivered by eligible mothers between __/__/__ and __/__/__
• Any birth between __/__/__ and __/__/__ to an eligible mother is eligible, even if the birth was at a different location.
• Eligible mothers are mothers who delivered during the eligible period and who reside in a household at the time of the survey – not visitors.
• If a mother is temporarily away at the time of a survey, she is still eligible.
• A neonatal death is a death in the first 28 days of life

3.2.1 Procedures for Surveying Clusters

• Upon arrival at the cluster location, first visit the head of the area (village chief, head of ward, etc.) to explain the purpose of the survey, general procedures (choice of first HH, which HHs will be visited, what kinds of questions will be asked) and request permission to perform the survey.

If a local guide was arranged in advance, meet the guide who can then introduce the head of the area.

If a local guide has not been arranged, ask the area head to appoint a guide (local health worker or administrative assistant who is familiar with the residents)

• Select the first household as described below.
• The local guide should make the introductions; then briefly explain the purpose of the survey.
• Explain that survey participation is not obligatory and that refusal to participate will not result in any negative consequences. Then ask if the household members are willing to participate, i.e., to give verbal informed consent.
• Interview the head of the household / resident women with eligible live births as described in Annex 6, completing Forms 1 and 2 as directed.
• Proceed to subsequent households, repeating the introduction, explanations, interviews and data collection, until the required number of live births for the cluster has been surveyed.
• If a neonatal death is identified, the supervisor should be contacted immediately. If the supervisor cannot be reached, the monitor should be contacted.
• Forms 1 and 2 should be submitted to the supervisor once a cluster has been completed – usually at the end of a work day when meeting with the supervisor and fellow surveyors.

Selection of the First Household in each Cluster

The first house to visit in each cluster should be selected at random. Several methods can be used:

Method 1: Areas where household lists are available.
The ideal situation is one in which there is a complete list of households in the cluster area that can be used to randomly select the first household to be surveyed. If such a list is available:
• Number the households on the list.
• Select a random number from 1 to the highest numbered household on the list (inclusive). Do this by using a table of random numbers or the serial number on a currency note.
• Find the household on the numbered list whose number corresponds to the random number selected. This is the first household to visit.

Method 2: Rural areas and urban subdivisions where household lists are not available.

In cluster sites where no there is no list of households (the most common situation):
• Select a central location in the village, town or ward, such as a market, a mosque or church. The location should be near the approximate geographical centre of the area.
• Randomly select a direction from the centre by throwing a pen spinning in the air. When the pen falls on the ground the point indicates the direction to be taken.
• Walk in the selected direction, counting all the houses passed until the edge of the area is reached.
• Select a random number between 1 and the total number of houses counted. The house with the corresponding number is the first house to visit. For example, if the randomly
selected number is 9, the ninth house from the central location is the first household to visit.

Note: if a village where a cluster is begun is known to have fewer HHs than will probably be needed to complete the cluster, surveying can start at any household because all households will be visited.

**Method 3: Choosing subdivisions in urban areas and large rural towns**

Often urban cluster sites are too geographically large and/or contain too many households to use Method 2 without first selecting a smaller portion of the cluster area. If the area already has official or locally recognized geographical or political subdivisions with approximately equal populations (or which can be grouped to obtain equal populations) these should be used. If such subdivisions don’t exist, use a map or sketch of the area and create subdivisions of approximately equal size (e.g., blocks of about 100 houses) with the help of local authorities.

- Number each subdivision and select a random number between 1 and the total number of subdivisions. The selected number indicates the subdivision in which the first household is located.
- If a household list exists for the subdivision identified, select the first household to visit by following the procedure described for Method 1.
- If a household list is not available, use Method 2 to identify the first household.

This subdivision method can also be used when more than 1 cluster site is located in a single urban ward or large rural village. To select the cluster locations within the ward or village:

- Use the pre-existing subdivisions or create them with the help of a map/sketch and local authorities. Ideally, there should be at least 2-3 times as many subdivisions as clusters to be surveyed in the ward or village.
- Number the subdivisions
- Choose random numbers (between 1 and the total number of subdivisions) to identify the subdivision for each cluster to be surveyed in the ward or village. The random numbers can be obtained using a table of random numbers or currency note serial numbers.
- If a household list exists for the subdivision identified, select the first household to visit by following the procedure described in Method 1.
- If a household list is not available, use Method 2 to identify the first household

A household is defined as a group of people sharing the same kitchen. In urban areas, there may be many households in a single building. To ensure an unbiased selection of households in such buildings, choose one floor at random. Number the households on the selected floor and randomly select the first household to visit.
Selection of Subsequent Households

The second (or next) household to visit is the one that is nearest to the first.

The next nearest household is the one whose front door is closest to the front door of the household just visited (see the figure below).

If the front doors of 2 households are at equal distances from the first, but one can be reached more quickly, go to that household next; otherwise, flip a coin to determine the next household.

In apartment buildings, the second household to visit is the door nearest to the first. After all the households on the floor have been visited, randomly choose a direction up or down to determine the next floor to visit. Visit all the households on that floor. Continue from floor to floor, visiting the next nearest floor which has not been visited previously. After all households in the building have been visited, go to the nearest door of the nearest building, and repeat the process.

Identifying the nearest household in hilly terrain with highly scattered dwellings can be difficult. If there is no map showing household locations, surveyors must rely on their local guides to direct them to the nearest household.

All households must be visited and counted for the survey to be valid.

3.2.2 Neonatal Death Investigations

Neonatal deaths are investigated using standardized verbal autopsy methods to determine if the death was caused by tetanus. The investigations must be conducted by trained physicians or other clinically-trained personnel (by the supervisor, or if he/she is not a trained physician, by the monitor).

Careful, thorough neonatal death investigations are critical for valid survey results.

NT is a clinical diagnosis; there is no confirmatory laboratory test.

The NT case definition is:

A neonate who feeds and cries normally for at least the first 2 days of life,

and, between 3 and 28 days of life

Stops sucking normally

and

Develops stiffness/rigidity and/or spasms

For a diagnosis of NT to be made, the criteria in the case definition must be met.
Additional information that supports the diagnosis of NT:
• Hypersensitivity to touch, sound and/or light, setting off spasms
• Presence of risk factors associated with NT such as lack of maternal TT immunization and/or unhygienic delivery and/or umbilical cord care

NT can be ruled out in cases where death occurs in the first 2 days of life.

Specific instructions for conducting the investigation and completing Form 3 can be found in Annex 7.

3.2.3 Collection of Survey Information

The information collected during the survey should be limited to data that are essential for evaluating the NTMR, TT and clean delivery coverage of mothers, and occasionally a few other epidemiological factors related to NT risk. Collection of non-essential information should be avoided as it may have a negative impact on the quality of the essential data.

Examples of data collection forms and instructions for surveyors and Medical Officers are provided in Annex 6 and 7. These forms must be translated into the local language before the survey starts.

The following summarizes the forms and essential data to be collected:

Form 1 – Household data (one per cluster):
• The number of residents in each household visited - used to verify the actual number of household visits needed to complete each cluster, and to calculate the total population surveyed and average household size. These estimates can be compared with other sources of data to validate the quality of the survey data.
• The number of pregnancies in the previous 2 years in each household, the outcome of those pregnancies, and the number of live births that occurred in the eligible period of the survey.¹

Form 2 – Live birth data (one per cluster):
• Information about each eligible live birth is recorded on a line on Form 2 - date of birth, survival status and, if the baby died, whether the baby died before reaching 28 days of age. (Eligible births are those occurring 1-13 months before the survey.)
• In addition, information about the delivery conditions, TT status and the use of traditional substances on the umbilical cord, of a sub-sample of mothers of the eligible live births is collected in first sample clusters of a double sample survey, and in all clusters in a single sample survey.

¹ While the information about the number of miscarriages and stillbirths is not used in final data analysis, it is collected on Form 1 as part of information gathering about pregnancy outcomes. Because it is not uncommon for babies who expired shortly after birth to be misclassified as stillbirths or late miscarriages, completion of the pregnancy outcome section of Form 1 helps remind the surveyors to try to ensure that early neonatal deaths are not missed. If a survey identifies fewer live births or neonatal deaths than expected, the information on Form 1 can be used to revisit households with stillbirths.
(A simplified version of Form 2 without columns for clean delivery and TT status is used for the second sample in a double sample plan.)

**Form 3 – Neonatal death investigations** (6-10 per Medical Officer, depending on assignment):
All neonatal deaths that occurred in identified eligible live births (i.e., the death of an eligible live birth that occurred in the first 28 days of life), must be investigated by an MO. Form 3 is used to record the information collected in the investigation, and the investigator’s conclusion about whether the death was caused by NT.

**Form 4 – Informed Consent – optional** (one per interviewee or group of interviewees):
Form 4 is a consent form (Annex 10). However, if the surveyor instructions presented in Annexes 8 and 9 are followed, informed consent can be obtained without the need for Form 4.

### 3.2.4 Survey Quality Assurance

The survey results are not valid unless the data collected are complete and accurate.

Common survey quality problems and the indicators used to monitor data quality are summarized, and then discussed in detail below.

<table>
<thead>
<tr>
<th>Quality Problem</th>
<th>Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not all HHs visited</td>
<td>survey CBR, compared to reference CBR</td>
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<tr>
<td></td>
<td>[ CBR = \left( \frac{#LBs}{#residents} \right) \times 1000 ]</td>
</tr>
<tr>
<td></td>
<td>% locked houses</td>
</tr>
<tr>
<td></td>
<td>[ %\text{locked} = \frac{#\text{locked HHs}}{#\text{all HHs}} \times 100 ]</td>
</tr>
<tr>
<td>Incomplete LB information</td>
<td>#LBs: #eligible LBs</td>
</tr>
<tr>
<td></td>
<td>Compare # total LBs to # eligible LBs – should be ~1.5x</td>
</tr>
<tr>
<td>NDs missed</td>
<td># NDs found, compared to the expected #NDs</td>
</tr>
<tr>
<td></td>
<td>[ \text{expected NDs} = \frac{(\text{reference NMR})(\text{sample size})}{1000} ]</td>
</tr>
<tr>
<td>Not following the correct methodology</td>
<td>Surveyors finishing early (very fast)</td>
</tr>
</tbody>
</table>

1. *Skipped Households / High Crude Birth Rate & % Locked Houses*

Occasionally, surveyors do not follow correct procedures and only visit households with young living children, skipping the other households. By skipping houses, the count and composition of all households and residents in the surveyed area is skewed, and households where neonatal deaths have occurred may be missed. This problem is most common when:
• Surveyors are focused on identifying live births but do not fully understand the goal of finding neonatal deaths. The tendency to focus on live children may be a consequence of past participation in vaccination campaigns and coverage surveys for which only live children are identified.

When surveyors work in familiar areas (areas where they live or normally work), the tendency is greater to try to save time by only visiting houses with known young children.

• Local guides lead surveyors preferentially to houses with live children (for the same reasons mentioned above)

**Indicator: a) CBR in the surveyed population compared with the reference CBR**

(district or regional CBR reference preferred; national CBR if local values unavailable)

\[
\text{Survey CBR} = \left( \frac{\# LBs}{\# \text{total residents}} \right) \times 1000
\]

If the survey CBR is substantially higher than the reference CBR, it suggests that HHs with young children might have been preferentially visited, while HHs without young children were skipped. In that case:

• Supervisors and monitors should recheck surveyed areas with the responsible surveyors, making sure that all HHs were visited (and that correct interview procedures were followed).

Note: it is not uncommon to find higher CBRs in poorer, more remote communities like those in districts selected for the LQA-CS survey. Thus, while rechecking must take place when survey CBRs are higher than expected, the conclusion may be that the high CBR is valid for the survey area.

**Indicator: b) % locked/missed houses (residents away temporarily) ≤10%**

\[
\% \text{locked} = \frac{\text{locked HHs}}{\text{all HHs}} \times 100
\]

To avoid bias, information should be obtained from at least 90% of HHs with residents who are residing there at the time of the survey. If many residents are away at the time that the surveyor arrives at their house (at the market, working in their fields) the houses must be revisited later, even if it means that surveyors must return to a cluster location a second time. Exclude HHs that are away long-term.

2. Incomplete Live Birth Information

If the total number of LBs is *not* more than the number of eligible LBs, surveyors may be going only to houses with young children (or where guide knows a baby was born in the
eligible period), or simply not recording information on LBs that took place outside of the eligibility period.

**Indicator: low ratio of total LBs: eligible LBs**

Compare # total LBs to # eligible LBs – should be ~1.5x

If the number of total LBs is similar to the number of eligible LBs:

- Supervisors and monitors should recheck surveyed areas with the responsible surveyors, making sure that correct interviewing technique was followed and that all HHs were visited.

Note: if the birth rate in the survey area is very high, it is possible that almost every house will have an eligible live birth. However, this must always be double-checked.

### 3. Missed Neonatal Deaths

The biggest and most common survey quality problem has been a failure to detect the expected number of neonatal deaths. If NDs are missed, it is possible that NT deaths also are missed.

Historically, the failure to detect neonatal deaths has undercut the results of many neonatal mortality surveys (including LQA-CS surveys and other forms of NT mortality surveys). Evaluations performed to identify the reasons that neonatal deaths are missed have identified the following causes:

- Discussion of infant/child deaths is culturally unacceptable, or so painful that parents avoid mention of such deaths
- Very early neonatal deaths are described as stillbirths (neonates dying within hours of birth are not considered live births)
- Recall bias – neonatal deaths occurring more than 6 months prior to the survey have been shown to be increasingly forgotten (or not recalled as having occurred during the survey eligibility period).
- Surveyors have preferentially visited houses with live young children, thereby skipping households where there was a neonatal (or infant/child) death.

**Indicator: #NDs found in the survey compared to the expected #NDs**

Calculate the expected #NDs using the reference NMR – preferably the district or regional NMR:

$$\text{Expected NDs} = \frac{\text{NMR} \times \text{(sample size)}}{1000}$$

For example, if the known NMR = 35/1000, then 35 NDs would be expected for a sample size of 1000

If the sample size is 1320, the expected NDs = \((35 \times 1320)/1000 = 46\)
The expected number of NDs per supervisor or per monitor also can be followed:

- Calculate the expected NDs per cluster (usually a fraction)

  \[
  \text{Expected NDs per cluster} = \frac{\text{total expected NDs}}{\text{total clusters}}
  \]

- Then calculate the expected NDs per supervisor (or monitor) by multiplying expected NDs per cluster by the number of clusters assigned to the supervisor.

  \[
  \text{Expected NDs per supervisor} = \left(\frac{\text{expected NDs/cluster}}{\text{clusters per supervisor}}\right)
  \]

For example, if the expected #NDs = 46, and total #clusters = 100, then 0.46 ND (~0.5 ND) would be expected per cluster; a supervisor responsible for 5 clusters would expect to find 2-3 NDs.

Monitors can calculate the number of NDs expected in their areas in the same way - multiply the #expected NDs per cluster by the total #clusters in their area of responsibility.

If the number of survey NDs is significantly below the expected (approximately 70% or less), several things should be done:

- Supervisors and monitors should recheck surveyed areas with the responsible surveyors, making sure that correct interviewing technique was followed and that all HHs were visited.
- Mothers reporting stillbirths should be re-interviewed to be sure that none of the stillbirths were actually early neonatal deaths. This re-interviewing must be performed gently, with awareness that repeated questioning about a tragic event is painful for the mother.
- If serious lapses in survey protocol or deficiencies in interviewing technique are identified, the cluster(s) must be re-surveyed.

If no problems with survey procedures are identified, monitors should talk to local health personnel or community leaders to verify that known neonatal deaths occurring in surveyed households have not been missed. If they have, the reasons they were missed should be identified, and corrective measures taken before the personnel involved proceed to their next survey areas.

4. Not following the correct methodology/ finishing early

When surveyors finish much faster than expected (based on past local experience or the experience with other surveyors), it is possible that corners are being cut – houses are being skipped, not all questions are being asked, complete information is not being recorded.

**Indicator: surveyor requires the expected time to finish a cluster**

If a surveyor finishes very early, the supervisor or monitor should first check the completed data collection forms to ensure they are complete and that the data look appropriate. Note:
if the household size in the area is very large, fewer houses need to be visited to complete a cluster and the work goes faster.

If the data forms look complete and plausible, recheck the surveyed area to see whether the houses have been marked systematically. Visit several households to verify the surveyor’s visit and that the information recorded for that household is correct. Observe the surveyor conducting several interviews to see if any systematic mistakes are being made.

While cutting corners is relatively common, falsification of data is rare, but has occurred.

3.2.5 Survey Data Entry
A customized excel spreadsheet is provided by WHO/HQ for data entry and analysis for every LQA-CS.

The summary data for each cluster (tallied by the supervisor and re-checked by a monitor) is entered into the survey analysis spreadsheet. The data entry can be shared by some or all monitors, or completed by a single designated data manager.

Once the data for every cluster has been entered into the analysis spreadsheet, survey results and statistical parameters are automatically calculated for the variables of interest.

A second spreadsheet for neonatal death investigation data is also available.

3.2.6 Analysis of Survey Data

The LQA-CS survey method is designed to assess whether the surveyed district(s) has an NT mortality rate that is greater than 1 NT death per 1000 live births. It is not designed to provide a point-estimate for the NT mortality rate and should not be used to calculate one.

The results of the NT LQA-CS are interpreted as follows:

- **if no NT deaths are identified** among the live births surveyed in the first sample of a double sample survey, or all clusters in a single sample survey, NT can be considered to have been eliminated in the district(s) surveyed.

- **if the number of identified NT deaths is less than or equal to the maximum acceptance number** after both the first and second samples in a double sample survey, or all clusters in a single sample survey are completed, NT has been eliminated in the surveyed district(s).

- **If NT has been eliminated in the districts at highest risk for NT in the country under evaluation**, it can be assumed that NT has been eliminated throughout the country.
• If the number of identified NT deaths is more than the maximum acceptance number, NT has not been eliminated in the survey district(s), Therefore the definition of NT elimination has not been met by the country being evaluated.

**Point estimates for TT coverage** of surveyed mothers are calculated by dividing the number of mothers immunized with a particular dose of TT by the total number of who have been sampled.

\[
\%\text{TT-x} = \left( \frac{\text{mothers with TT-x}}{\text{mothers-total}} \right) \times 100
\]

For example, if a TT vaccination history was obtained from a subsample of 250 mothers, of whom 220 had received TT1 and 200 TT2, then TT1 coverage is 220/250 = 88% and TT2 coverage is 200/250 = 80%.

**Point estimates for all other variables or subsamples** (e.g., health facility deliveries, skilled attendance at birth; TT coverage in CBAW, use of traditional substances on the umbilical cord) are calculated in the same way.

Calculation of confidence intervals for the point estimates must take the cluster sample design of the survey into account. A data analysis spreadsheet prepared by EPI-WHO is available to assist with the necessary calculations. Survey personnel enter the data collected from each cluster into the spreadsheet, and, once all data are entered, the spreadsheet automatically provides the point estimates and 95% confidence intervals for each variable.
ANNEXES
ANNEX 1. EXAMPLE OF DISTRICT-LEVEL DATA SHEET

(spreadsheet shown in halves, normally is continuous)

<table>
<thead>
<tr>
<th>Country:</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.No.</td>
</tr>
<tr>
<td>Target Population under 1yr</td>
</tr>
<tr>
<td>number</td>
</tr>
<tr>
<td>a</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

Year (Use separate sheet for each year):

<table>
<thead>
<tr>
<th>System indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC (≥ 1 visit) reported by state</td>
</tr>
<tr>
<td>%</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>
### ANNEX 2.

**PLANNING CHECKLISTS**

National Checklist (generic - modify as needed)

<table>
<thead>
<tr>
<th>Checklist of preparations</th>
<th>Name of person responsible</th>
<th>Date completed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preparations to be completed well in advance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol, objectives, and expected outcome discussed with national staff</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objectives, terms of reference &amp; dates agreed upon with MOH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Village-level population data obtained from selected districts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clusters selected</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Microplanning (with district(s))</strong>:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detailed maps obtained of selected clusters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of required staff calculated (surveyors, supervisors, MOs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surveyors, supervisors, MOs, drivers identified and contracts prepared / signed (as required - all must agree to dates, responsibilities, conditions of work)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicles/source of petrol identified and reserved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budget calculated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial resources identified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial resources mobilized so that they can be rapidly accessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Training dates set (all levels)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Training locations (s) identified &amp; reserved (including field exercise site) - all levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accommodations &amp; meals for trainers &amp; trainees set?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interview forms prepared (adapted to the local situation; translated &amp; field tested)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearance obtained from districts where the survey will be conducted</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Preparations to be completed just before the start of the survey</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Money accessed to pay per diems and petrol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staff trained (including field exercise)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interview forms and other stationary prepared for each interview team</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Means and frequency of communicating with survey teams established</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activities</td>
<td>Check</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>1. Discuss plan, time line and itineraries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Maps of the district and all villages / wards</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Listing of subdivisions and villages / wards in each subdivision.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Letter from district head to supervisors of all staff identified for the validation exercise (one week before)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. List of available health workers (interviewers) in each subdivision with names and place of postings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. List of available teachers / other potential interviewers in each subdivision with names and place of postings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. List Village Guides (for each village/cluster) to be surveyed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. List of Health Supervisors in subdivision with names and place of posting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Discuss team and supervisor allotments and route maps/ movement plan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. List of Doctors in each block with names and place of posting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. List of Pharmacists in each block with names and place of posting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. List of any Medical College in the district.(Contact details of Principal, Vice Principal, SPM deptt)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Names of District data handler/ statistician/ Computer assistant (identify the computer he will work on)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Identify reserve / floater staff for absent teams ( train them along with the identified staff)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Identify agencies who could carry out the validation survey in case of manpower shortage.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Identify the agency/ firm that can provide vehicles for hiring (vehicles reqmt will depend on microplanning). Use Govt. vehicles whenever possible. Gasoline expenses can be paid from the budget</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. Identify the place for stationary products (with contact edtails)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. List of closest identified photo copy points in each subdivision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. Site(s) for training of identified Health workers, supervisors, doctors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. Is generator back up present at the site of training? If NO, identify the place from where to hire this for 2-3 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. Identify the place from where the refreshments will be ordered for the trainers and trainees.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22. Identify the hotels for the stay of the State /National level staff (with contact details)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23. Identify the sites where the teams can stay at the district and subdivision levels (training center, hostel, hotel, etc)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24. Identify sites for training field exercise(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25. Explain budget assumptions- plan for effective fund flow. Identify the staff who will deal with fund flow and documentation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26. Briefing of role of data handlers/ statistician/ steno</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MNTE Survey: District Level Check list
(generic - modify for specific survey site as needed)
## ANNEX 3.
### BUDGET CALCULATOR
(available as an excel spreadsheet from WHO/HQ)

### BUDGET CALCULATION MNT LQA

<table>
<thead>
<tr>
<th>Parameters/Assumptions regarding the NT survey</th>
<th>Cost</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>is the average number of HHs that a surveyors can visit in 1 day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the average number of people per HH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the average crude birth rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the total sample size of LBs needed for the survey (use table to decide)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the desired number of days of field work (all samples combined, excluding training)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the desired number of surveyors per supervisor (usually 3-5 depending on conditions)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the desired number of spare surveyors (usually ~2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the estimated number of surveyors per medical officer (if supervisors are not MOs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the estimated number of days for training of national monitors (usually 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the estimated number of days for training of supervisors &amp; MOs (usually 2-3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the estimated per diem in USD for national/provincial monitors during national training</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the estimated per diem in USD for national/provincial monitors during field implementation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the estimated per diem in USD for surveyors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the estimated per diem in USD for local guides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the estimated per diem in USD for supervisors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the estimated per diem in USD for drivers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the estimated per diem in USD for medical officers - if supervisors are not MOs or paramedics doing ND investig</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the estimated cost in USD of vehicle rental per day - modify if motorcycles required (add rows or itemize separately)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>is the estimated cost in USD of petrol per car per day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Survey characteristics based on assumptions above
- live births can be found by one team in one day
- clusters in the survey
- surveyors needed (including spare teams)
- local guides needed (survey=1 per cluster, plus 4 for training field exercises - adjust if needed)
- supervisors needed
- medical officers - if supervisors are not MOs, adjust based on expected NDs per supervisor
- national/provincial monitors (usually 3-5 per survey)

### Number of international consultants
- vehicles needed per day of activity for Monitors (including inf' consultants) - in general 1 vehicle per monitor
- vehicles needed per day of activity for supervisors - in general 1 vehicle per supervisor - add rows for motorcycles/boats
- vehicles needed per day of activity for medical officers (if needed) - in general 1 vehicle per MO
- vehicles needed per day of activity for teams - add rows for motorcycles/boats

<table>
<thead>
<tr>
<th>Budget item</th>
<th>Cost</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perdie monitors</td>
<td>During national training</td>
<td></td>
</tr>
<tr>
<td>Perdie monitors</td>
<td>During survey implementation</td>
<td></td>
</tr>
<tr>
<td>Perdie-local guides</td>
<td>For training plus implementation</td>
<td></td>
</tr>
<tr>
<td>Perdie-supervisors</td>
<td>For training plus implementation</td>
<td></td>
</tr>
<tr>
<td>Perdie-medical officers</td>
<td>For training plus implementation if supervisors are not MOs or paramedics doing ND investigations too</td>
<td></td>
</tr>
<tr>
<td>Perdie-drivers</td>
<td>Only if car rental does not include driver</td>
<td></td>
</tr>
<tr>
<td>Vehicle rental</td>
<td>All - if motorcycles or boats are required, add rows or itemize separately and add to grand total</td>
<td></td>
</tr>
<tr>
<td>Petrol</td>
<td>Only if car rental does not include petrol</td>
<td></td>
</tr>
<tr>
<td>Training Facility</td>
<td>For training of monitors (all days of &quot;national training&quot;)</td>
<td></td>
</tr>
<tr>
<td>Training Facility</td>
<td>For training of surveyors/supervisors/MOs (all days of training; include cost of meals &amp; breaks)</td>
<td></td>
</tr>
<tr>
<td>Transport capital - field</td>
<td>For monitors / other staff, round trip, if not included in car rental days.</td>
<td></td>
</tr>
<tr>
<td>Administrative support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communications</td>
<td>E.g., phone cards for all survey personnel</td>
<td></td>
</tr>
<tr>
<td>Stationary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidents</td>
<td>Use approx 5-10% of total</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### ANNEX 4.
### TABLE OF SINGLE & DOUBLE SAMPLE PLANS

(for populations with the indicated numbers of annual live births; sample sizes have similar probabilities of acceptance)

<table>
<thead>
<tr>
<th>Pop. (LBs)</th>
<th>Sample size (n)</th>
<th>d*</th>
<th>α</th>
<th>β</th>
<th>1st sample size (n₁)</th>
<th>2nd sample size (n₂)</th>
<th>a₁</th>
<th>a</th>
<th>β</th>
<th>p₀</th>
<th>p₁</th>
<th>p₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,000</td>
<td>1,360</td>
<td>1</td>
<td>0.099</td>
<td>0</td>
<td>1,050</td>
<td>0</td>
<td>380</td>
<td>1</td>
<td>0.049</td>
<td>0.099</td>
<td>0</td>
<td>0.33</td>
</tr>
<tr>
<td>4,000</td>
<td>1,480</td>
<td>1</td>
<td>0.098</td>
<td>0</td>
<td>1,140</td>
<td>0</td>
<td>410</td>
<td>1</td>
<td>0.048</td>
<td>0.099</td>
<td>0</td>
<td>0.25</td>
</tr>
<tr>
<td>5,000</td>
<td>1,560</td>
<td>1</td>
<td>0.098</td>
<td>0</td>
<td>1,200</td>
<td>0</td>
<td>430</td>
<td>1</td>
<td>0.049</td>
<td>0.1</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>6,000</td>
<td>1,610</td>
<td>1</td>
<td>0.099</td>
<td>0.072</td>
<td>1,240</td>
<td>0</td>
<td>450</td>
<td>1</td>
<td>0.049</td>
<td>0.1</td>
<td>0.074</td>
<td>0.33</td>
</tr>
<tr>
<td>7,000</td>
<td>1,650</td>
<td>1</td>
<td>0.1</td>
<td>0.056</td>
<td>1,270</td>
<td>0</td>
<td>470</td>
<td>1</td>
<td>0.049</td>
<td>0.099</td>
<td>0.057</td>
<td>0.29</td>
</tr>
<tr>
<td>8,000</td>
<td>1,690</td>
<td>1</td>
<td>0.098</td>
<td>0.045</td>
<td>1,300</td>
<td>0</td>
<td>470</td>
<td>1</td>
<td>0.049</td>
<td>0.099</td>
<td>0.045</td>
<td>0.25</td>
</tr>
<tr>
<td>9,000</td>
<td>1,710</td>
<td>1</td>
<td>0.099</td>
<td>0.095</td>
<td>1,320</td>
<td>0</td>
<td>480</td>
<td>1</td>
<td>0.049</td>
<td>0.099</td>
<td>0.097</td>
<td>0.33</td>
</tr>
<tr>
<td>10,000</td>
<td>1,730</td>
<td>1</td>
<td>0.1</td>
<td>0.079</td>
<td>1,330</td>
<td>0</td>
<td>490</td>
<td>1</td>
<td>0.05</td>
<td>0.1</td>
<td>0.081</td>
<td>0.3</td>
</tr>
<tr>
<td>15,000</td>
<td>2,370</td>
<td>2</td>
<td>0.099</td>
<td>0.031</td>
<td>1,340</td>
<td>0</td>
<td>1,220</td>
<td>2</td>
<td>0.049</td>
<td>0.099</td>
<td>0.034</td>
<td>0.33</td>
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<tr>
<td>20,000</td>
<td>2,440</td>
<td>2</td>
<td>0.099</td>
<td>0.043</td>
<td>1,380</td>
<td>0</td>
<td>1,250</td>
<td>2</td>
<td>0.049</td>
<td>0.099</td>
<td>0.048</td>
<td>0.35</td>
</tr>
<tr>
<td>25,000</td>
<td>2,440</td>
<td>2</td>
<td>0.099</td>
<td>0.036</td>
<td>1,380</td>
<td>0</td>
<td>1,240</td>
<td>2</td>
<td>0.049</td>
<td>0.1</td>
<td>0.039</td>
<td>0.32</td>
</tr>
<tr>
<td>30,000</td>
<td>2,470</td>
<td>2</td>
<td>0.1</td>
<td>0.043</td>
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<td>1,260</td>
<td>2</td>
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<td>0.052</td>
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*Acceptance number
†Upper and lower NTMR thresholds - see Statistical Supplement

Note: sample sizes were determined based on the assumptions that NT mortality is approximately 80% and that 90% of all NT deaths will be identified (see Statistical Supplement).

If these assumptions are not appropriate for a given survey, the required sample sizes can be recalculated with the “LQASdesign” package written for the computer program R.¹

¹ Contact Dr. Nasir Yusuf, Senior Health Specialist - Monitoring, MNTE & GVAP, for the necessary statistical package and instructions: yusufn@who.int
## ANNEX 5.
### SAMPLE TRAINING WORKSHOP AGENDAS

National-level workshop for monitors

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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</table>
| 9:00 - 9:15 | Opening Session:  
• Greetings  
• Self-Introduction  
• Purpose of the workshop |
| 9:15 - 09:30 | Address by dignitaries                                                  |
| 9:30 - 10:15 | Neonatal tetanus (NT) and NT elimination  
• Global Overview & Regional Overview  
• Country Update |
| 10:15 - 10:30 | Tea Break                                                              |
| 10:30 - 11:00 | Assessing MNT Elimination: an overview of the validation methodology  |
| 11:00 - 11:30 | Summary of process to select districts for LQA                         |
| 11:30 - 11:45 | Sample Size Determination                                               |
| 11:45 - 12:00 | Determination of number of clusters and cluster size                    |
| 12:00 - 12:15 | How to select the clusters                                              |
| 12:15 - 12:30 | Finding the first and subsequent households                            |
| 12:30 - 13:30 | Lunch                                                                   |
| 13:30 - 14:30 | Review of the forms / questionnaires                                    |
| 14:30 - 15:30 | Group Work: role play on using the forms                                |
|           | **Working Tea**                                                        |
| 15:30 - 16:00 | Frequently encountered problems and issues                             |
| 16:00 - 16:30 | Quality Issues related to the LQA                                      |
| 16:30 - 17:00 | Survey Preparations : things to consider                                |
| 17:00 - 17:30 | Summary and clarifications                                             |
| 08:00 – 11:00 | *Field Work in the city: Example of real-life survey implementation*   |
| 11:00 - 13:00 | Feedback from Field work and clarifications                            |
| 13:00 - 14:00 | Lunch                                                                   |
| 14:00 - 14:30 | Data Entry, data analysis, report writing                              |
| 14:30 - 15:00 | Practical arrangements for the LQA(s): Staffing, funding, accommodation, transport, supplies, communication. |
| 15:00 - 15:30 | Final wrap-up                                                          |
| 15:30 - 15:45 | Tea Break                                                               |
### 15:45 – 16:45 Preparation for field work: training surveyors, schedule, assignments, administrative and logistical matters

**District-level workshop for surveyors and supervisors**

<table>
<thead>
<tr>
<th><strong>Opening session and welcome</strong></th>
<th><strong>Focus on:</strong></th>
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<tbody>
<tr>
<td>Objectives of the training session</td>
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<tr>
<td>Introduction of facilitators and participants</td>
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<table>
<thead>
<tr>
<th>Day 1</th>
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<tbody>
<tr>
<td>1</td>
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<td>2</td>
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</tbody>
</table>
| 3 | Starting the Survey:  
   • Introduction to the Village Chief  
   • The starting-point in the cluster: first and subsequent HH  
   • Eligible HH respondents | How to start and move around in the villages |
| 4 | The use of the forms:  
   • form 1: demographics  
   • form 2: live-births | Asking the right questions: focus initially on past pregnancy, how to identify neonatal deaths |
| 5 | Role-play and/or game:  
   • finding the starting-point in the cluster  
   • completing forms | Use Game provided |

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<tr>
<th>Day 2</th>
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</table>

Teams covering distant clusters should leave the same day as the training.
ANNEX 6.
EXAMPLES OF FORMS & SURVEYOR INSTRUCTIONS²

1. Find the first household (HH) in the village/ward as explained in the training. Introduce yourself and collect the survey information following the script below.

2. Proceed to the nearest household and repeat; continue until you have identified the total Live Births (LBs) to be surveyed in the cluster.

3. If the village you are visiting has insufficient live births after you have visited all the HHs, continue to the next village. The “next” village is the one nearest to the first.

Remember: the purpose of this survey is to find the neonatal deaths from among all babies who were born in the eligible period. Do not look for living children – look for pregnancies to find ALL live births and ALL neonatal deaths. Make sure to ask specifically if any girls were born, especially in cultures where high emphasis is placed on male children.

² Note: The forms provided at the end of this Annex, and the instructions for their use, should be modified to fit the needs of the specific country and survey. The forms should be translated into the local language. Please note that the instructions are meant for training and as references only - they are too exhaustive to be used during the survey itself.
Completing Form 1
In each HH, ask all of the following questions and mark the answers on the relevant forms (only take information from adults). First, introduce yourself:

I am [NAME] and I work at the [ORGANIZATION NAME] in [CITY]. We are conducting a survey to find out how many children in this area still die because of neonatal tetanus [USE LOCAL NAME IF IT EXISTS] so that the government can have a better idea whether any specific action is needed.

We would like to ask some questions to as many women who have been pregnant recently as possible. Are you willing to talk with us? If the answer is yes, proceed.

How many people live in this household? Write the number on Form 1 (one line per household).

Are there any women living in this household whose age is between 15 and 49 years old (even if they are not here right now and depending on the age range used by the country for women of reproductive age)? Ask specifically if there is more than 1 woman.

• If No, mark 0 for "#Resident women" and all the other columns; thank the person for his/her time and explain that they are not the target group for the survey. Mark the HH number from Form 1 on the door with chalk; go to the next HH.
• If Yes, mark the number in the column for "#Resident women" and ask:

Were any women pregnant in the past 2 years?

• If No, mark 0 for #Resident women pregnant during last 2 yrs" and the other columns; thank the person; mark the HH number on the door; go to the next HH.
• If Yes, mark the number in the column for “#Resident women pregnant”, and ask:

May I speak to her/them? Interview each woman who was pregnant in the past 2 years (see next page). If unavailable, obtain the information from another adult HH member.

• If a woman normally is a resident in the HH, but is absent temporarily, include her in the survey
• Resident women who have gone somewhere else to deliver (e.g., parent’s house) should be included in the survey
• Women who normally live elsewhere, but are visiting, should NOT be included in the survey. (Visitors are those whose residence has been elsewhere in the past year, and whose presence is temporary)
**Were you pregnant in the past 2 years?** (Explain that you are asking about *any pregnancy*, regardless of the outcome or if the child is still alive).

- **If No,** revise count in Form 1 if necessary; thank her for her time; mark the HH number on the door; go to the next HH
- **If Yes,** ask: What was the outcome of the pregnancy?
  
  There are 4 choices for pregnancy outcome on Form 1: still pregnant, Live Birth, or Abortion/Miscarriage and Stillbirth.
  - If the woman is still pregnant, ask if she has been pregnant earlier as well during the last 2 years. Fill the forms and thank her for her time. Continue with other women in the HH who were pregnant during the last 2 years.
  - **In the case of a reported stillbirth, it is very important to make sure that the baby was not alive at birth** and then died shortly thereafter. First let the mother know that you understand how painful her loss must be and extend your sympathy. Then try to gently confirm that there were no signs of life when the baby was born (no spontaneous movement, breathing, or crying) to rule out the possibility of an early neonatal death.
  - **If there was a live birth,** ask:

    **Was the child born between __/__/__ and __/__/__?** (inclusive). Ask the child’s immunization card to verify the date of birth.

    *(Note that this includes children who have since passed away, not just children still alive).*

    - **If No,** thank her for her time; mark the HH number on the door; go to the next HH
    - **If Yes,** mark the number of eligible live births on *Form 1*, and complete one line for each on *Form 2*

    **Note:** before leaving a HH, try to make sure a neonatal death was not missed, ask if the household ever lost a child, and if yes, if that child was born during the eligible period.

    - Be sensitive to the fact that child deaths cause the family great pain and grief. Always be respectful, sympathetic and gentle when probing for sensitive information.
    - Before leaving a HH with a live birth born in the Eligible Period, make sure you filled in all the necessary information in Form 2.
    - No index entries found. If there was a NEONATAL DEATH, did you call your supervisor?
    - When the HH is completed, mark the HH number on the door before proceeding.
Completing Form 2

Form 2 is for all live births in the Eligible Period (__/__/__ to__/__/__, inclusive).

Each line should be completed for every eligible Live Birth.

Note the HH number (from Form 1) in the first column, then ask the following questions:

What is your (the mother’s) name? Alternatively, ask for the child’s name or father’s name.

When was the child born? Write the date as day-month-year. Double-check that the date is within the Eligible Period.

Was it a boy or a girl? Write “M” if it was a boy, “F” if it was girl.

Did the child die?

● If No, mark “N” in the column “Died”.
  If you are talking with one of the first few women in your cluster, (usually 3 or 4, with the number being determined by the total number of clusters to be surveyed in a single sample survey design or the total number of clusters for the first sample in a double sample design), continue with the questions about delivery and TT status (see below)

  Otherwise, thank the person for her time and continue with any other mothers of eligible live births in the household. When finished with all live births, mark the HH number on the door; go to the next HH.

● If Yes, (the baby died), first read the following text, or explain in your own words:
  I am sorry that your child has passed away. We understand that this must cause you great grief. However, we would like to ask you some more questions about the circumstances under which your child died.

Did the baby die when he/she was 28 days old or less? (in first 28 days of life)

● If No, double-check by asking how old the child was at death. Obtaining correct information is very important. If not 28 days or less, write “N” in the column “died when < 28 days old?”.
  For the first few mothers as agreed continue with the questions about delivery and TT status. For the other mothers, thank the person for her time. Mark the HH number (Form 1) in chalk on the door and go to the next HH.
• If Yes, mark “Y” in the column “died when less than 29 days old”, and immediately call your supervisor to let them know you have identified a neonatal death.

Explain to the mother that a doctor will come to ask her some additional questions to try to understand what caused the baby’s death.

For the first few mothers as may be determined, continue below

The following questions are for the first agreed number of mothers per cluster only:

**Did you deliver in a Health Facility?** Mark “Y” or “N”.

**If you did not deliver in a health facility, was there a medically trained person with you to assist with the delivery?** (includes doctors, nurses, midwives; but excludes TBAs)

Mark “Y” if there was a medically trained attendant. (Note: for mothers who delivered in a health facility, this question is automatically “Y”.)

**Do you have an immunization card (mother’s card)?**

• If she can show her card:
  – mark “Y” in the column “Mothers Imm Card Available”, and
  – write the dates of TT doses listed on the card in the relevant columns.

• If she cannot show her card or says she does not have a card:
  – mark “N” in the column “Mother’s Imm Card Available”;

**Have you received any doses of Tetanus Vaccine (a vaccine given in the upper arm) during a pregnancy, during a vaccination campaign, after an accident, or on any other occasion?** If yes, how many times did you receive a dose (total during your life)?

• Mark a “Y” in the first column under TT1 if one dose was received; mark “Y” in the first column under TT1 and TT2 if 2 doses were received; mark “Y” under TT1, TT2, and TT3 if 3 doses were received, etc.

• Write the date in the second column of the concerned dose when the immunization card is available. If no card is available and information is based on history only, mark “-” in the second column of the concerned dose.

• When there is a card but no date is mentioned, only “V”, mark “V” in the second column of the concerned dose.
When finished, quickly check that you have filled in all the necessary information, thank the mother (or other respondent) for her time; mark the HH number (Form 1) on the door; go to
the next HH.

**Form 1: Household Tally - use one line per household**

<table>
<thead>
<tr>
<th>Cluster No:</th>
<th>Village:</th>
<th>Location 1st HH:</th>
<th>District</th>
<th>Eligibility Period for Live Births: d/m/y to d/m/y</th>
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</thead>
</table>

**Interviewer’s name(s)**

<table>
<thead>
<tr>
<th>HH #</th>
<th># residents</th>
<th># Women (age 13-49)</th>
<th># Women pregnant (last 2 years)</th>
<th>Outcomes of pregnancies (last 2 years)</th>
<th># Eligible Live Births (born between d/m/y and d/m/y?) → Form 2</th>
<th>Ever loose a child? If yes, born d/m/y and d/m/y?</th>
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Subtotal
Form 2 - Live Births, Conditions at Birth and Mother’s TT Status

Eligibility Period for Live Births: _/__/__ to _/__/__

Cluster No: ___________ Interviewer’s name: ___________ (__________ Live Births per Cluster)
Supervisor’s name: _______________________________ Supervisor’s phone number: _____________________________________

<table>
<thead>
<tr>
<th>Part A. Identifier</th>
<th>Part B. Baby’s information</th>
<th>Part C. Mother’s information related to this Live Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serial No</td>
<td># HH</td>
<td>Mother’s or Father’s Name</td>
</tr>
<tr>
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<td>2</td>
<td>3</td>
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</table>

# LB: Males | Deaths | NDs |
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<tr>
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</thead>
<tbody>
<tr>
<td># M:</td>
<td># Y:</td>
<td># Y:</td>
</tr>
</tbody>
</table>

(HF) # Y: (Skilled) # Y: (Card) # Y: TT1 # Y: TT2 # Y: TT3 # Y: TT4 # Y: TT5 # Y: with date #:

Annexes
ANNEX 7.
EXAMPLE OF FORM 3 AND INSTRUCTIONS

Form 3 - Neonatal Death Investigation Form – to be completed by a Medical Officer

This form needs to be completed for all eligible children who died in the neonatal period, that is, in the first 28 days of life (between birth and the end of the 28th day).

It should NOT be completed for children who are still alive, who were stillborn, or who died on or after their 29th day of life.

If you (the investigating MO) conclude that the cause of death was NT, one of the survey monitors or coordinators must be contacted immediately. In case of any doubt, consult a monitor!

NT is a clinical diagnosis; there is no confirmatory laboratory test.

The NT case definition is:

A neonate who feeds and cries normally for at least the first 2 days of life, and, between 3 and 28 days of life

Stops sucking normally and

Develops stiffness/rigidity and/or spasms

For a diagnosis of NT to be made, the criteria in the case definition must be met.

Additional information that supports the diagnosis of NT:

- Hypersensitivity to touch, sound and/or light, setting off spasms
- Presence of risk factors associated with NT such as lack of maternal TT immunization and/or unhygienic delivery and/or umbilical cord care

NT can be ruled out in cases where death occurs in the first 2 days of life.

Before beginning your interview with the mother (or available family member), Introduce yourself, express empathy with her grief and willingness to answer additional questions.

If the mother (or family member) agrees to the interview:

First complete the initial sections of Form 3 covering the child’s identity and information about the mother’s TT vaccination history, antenatal care, and delivery condition.
Then ask the mother to provide the history of the child’s birth, illness and death in her own words. This narrative history should be recorded on the blank box of Form 3. The specific questions on the form in the section about the child’s history of illness and death should be asked afterwards. The questions should NOT be read to the mother; leading questions should be avoided.

In the final section of the form, record the respondent’s understanding of the child’s cause of death, followed by your own impression; then provide your judgement as to whether the child died of NT or not.

If there is uncertainty about whether a death was caused by NT, and the child was taken to a health facility or private medical office, the facility or consulting medical provider must be contacted to obtain the diagnosis given at the time of assessment.

When finished, ask again if there are any questions. Thank the mother for her willingness to participate.
### Form 3: Neonatal death investigation form
(To be completed by the Medical Officer)

**District:** ________________________________

**Cluster No:** ________ **Household no (Forms 1&2):** ____________ **Medical Officer’s name:** ________________

### Case identification & household location

- **Name of respondent:** __________________________
- **Address of respondent:** __________________________
- **Baby’s date of birth:** ___ / ___ / ___
- **Age at death in days:** __________________________
- **Sex of baby:** M [ ] F [ ]
- **Village/Ward:** __________________________
- **Discharge diagnosis:** __________________________
- **Medical Officer’s name:** __________________________
- **To be completed by the Medical Officer**

### Mother’s immunization status

- Did the mother have an immunization card (circle)? [ ] Yes [ ] No
- Immunization history by: [ ] card [ ] memory [ ] both [ ] unknown
- How many TT doses did the mother receive in the last pregnancy: __________________________
- How many TT doses has the mother received before the last pregnancy: __________________________ (on any occasion)
- Dates (all TT doses): ___ / ___ / ___ ___ / ___ / ___ ___ / ___ / ___ ___ / ___ / ___ ___ / ___ / ___ ___ / ___ / ___

### Mother’s antenatal care history

- How many antenatal care visits were made during this pregnancy: __________________________
- **Dates:**
  - How many TT doses has the mother received before the last pregnancy: __________________________
  - Dates (all TT doses): ___ / ___ / ___ ___ / ___ / ___ ___ / ___ / ___ ___ / ___ / ___ ___ / ___ / ___ ___ / ___ / ___

### Delivery practices

- **Where was the baby delivered:** [ ] Health facility [ ] Home [ ] Unknown [ ] Other: __________________________
- **Who assisted with the delivery:** [ ] Doctor [ ] Nurse [ ] Midwife [ ] TBA [ ] Relative [ ] Other: __________________________
- **On what surface was the baby delivered:** __________________________________________
- **Was any substance put on the cord stump:** [ ] Yes [ ] No
- **What was used to cut the cord:** __________________________________________
- **Was the sick baby taken to a health facility:** [ ] Yes [ ] No
- **If yes, specify:** __________________________

### Baby’s signs/symptoms:

- **Asks respondent to describe the symptoms and the history (use open-ended questions)**

- **At birth, did the baby seem normal:** [ ] Yes [ ] No [ ] Unknown
- **At birth, did the baby suck normally:** [ ] Yes [ ] No [ ] Unknown
- **How old (in days) was the baby when signs of illness began:** ___ days
- **Did the baby stop suckling:** [ ] Yes [ ] No
- **If yes, how many days after birth:** __________________________
- **Did the baby have spasms, or stiffness:** [ ] Yes [ ] No
- **Did the baby have the following signs of illness:**
  - Spasm when stimulated by touch, sound or light? [ ] Yes [ ] No
  - Become rigid or stiff as illness progressed? [ ] Yes [ ] No
  - Developed “pursed lips” and/or clenched fists or feet? [ ] Yes [ ] No

### Treatment & outcome

- **Was the sick baby taken to a health facility:** [ ] Yes [ ] No [ ] Unknown
- **If yes, record name of health facility:** __________________________
- **(Visit the health facility if there is doubt whether the case died of neonatal tetanus)**
- **Health Facility Confirmation - if symptoms suggest tetanus - call monitor**

- **Conducted:** [ ] Yes [ ] No
- **If no, why not:** __________________________
- **Facility Name:** __________________________
- **Date Visited:** ___ / ___ / ___ (dd/mm/yy)
- **Location:** __________________________
- **Attending doctor’s name:** __________________________
- **Baby’s medical record available:** [ ] Yes [ ] No
- **Admitting date:** ___ / ___ / ___ (dd/mm/yy)
- **Admitting diagnosis:** __________________________
- **Discharge date:** ___ / ___ / ___ (dd/mm/yy)
- **Discharge diagnosis:** __________________________
- **Comments:** __________________________

### Conclusion

- **What does the respondent say was the cause of the baby’s death:** __________________________
- **Your impression of cause of death:** __________________________
- **Based on the information you received, was this a case of neonatal tetanus:** [ ] Yes [ ] No [ ] Unknown
- **Comments:** __________________________

**Signature & Date:** __________________________

(Medical Officer and/or other medical personnel investigating the case)
ANNEX 8.
FORM 4 - INFORMED CONSENT

The surveyor instructions as outlined in annex 8 and 9 contain a series of questions to obtain informed consent from the respondents. In case it is decided to change these surveyor instructions, the informed consent form below can be used instead.

Informed Consent Form for Neonatal Tetanus Mortality Surveys

[INSTITUTIONAL LETTER HEAD]

[Name of Principle Investigator]
[Name of Organization]
[Name of Sponsor]

Information Sheet for the Group of Individuals Participating in the Research “Assessment of Neonatal Tetanus Mortality” in [COUNTRY]

[PART 1: To be read to the person opening the door of the house: Introduce yourself and what you are doing]

I am [NAME] and I work at the [ORGANIZATION’S NAME] in [CITY NAME]. We are conducting a survey to find out how many children in this area still die because of neonatal tetanus [USE LOCAL NAME IF IT EXISTS] so that the government can have a better idea whether any specific action is needed. For this, we would like to ask some questions to as many women as possible who have been pregnant recently.

How many people live in this household? Are there any women in this household aged between 15 and 49 years old? If yes, was any of them pregnant between [DATE] and [DATE]? [Record responses on form1] If so, may we ask them if they would they be prepared to take part in this survey, which will consist of a number of questions only?

[If yes, continue below. If no, explain that they are not the target group for the survey and thank the person for their time. Move to the next house].

[PART 2: To be read to the women who was pregnant between [DATE] and [DATE]]

[Introduce yourself and what you are doing]

I am [NAME] and I work at the [ORGANIZATION’S NAME] in [CITY NAME]. We are conducting a survey to find out how many children in this area still die because of neonatal tetanus [USE
LOCAL NAME IF IT EXISTS], so that the government can have a better idea whether any specific action is needed.

This study involves asking some questions in two parts.

In the first part of the study we will ask you 4 or 5 questions related to your pregnancy and its outcome covering the period of up to one month after delivery. This will not take more than 10 minutes. After the first part of the study, if it is necessary to ask you more questions, we will give you more information about the second part of the study and take your permission again to continue.

This household was selected by chance. You can refuse the interview, stop it at any time, or ask questions, without any negative effect. By participating, you personally will not gain any direct benefit. The information you give will be kept confidential to the group conducting the survey only.

The person accompanying me [Give name of the person] will sign on your behalf to certify that you have agreed to take part in this study, after having been provided with the above information.

Do you have any questions now? -- If later you have more questions, you can contact [name and address — add telephone number and e-mail if available]

Do you agree to take part in the study?

Is it OK to continue with the questions now?

[Ask the questions related to the survey, including the questions on TT immunization, and complete the form 2 as explained in the training]

[If the respondent's child is still alive, complete the tables and at the end thank the person for her collaboration]

[If the respondent's child (born between the dates stated above) has died, proceed to part 3 before asking questions about the circumstances of the child's deaths]

[PART 3: To be read only in a situation where the child has passed away]

I am sorry to hear that your child has passed away. We understand that this must cause you a lot of grief. However, we would like to ask you some more questions about the circumstances under which your child died. Some of these questions may cause you grief and pain. As said above, you are under no obligation to continue and you can stop this interview at any time without any loss of benefits that you may be getting from your health centre. Your responses will not be divulged to anyone, except [NAME AS APPLICABLE] and the form on which we take down your answers will not have your name on it, only a code that will be known only to the researchers.
We would like to do this interview in a place that guarantees privacy. No one else needs to be present with you at this interview. Do you have any questions now?

If you have any questions in the future, you may contact the person whose name is given above.

Is it OK that we continue?

[If yes, complete the question on whether the child died within 29 days, and if yes, also the neonatal death investigation form (form3)]

[At the end, thank the person for her cooperation]
ANNEX 9.
STATISTICAL SUPPLEMENT TO THE GUIDE FOR VALIDATION OF MATERNAL AND NEONATAL TETANUS ELIMINATION³

By Lauren Hund and Marcello Pagano⁴

INTRODUCTION

For a country to declare maternal and neonatal tetanus elimination (MNTE), a lot quality assurance cluster sampling survey is conducted to confirm whether the nation achieved that goal. In this supplement to the survey guide, we discuss technical issues in the design of the MNTE LQA-CS survey (hereafter referred to as the ‘MNTE survey’). In Section 1, we describe issues with identifying the target population, or highest risk district, for the survey. In Section 2, we introduce the lot quality assurance sampling (LQAS) methodology and discuss extensions of this methodology that are used in surveys to validate MNTE, including cluster sampling, finite population adjustments, and double sampling designs. In Section 3, we discuss the sensitivity of the survey instrument to detect neonatal tetanus (NT) cases and the implications of measuring a marker for NT incidence, namely the NT mortality rate (NTMR). In Section 4, we describe the statistical calculations used to construct the survey design and the metrics used to evaluate the properties of the design. Finally, in Section 5, we present a recommended survey design for validation of MNTE.

9.1 SELECTION OF DISTRICTS FOR THE SURVEY

Surveys to validate MNTE are conducted at district-level (third administrative level) in keeping with the definition of MNT elimination: less than 1 NT case per 1000 live births in every district. As discussed in the body of this manual, the first step in the design of the survey is deciding which district in a country is likely to have the highest NT incidence. This district will be the target population for the survey.

The implications of this definition are important to consider when designing an MNTE survey. NT rates less than 1 in 1000 live births must be achieved in every district. The survey is only conducted in the highest-risk district, under the logic that if the rates of NT are less than 1 in 1000 in that district, then the rates are also below this threshold in all the lower risk districts. This reliance on a prior ranking of NT risk among districts should

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be emphasized since the validity of subsequently declaring a country as having achieved elimination depends on this ranking. If it is not possible to choose between highest risk districts, then all high-risk districts must be surveyed to avoid running the risk of failing to select the district that has not achieved elimination.

The smaller the district to be surveyed, the more precise we can be in our classification of elimination within that district because, in small districts, we sample a large fraction of all live births. However, if a district population is too small, it may not be logistically feasible to survey only that district due to an insufficient number of live births. In such a situation, the target population can be redefined by combining multiple small high-risk districts into one survey. However, by combining districts, we are changing the definition of elimination, which should be clearly stated and approved by the assessment team before the survey is conducted. The revised definition of elimination for the country is now "an average NT incidence rate < 1 in 1000 live births among the worst performing districts in the country."

It is important not to overlook the implications of pooling information across multiple districts and changing the definition of elimination. For instance, consider a situation in which we identify three high risk districts with a low number of live births. We decide to conduct one survey, sampling from all three districts combined. Even if one of the three districts has an NT incidence rate greater than 1 in 1000 live births (definition of MNTE not met), the country will be declared as having achieved elimination if the average incidence rate across the three high risk districts is less than 1 in 1000, which is possible.

**9.2 INTRODUCTION TO THE LQA-CS SURVEY METHODOLOGY**

The LQA-CS survey method is appropriate for selected populations in the final stage of MNT elimination when there is evidence suggesting that NT incidence has been reduced to less than 1 case/1000 live births and only occurs sporadically (not in clusters). The method enables a binary decision: has MNT elimination occurred, yes or no? No further requirement is made to also provide an actual estimate of the NTMR. In contrast, conventional surveys designed to estimate the NTMR with any degree of confidence require very large sample sizes - tens of thousands of live births - due to the extremely low incidence of NT in the final stages of MNT elimination. The LQA-CS method requires relatively smaller sample sizes than the traditional estimation surveys, making the survey feasible and affordable in countries ready to demonstrate MNT elimination.

In an LQA-CS MNTE survey, the number of NT deaths detected during the survey is compared to a pre-determined maximum acceptance number of NT deaths that defines whether the district "passes" (elimination achieved) or "fails" (elimination not achieved). The acceptance number is calculated to ensure that there is a high probability that a district with a high NT incidence rate during the 12-month interval covered by the survey does not "pass", and that districts with truly low NT rates do not "fail".
While NTMR point estimates and confidence intervals can be calculated using LQA-CS data, this is not recommended because the estimates have large variances (resulting in not very informative, really wide confidence intervals). If a survey is stopped before all clusters are completed (in a double sampling survey, see below), the estimate is susceptible to selection bias and must not be used. Instead of calculating NTMR point estimates and confidence intervals, the number of sampled live births and observed NT deaths should be reported. Lot quality assurance sampling (LQAS) survey designs in public health have been described extensively in the literature [e.g., Valadez and Robertson and Valadez]. We briefly describe the LQAS methodology to aid in the interpretation of the final survey design.

9.2.1 Review of LQAS methodology
To declare MNTE in a district, we need to decide whether the NTMR during the 12-month interval covered by the survey is sufficiently low. We denote the district-level NTMR as $p$. In the district, we sample $n$ live births, and let $X$ denote the number of NT deaths.

Assuming the population size/annual number of live births in a district is large (> 50,000), we can model $X$ using a binomial distribution, specifically $X \sim \text{Binomial} (n, p)$. For some number $d$ (the acceptance number), if $X > d$, we conclude that elimination has not occurred; if $X \leq d$, we conclude elimination has been achieved. In choosing a sampling design for an LQAS survey, the goal is to select a sample size $n$ and corresponding acceptance number $d$ such that we run as small a risk as possible of misclassifying districts as having achieved or not achieved elimination. The lot quality assurance sampling (LQAS) survey design is determined by the following two equations, which control the error of the classification procedure:

$$P(X \leq d \mid n, p_u) \leq \alpha$$
$$P(X > d \mid n, p_l) \leq \beta$$

For a given choice of $n$ and $d$, $\alpha$ is the probability that we classify a district as having achieved elimination when the NTMR is greater than or equal to $p_u$; and $\beta$ is the probability that we classify a district as not having achieved elimination when the NTMR is less than or equal to $p_l$. To select an appropriate sample size $n$ and decision rule $d$, we first need to decide what the appropriate choices of $p_l$, $p_u$, $\alpha$, and $\beta$ are.

As an example, if we choose $\alpha = 0.1$ and $\beta = 0.1$, we then find a sample size $n$ and acceptance number $d$ such that we can make the following statement about our survey:

"In an area with a true NTMR equal to 0.0021 ($p_u$) or more, if we repeat the MNTE elimination survey a very large number of times, we would incorrectly conclude that neonatal tetanus has been eliminated at most 10% ($\alpha$) of the time. In an area with a true NTMR equal to 0.00035 ($p_l$) or less, if we repeat the MNTE survey a very large number of times, we would correctly conclude that neonatal tetanus has been eliminated at least 90% ($1-\beta$) of the time."
times, we would incorrectly conclude that elimination has not occurred at most 10% (β) of the time.”

If a district has a true NTMR between $p_l$ and $p_u$, we say that the NTMR lies in the “grey region.” We do not restrict the classification errors within the grey region. Within this region, the risk of misclassification is higher than the smaller of $\alpha$ and $\beta$. To fully understand classification properties for districts with true NTMR in the grey region, we must examine the operating characteristic curve or the risk curve (see Section 4 below).

For MNTE surveys, we have selected $p_l$ and $p_u$ such that some districts with true NTMRs in the grey region may not have technically met the definition of elimination, but have achieved low enough NTMRs that it is not a serious error to declare elimination if that mistake were to occur. Validation surveys are only conducted when we have some confidence that elimination has been achieved; ideally, most survey districts will not have true NTMRs that lie within the grey region. However, it is important to understand the inherent risk in the classification procedure.

In an LQAS survey, decreasing the width of the grey region (narrowing the distance between $p_l$ and $p_u$) results in more precise classifications. However, the size of the grey region is directly related to the sample size of the survey. When searching for a rare event in the population, required sample sizes are generally large, and we must balance precision against feasibility in our selection of $p_l$ and $p_u$.

Table 1 below illustrates the impact of decreasing the grey region, lowering $p_u$ when $p_l = 0.00035$, $\alpha = 0.1$ and $\beta = 0.1$ (as above). To convert the NTMR thresholds in Table 1 back to NT incidence rates, see the discussion about sensitivity and specificity in Section 3. Assuming sensitivity is 70% and specificity is 100%, these upper thresholds for NTMR correspond to NT incidence rates of 3, 2, 1.5, and 1 cases/1000 live births; the lower NTMR threshold corresponds to an incidence rate of 0.5 cases/1000 live births.
Table 1: Shows the impact of the width of the grey region on the sample size. Single and double sampling plans are presented for large populations (> 50,000 live births per year) and a population with 5,000 live births per year.

<table>
<thead>
<tr>
<th></th>
<th>&gt;50,000 live births</th>
<th>5,000 live births</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single Sampling</td>
<td>Double Sampling</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>d</td>
</tr>
<tr>
<td>2.1</td>
<td>2,540</td>
<td>2</td>
</tr>
<tr>
<td>1.4</td>
<td>4,780</td>
<td>3</td>
</tr>
<tr>
<td>1.05</td>
<td>8,840</td>
<td>5</td>
</tr>
<tr>
<td>0.7</td>
<td>28,760</td>
<td>14</td>
</tr>
</tbody>
</table>

9.2.2 Finite population size effect

When the number of live births in a district is not sufficiently large (<50,000 live births in the population), we model X using the hypergeometric distribution, \( X \sim \text{Hypergeometric}(n, N, m) \), where \( n \) once again denotes the number of live births sampled; \( N \) is the total number of live births; and \( m = Np \) is the number of NT deaths in the district over the 12-month survey period for a given NTMR \( p \). When \( N \) is large, the binomial and hypergeometric distributions are equivalent; the sample size and acceptance number for the survey will be identical regardless of which distribution is used for the calculations.

To design an LQAS survey, we calculate the parameter \( m \) using \( p_u \) and \( p_l \). The consequences of searching for a rare event in a finite population on the survey design are not trivial. The NTMR \( p \) can only take on a finite number of values, since \( m \) is an integer by definition (\( m \) being the number of NT deaths). For example, consider a population of 2,500 live births. The NTMR can only take on certain values in the population: \( p = 0 \) with 0 NT deaths; \( p = 0.4/1000 \) live births with 1 NT death; \( p = 0.8/1000 \) live births with 2 NT deaths; \( p = 1.2/1000 \) live births with 3 NT deaths; and so on.

Thus, in practice, the grey region in an LQAS survey usually is not truly from \( p_l \) to \( p_u \), but is wider because \( p \) can only take on a finite number of values. For instance, in the example above with a population size of 2,000, if we select \( p_l = 0.0005 \) and \( p_u = 0.002 \), then the true grey region spans from 0.0004 to 0.002, because \( p \) cannot take on the value 0.0005.

The widening of the grey region impacts smaller population sizes more than larger ones where \( p \) can take on a wider range of values. It is important to consider the appropriateness of the grey region when designing a survey with finite population sizes. For instance, if only 500 live births occur in a district, designing an elimination survey based on \( p \) and \( p_u \) is difficult. Elimination has only been achieved if 0 NT deaths occur in the district. The narrowest possible grey region is from 0 to 0.002, as \( p \) can only take on the values 0,
0.002, 0.004, etc. It is more intuitive and more appropriate to discuss absolute numbers of events, instead of focusing solely on rates, when dealing with very rare events in a finite population.

Lastly, because tetanus cannot be eradicated, NT cases can occur sporadically even when MNTE has been achieved. The size of the target population should be sufficiently large to allow for an occasional random case without triggering the conclusion that elimination has not been achieved. For example, with a population of 1,000 and an NT rate of 0.9/1,000, the probability of observing one or more NT cases is better than 59%. Therefore, the total number of eligible live births in a district should exceed 3,000 to conduct a meaningful MNTE survey.

9.2.3 Cluster Surveys

Standard LQAS surveys usually select a simple random sample from the target population. Simple random sampling requires an enumeration of the entire population in the district, sampling from this list, and then locating the sampled individuals. Because it is impractical to implement simple random sampling for MNTE surveys, the logistically easier cluster sampling method is used instead.

The cluster sampling method used for MNTE surveys, "probability proportional to size" (PPS), is the same method used for standard 30 x 7 cluster surveys to measure immunization coverage. With PPS sampling, the probability of selecting a sampling unit (e.g., village, census tract, etc.) is proportional to the size of its population. Larger sampling units have a larger probability of being selected and each cluster consists of the same number of sampled individuals (live births for MNTE surveys). Using this design, each individual has the same probability of being sampled, yielding a probability sample that is random and representative.

Note that the total number of clusters and households to visit within each cluster are different in the MNTE survey than in a 30 x 7 cluster survey. Usually, cluster sampling increases the amount of variability in a survey because outcomes are more likely to be similar for individuals in the same cluster than for individuals in different clusters. To obtain a representative snapshot of the population, one needs to sample from many clusters. This within-cluster similarity is often quantified using the intracluster correlation coefficient (ICC or ρ). The relative size of the variability in the survey estimators is measured by the design effect (DEFF), defined as the ratio of the variance of the survey using cluster sampling to the variance using simple random sampling. DEFFs are usually greater than one.

To obtain the same level of precision with a cluster sample as one would have with a simple random sample, one needs to sample n x DEFF individuals for the survey (often referred to as the effective sample size). When the number of clusters is large, and the population
size within each cluster is large and approximately equal across clusters, \( \text{DEFF} \approx 1 + (c-1) \rho \), where \( c \) is the number of individuals sampled in each cluster.

When \( \rho \) is small relative to \( m \), such that \( \text{DEFF} \approx 1 \), we can treat the cluster sample like a simple random sample. Historically, low design effects have been observed in surveys estimating NTMR. Additionally, MNTE surveys are only conducted when there is sufficient evidence that districts have low NT rates without any clustering of cases, adding credibility to the operative assumption that the DEFF approximates 1. Lastly, in 41 MNTE surveys conducted from 2000–2011, only 42 neonatal deaths attributable to tetanus were identified in a total of 4,571 clusters and no cluster had more than one NT death. Thus, based on the strong evidence that clustering effects are negligible in MNTE surveys, a cluster survey is conducted but the data is analyzed by treating it as a simple random sample without adjustment.

### 9.2.4 Double sampling

A double sample procedure divides the total sample into two parts; these parts are then surveyed sequentially. Whether the second sample is carried out is conditional on the results of the first sample. This sampling procedure is analogous to interim monitoring in clinical trials, for example. For additional sequential LQAS designs, see the examples described in Myatt and Bennett and Olives.

The double sampling plan has the advantage of allowing elimination to be declared from the results of the first sample if the number of NT deaths detected is very low (e.g. 0). The second sample is necessary if the number of NT deaths in the first sample is not low enough to declare elimination and not high enough to confirm failure to achieve elimination (does not exceed the acceptance number). This design has the potential to save on the total sample size required to reach a decision.

To construct a double sampling survey plan, we again specify thresholds \( p_l, p_u, \alpha, \) and \( \beta \). We also need to specify an additional parameter, \( \alpha_1 \), which is the probability of declaring elimination after the first sample given \( p_u \). This additional parameter does not affect the overall \( \alpha \) level of the survey design, but instead serves as a guide to select the sample size and decision rule for the first sample. Based on these parameters, we can find the minimum sample sizes for the first and second samples, \( n_1 \) and \( n_2 \), and the corresponding acceptance numbers \( d_1 \) and \( d_2 \), to meet our survey design specifications.

The proposed double and single sampling plans are designed using identical overall survey parameters \( p_l, p_u, \alpha, \) and \( \beta \). Therefore, as discussed in the main MNTE survey guide (Section_2.2.2), to decide between a single and double sampling plan, we evaluate cost-effectiveness and feasibility and are not concerned about the statistical precision of double versus single sampling (as they have the same precision, by design). The main reason that
one would use a double sampling design is to reduce the amount of money/time spent conducting the survey.

Regardless of whether a single or double sampling plan is used, ‘failure to achieve elimination’ can be declared at any point in the survey if the number of detected NT deaths surpasses the acceptance number. However, to collect accurate, representative data on NT risk factors (TT coverage, proportion of deliveries conducted in health facilities and assisted by medically trained birth attendants, and use of traditional substances on the umbilical stump), data collection from all planned clusters should be completed for a single sampling survey or the first sample in a double sampling survey, even if the number of NT deaths detected exceeds the acceptance number. The second sample in a double sampling survey can be stopped early if the acceptance number has been exceeded because sufficient representative data was collected in the first sample.

Double sampling is only more cost-effective if we expect that the district has achieved elimination with a high level of confidence. If the second sample is required, the total sample size required for a double sampling survey is always greater than the sample size for a single sampling survey. That is because we perform two data analyses during the survey period and thus have 2 different opportunities to declare elimination. This is often referred to as “multiple comparisons”; we must adjust the classification errors to account for the fact that we look at the data twice. To obtain the desired classification errors $\alpha$ and $\beta$, we must sample more individuals in the double sampling plan to account for the inflated classification errors caused by looking at the data twice. As a general rule, we want to minimize the probability that we will need the second part of the sampling.

When choosing between a single versus double sampling plan, the deciding factor should be: “Is the cost/time savings that are potentially associated with double sampling worth the additional logistics that go into planning a double sampling survey and the potential extra cost of the second part?” If we are uncertain about whether or not elimination has been achieved, then we should choose a single sampling plan to save both time and money. In addition, logistical constraints such as lack of communication infrastructure and/or difficult terrain and a highly dispersed population often make a double sampling survey infeasible.

**9.3 SENSITIVITY, SPECIFICITY AND SELECTION BIAS IN MORTALITY SURVEYS**

The definition of NT elimination is < 1 case of NT per 1000 live births. *However, it is operationally easier to monitor NT deaths accurately, rather than to try to detect all cases of NT (deaths and survivors).* Historically, NT mortality has been very high in areas where NT most commonly occurs (>80%), making NT mortality a suitable marker for what we ideally
would like to measure, i.e., NT incidence. Nonetheless, we must consider the implications of measurement error produced by measuring a proxy of the outcome of interest.

We can rephrase this issue in terms of the sensitivity and specificity of the survey instrument/protocol. In an MNTE survey, sensitivity is the probability that an NT case is detected given that the NT case is included in the sample. Alternatively, we can state the sensitivity as the proportion of NT deaths in the sample that are detected by the survey instrument. An NT case can fail to be detected in several ways:

1. the case is not fatal,

2. the case is fatal, but NT is not identified as the cause of death, or

3. a neonatal death caused by NT is not detected.

NT deaths are diagnosed using the verbal autopsy method for all identified neonatal deaths. If we can assume that all deaths due to NT are diagnosed correctly, then the sensitivity for our survey is equal to the case fatality rate (CFR; %deaths) among cases of NT in the population. If the NT CFR is low, then sensitivity will be further decreased and we will need to adjust the survey parameters accordingly. Low sensitivity can result in declaring that elimination has been achieved when it truly has not.

Selection bias and recall bias are also common issues in retrospective neonatal mortality surveys. Omission of live births and subsequent deaths for children who are not living at the time of the interview is a common source of non-sampling error in surveys of live births; children who die in early infancy are the most commonly omitted births. Additionally, there is a tendency on the part of local guides assisting with surveys to lead to households with live young children; houses with potential infant deaths are consequently bypassed. Some surveys have found that post-neonatal infant mortalities may be incorrectly displaced into the neonatal period when there is pressure to find neonatal deaths. Poor quality in the reporting of age at death also can lead to underreporting of infant deaths. Lastly, in some surveys, mothers with children were more likely to be at home at the time of the survey, as opposed to women without children, increasing the potential to miss some live births and neonatal deaths. Selection bias could result in declaring that elimination has occurred when it has not.

To obtain accurate survey results, it is important to recognize the potential for selection and recall bias to result in an underestimation of NT mortality, and therefore of NT incidence. We can adjust the assumed sensitivity of the survey instrument downward to account for underestimation caused by these biases.

Specificity is the probability that a live birth included in the survey is correctly classified as not being an NT case. The specificity of the survey is a function of the neonatal mortality
rate and the specificity of the verbal autopsy method; specificity should be very high for MNTE surveys. If the verbal autopsy method for detecting NT deaths correctly confirms all non-NT deaths, the specificity of the survey instrument is 1 and no neonatal deaths are misclassified as NT cases. Low specificity could result in declaring that elimination has not occurred when it truly has.

To adjust the survey design parameters \( p_l \) and \( p_u \) for the sensitivity and specificity of the survey instrument, we can exploit the relationship:

\[
p = p_l \times \text{sensitivity} + (1- p_l) \times (1- \text{specificity})
\]

where \( p \) is the measured NTMR using current survey protocol, and \( p_l \) is the true incidence rate of NT in the population.

The mortality rate (CFR) among live births with NT sets an upper bound for the sensitivity. For example, if we assume that the NT CFR is 80%, then the highest possible sensitivity for the survey is 80%. In this case, we assume that NT mortality is high (80%), all NT deaths in the sample are detected, and selection and recall biases are not an issue. When NT mortality is lower, e.g., a CFR of 50% and we expect that only 80% of NT deaths would ever be detected (due to selection and recall bias), then the sensitivity is 80%*50% = 40%. In that case, we need to adjust \( p_l \) and \( p_u \) downward by 40%. It is unreasonable to assume that recall and selection bias will not cause downward bias in NTMR estimates since they have been shown repeatedly to affect the results of retrospective child mortality surveys. Thus, the assumed sensitivity of MNTE surveys should be adjusted accordingly to reflect these biases.

Underestimating sensitivity is more conservative (i.e., harder to declare elimination) than overestimating sensitivity. Failing to adjust for sensitivity of the survey instrument will produce survey results that are difficult to interpret. It is much more likely that NT elimination could be incorrectly declared if the potentially low sensitivity of the survey instrument is ignored.

### 9.4 AN EXPLANATION OF PROBABILITY CALCULATIONS FOR OPERATING CHARACTERISTIC CURVES

The LQA-CS method is considered the most practical method for assessing whether MNTE has been achieved; if districts at highest risk are surveyed and a PASS decision is made, we conclude that other districts at lower risk have also achieved MNTE (as discussed in Section 1).

The operating characteristic (OC) curve is defined as the probability of finding no more than \( d \) NT deaths (the acceptance number) as a function of the true NTMR in a survey district.
OC curves for both the single and double sampling plans are shown in Figures 1 and 2. They were generated using the Binomial distribution to model the number of NT deaths.

For a single sampling plan with a sample size \(n\) and acceptance number \(d\), and where \(p\) is the true NTMR in the district, the points on the OC curve are calculated as follows:

\[
OC(p) = P(X \leq d \mid p) = \sum_{k=0}^{d} \binom{n}{k} p^k (1 - p)^{n-k}
\]

To construct the graphs in Figures 1 and 2, \(OC(p)\) is calculated for a range of \(p\) for the values of \(n\) and \(d\) selected in Section 5 below and the results are plotted. The objective in survey design is to make the right tail of the curve as small as possible (minimize the probability of declaring elimination when \(p\) is large) and the left tail as large as possible (maximize the probability of declaring elimination when \(p\) is sufficiently small).

Sample OC curves

**Figure 1: OC curve for single sampling plan.** Sample size \(n = 2,540\), acceptance number \(d = 2\). Declare elimination if \(X \leq d\). Sample size and acceptance number calculated based on the parameters: \(p_l = 0.35\) NT deaths/1000 live births and \(p_u = 2.1\) NT deaths/1000 live births, \(\alpha = 0.1\) and \(\beta = 0.1\).

**Figure 2: OC curve for double sampling plan.** Sample size \(n_1 = 1,430\), \(n_2 = 1,310\) acceptance number \(d_1 = 0\), \(d_2 = 2\). Declare elimination if \(X_1 \leq d_1\) or \(X_1 + X_2 \leq d_2\). Sample size and acceptance number calculated with parameters: \(p_l = 0.35\) NT deaths/1000 live births and \(p_u = 2.1\) NT deaths/1000 live births, \(\alpha = 0.1\) and \(\beta = 0.1\).

Given the very low incidence of NT in countries seeking validation of MNTE, if the number of live births in the district is less than 50,000, the hypergeometric distribution is used to calculate the OC curve to take into account the finite population size. (The hypergeometric distribution is otherwise identical to the binomial distribution which assumes an infinite population size). For populations with fewer than 50,000 live births, the OC curve is calculated as follows:
where \( p = m/N \). Note that \( p \) can only take on a finite number of values when we use the hypergeometric distribution, since \( m = \{0, 1, 2, \ldots, N\} \) is finite.

Calculations for the OC curve using a double sampling plan are slightly more complex. The surveys are designed so that the probability of declaring elimination when \( p > p_u \) is approximately the same for the single and double sampling plans. Equivalently, the \( \alpha \)-error of the single sampling plan is equal to the \( \alpha \)-error of the double sampling plan. We also ensure that these plans have approximately equal \( \beta \)-errors.

To calculate an OC curve for a double sampling plan, we again calculate the probability that we declare elimination (pass) for a given NTMR in the population, but need to consider the fact that we can declare elimination at two different time points. We calculate (1) the probability of passing at the first stage of sampling; and (2) the probability of passing at the second stage of sampling given that we did not pass at the first stage (first sample result indeterminate). To obtain the total probability of passing a district when using a double sampling plan, these two probabilities are added (because the events are mutually exclusive).

\[
OC(p) = P(\text{pass} \mid p) = P(\text{pass at stage 1} \mid p) + P(\text{pass at stage 2 and not at stage 1} \mid p) = OC_1(p) + OC_2(p)
\]

where

\[
OC_1(p) = P(X_1 \leq d_1 \mid p) = \sum_{k=0}^{d_1} \binom{m_1}{k} p^k (1-p)^{n_1-k}
\]

\[
OC_2(p) = \sum_{k=d_1+1}^{d_2} \{ P(X_1 = k \mid p) P(X_2 \leq d_2 - k \mid p) \} = \sum_{k=d_1+1}^{d_2} \left\{ \binom{n_1}{k} p^k (1-p)^{n_1-k} \sum_{j=0}^{d_2-k} \binom{n_2}{j} p^j (1-p)^{n_2-j} \right\}
\]

Note that we first calculate the first stage sample size and acceptance number, \( n_1 \) and \( d_1 \), using thresholds \( p_r, p_u, \alpha_r \), and set \( \beta_1 = 1 \) (because we use the first sample to `stop early' if we can declare elimination). Then, to finalize the second-stage sampling design, we calculate \( OC(p) \) over a range of \( n_2 \) and \( d_2 \), fixing \( n_1 \) and \( d_1 \), searching for a sample size and acceptance rule with the pre-specified design properties. Using \( OC(p) \), we examine whether the selected sample sizes and acceptance numbers meet the design specifications (governed by \( p_r, p_u, \alpha \), and \( \beta \)).
Similar to the single sampling plan, we can use the hypergeometric distribution to calculate the OC curve for a double sampling plan when the annual number of live births in a district is less than 50,000. In this case, we would calculate $OC_1(p)$ and $OC_2(p)$ using the hypergeometric as follows:

$$OC_1(p) = P(X_1 \leq d_1 | p) = \sum_{k=0}^{d_1} \frac{\binom{m}{k} \binom{N-m}{n_1-k}}{\binom{N}{n_1}}$$

$$OC_2(p) = \sum_{k=d_1+1}^{\min(n_1,d_2)} \{P(X_1 = k | p)P(X_2 \leq d_2 - k | p)\}$$

$$= \sum_{k=d_1+1}^{\min(n_1,d_2)} \left\{ \binom{m}{k} \binom{N-m}{n_1-k} \right\} \sum_{j=0}^{d_2-k} \frac{\binom{m-k}{j} \binom{N-n_1-(m-k)}{n_2-j}}{\binom{N-n_1}{n_2}}$$

### 9.4.1 Risk Curve

A closely related concept to the OC curve is the risk curve. The risk curve is a function that gives the risk of making a mistake in the classification. Its definition requires the same values as the OC curve plus a cut-off point, $p^*$, to demarcate the acceptable NTMR from the unacceptable. Minimization of the risk curve is essential to a good design. Plotting the risk curve clearly indicates the true NTMR at which we are most likely to “make an error” in declaring that elimination has or has not occurred. Adjusting $p^*$ for the imperfect sensitivity and specificity of the survey, we define $p^* = \text{sensitivity} \times \frac{1}{1000} + (1-\text{specificity})\times\frac{1}{1000} = 0.7/1000$ NT deaths per 1000 live births when sensitivity = 70% and specificity = 100%.

Figures 3 and 4 below show the risk curves corresponding to the OC curves in Figures 1 and 2 when $p^* = 0.7$ deaths/1000 live births. Using these figures, it is clear that the risk of misclassifying a district as having achieved elimination is high when the true NTMR in a district is between 0.7 and 2 NT deaths/1000 live births. We are willing to accept this risk, because an NTMR in this range is very close to meeting the formal definition of elimination; for practical purposes, the goal of eliminating MNT as a public health problem has been achieved.
Sample Risk Curves

Figure 3: Risk curve for single sampling plan. Sample size \( n = 2,540 \), acceptance number \( d = 2 \). Declare elimination if \( X \leq d \). Sample size and acceptance number calculated based on: \( p_l = 0.35 \) NT deaths/1000 live births and \( p_u = 2.1 \) NT deaths/1000 live births, \( \alpha = 0.1 \) and \( \beta = 0.1 \).

Figure 4: Risk curve for double sampling plan. Sample size \( n_1 = 1,430, n_2 = 1,310 \) acceptance number \( d_1 = 0, d_2 = 2 \). Declare elimination if \( X_1 \leq d_1 \) or \( X_1 + X_2 \leq d_2 \). Sample size and acceptance number calculated based on: \( p_l = 0.35 \) NT deaths/1000 live births and \( p_u = 2.1 \) NT deaths/1000 live births, \( \alpha = 0.1 \) and \( \beta = 0.1 \).

The risk of declaring that a country has not achieved elimination when it truly has remains relatively low (<30%). This property of the survey design is a consequence of choosing a value of \( p_l \) that is closer to \( p^* \) than \( p_u \). If we select \( p_l \) and \( p_u \) such that they are equidistant from \( p^* \) (and choose \( \alpha = \beta \)), the risk of incorrectly declaring that a country has or has not achieved elimination should be close to 50% when the true NTMR \( p \) is very close to \( p^* \) (irrespective of whether it is higher or lower).

9.5 CHOOSING A SAMPLING PLAN

To design a specific LQA-CS survey for MNTE, we progress through the following steps, with a specific example in bold letters:

1. Select \( p_{l,i} \) and \( p_{u,i} \), the relevant upper and lower thresholds for an LQA-CS survey based on NT incidence.
   We select \( p_{l,i} = 0.5 \) cases/1000 live births and \( p_{u,i} = 3 \) cases/1000 live births.

2. Select error rates \( \alpha \) and \( \beta \). We select \( \alpha = 0.1 \) and \( \beta = 0.1 \).
   The choice of \( p_{l,i}, p_{u,i} \) and \( \alpha \) and \( \beta \) is equivalent to stating: “In a district with a true NT rate equal to 0.003 (\( p_u \)) or more, if we repeat the MNTE elimination survey a number of times, we would incorrectly conclude that neonatal tetanus has been eliminated less than or
equal to 10% (\(\alpha\)) of the time. And in a district with a true NT rate equal to 0.0005 (\(p_l\)), if we repeat the MNTE survey a very large number of times, we would incorrectly conclude that elimination has not occurred 10% (\(\beta\)) of the time.”

3. Adjust the thresholds \(p_l\) and \(p_u\) for the estimated sensitivity and specificity of the survey instrument (includes adjustment for CFR), to obtain new thresholds \(p_{l'}\) and \(p_{u'}\).

   We assume the sensitivity is 0.7 and specificity is 1, resulting in mortality thresholds \(p_{l'} = 0.35\) NT deaths/1000 live births and \(p_{u'} = 2.1\) NT deaths/1000 live births.

4. Calculate the required sample size based on \(\alpha\), \(\beta\), \(p_{l'}\) and \(p_{u'}\). If the size of the target population is known and is less than 50,000 live births, we use the formulas based on the hypergeometric distribution for the calculations. Otherwise, we use the binomial distribution. Usually, the hypergeometric distribution will be more appropriate, as the target population of live births is usually substantially less than 50,000.

For a large target population (> 50,000 live births), we arrive at the following designs:
- When using a single sampling plan, we need to sample 2,540 live births, and declare elimination if we observe less than or equal to 2 NT deaths.
- With a double sampling plan, we should initially sample 1,430 live births.
   - If we do not observe any NT deaths, we declare elimination.
   - If we observe more than 2 NT deaths, we declare failure to eliminate.
   - If we observe 1 or 2 NT deaths, we sample an additional 1,310 live births. If a total of 2 or less NT deaths are identified among all 1,430 + 1,310 = 2,740 live births, then we declare elimination. Otherwise, we conclude NT elimination has not been achieved.

For a smaller target population (< 50,000 live births), see section 5.1 below.

The OC curves and risk curves corresponding to these sampling designs are plotted in Figures 1-4 above. Single sampling plan curves are in Figures 1 and 3; double sampling curves are shown in Figures 2 and 4. Note that the single and double sampling curves appear nearly identical, reflecting the fact that the single and double sampling plans were designed to have comparable statistical classification properties.

In Table 3 below, we list the probability of declaring that elimination has occurred for various values of \(p\) (these are plotted in the OC curves, but are listed below for reference).
**Table 3:** OC calculations for single and double sampling plans. Upper and lower thresholds are denoted with a *. Sample size and acceptance number calculated based on the parameters: $p_l = 0.35 \text{ NT deaths/1000 live births}$ and $p_u = 2.1 \text{ NT deaths/1000 live births}$, $\alpha = 0.1$ and $\beta = 0.1$.

<table>
<thead>
<tr>
<th>Probability (NT deaths/1000 live births)</th>
<th>OC Single Sampling</th>
<th>OC Double Sampling</th>
</tr>
</thead>
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<tr>
<td>0</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>0.1</td>
<td>0.998</td>
<td>0.997</td>
</tr>
<tr>
<td>0.2</td>
<td>0.985</td>
<td>0.984</td>
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<tr>
<td>0.35*</td>
<td>0.939</td>
<td>0.934</td>
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<tr>
<td>0.5</td>
<td>0.864</td>
<td>0.855</td>
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<td>0.7</td>
<td>0.737</td>
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<td>1.0</td>
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<td>0.518</td>
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<tr>
<td>2.0</td>
<td>0.118</td>
<td>0.117</td>
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<tr>
<td>2.1*</td>
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<td>0.099</td>
</tr>
<tr>
<td>3.0</td>
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<td>0.022</td>
</tr>
<tr>
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<td>0.002</td>
<td>0.004</td>
</tr>
<tr>
<td>5.0</td>
<td>0.0003</td>
<td>0.001</td>
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</table>

**9.5.1 Finite Sample Size Plans**

In Table 4, we present sample sizes and decision rules using the design parameters in the above section, when the target population size is less than 50,000 live births.

**Table 4:** Sample sizes for finite population sizes. $p_l = 0.00035; p_u = 0.0021; \alpha = 0.1; \beta = 0.1; \alpha_1 = 0.05$. In single sampling plan, sample N live births and denote number of NT deaths detected as X. Declare elimination if $X \leq d$. In the double sampling plan, sample $N_i$ live births at stage $i$ and denote number of NT deaths as $X_i$. Declare elimination when $X_1 \leq d_1$ and when $X_1 + X_2 \leq d_2$.

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<thead>
<tr>
<th>Pop.</th>
<th>$p_l$</th>
<th>$p_u$</th>
<th>$d$</th>
<th>$N$</th>
<th>$\alpha$</th>
<th>$\beta$</th>
<th>$d_1$</th>
<th>$n_1$</th>
<th>$d_2$</th>
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<td>0.099</td>
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<tr>
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<td>0</td>
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<td>0.099</td>
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<tr>
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<td>0</td>
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<td>1</td>
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<td>0.049</td>
<td>0.099</td>
<td>0.057</td>
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<td>0.098</td>
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<td>0</td>
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<td>1</td>
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<td>0.049</td>
<td>0.099</td>
<td>0.045</td>
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<td>0.097</td>
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<td>0</td>
<td>1,330</td>
<td>1</td>
<td>490</td>
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### Single Sampling Plan vs. Double Sampling Plan

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<td>0,138 2</td>
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<tr>
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<td>0,140 2</td>
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<tr>
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<td>2.10</td>
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<td>0,140 2</td>
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<tr>
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<td>0.34</td>
<td>2.10</td>
<td>2,500 .099 .050</td>
<td>0,141 2</td>
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</tbody>
</table>

### 9.6 References


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Verbal Autopsy of Stillbirths and Neonatal Deaths in a Rural Area of Burkina Faso

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Abstract

Introduction: In developing countries, many neonatal deaths still occur at home and the causes of these deaths are not ascertained. Objective: To identify the causes of stillbirths and neonatal deaths that occur at home and the factors that have contributed to these deaths. Materials and Method: We have used the method of verbal autopsy to investigate the stillbirths and neonatal deaths in nine villages in the health area of Namsiguia, health district of Ouahigouya, Burkina Faso, during the period January 1, 2007 to December 8, 2012. Results: Over these six years, we have recorded 19 stillbirths and 36 neonatal deaths among 1507 live births, demonstrating a neonatal mortality rate of 28.8 per 1000 and a rate of stillbirths of 12.6 per 1000. The average age of newborns at death was 5.6 days and the sex-ratio was 1.6. The major cause of stillbirths was antenatal hypoxia and birth asphyxia (42.1%). The direct causes of neonatal deaths were neonatal sepsis (41.7%), preterm birth (19.4%) and hypoxia and birth asphyxia (11.1%). There were 42.1% deliveries and 58.3% neonatal deaths, which occurred at home. We have noted 89.5% fresh stillbirths. Death occurred more often during the early neonatal period (55.5%). Factors significantly associated with neonatal death were, lack of school education of mothers (OR = 4), precocious marriage of the mother (OR = 8), poor follow-up of pregnancies (OR = 3), birth at home (OR = 4), low socioeconomic level (OR = 6), and low geographical access to the health facility (OR = 4). Conclusions: Strengthening of the health infrastructure and improving their accessibility, reinforcement of the staff for high quality care, and communication for a change in behavior in rural communities, will contribute toward reducing neonatal mortality in the area of health of Namsiguia.

Keywords

Verbal Autopsy, Neonatal Deaths, Stillbirths, Cause of Death


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1. Introduction

Of the 130 million annual births worldwide, there are approximately four million neonatal deaths, an equivalent of stillbirths is counted, and more than 98% of these deaths occur in developing countries [1]-[3]. Furthermore, most of these neonatal deaths occur at the community level and are, therefore, not recorded and their exact causes not elucidated. Verbal autopsy is a method that aims to identify the causes and factors that contribute to these deaths when they occur outside a health facility [4]. This method is an alternative to medical audit, in the context of low accessibility to health services, in order to determine the avoidable factors of death and take appropriate corrective measures. It is, therefore, particularly suitable for poor countries like Burkina Faso, where the neonatal mortality rate is estimated at 28 per 1000, where more than 77% of the population live in rural areas, and where 45% live under the threshold of poverty, with a low attendance of health services [3]. This verbal autopsy, which was carried out in a rural area was designed to determine the causes of stillbirths and neonatal deaths, as well as the factors leading to the deaths. Taking account of the identified modifiable factors should enable the reduction of neonatal mortality and contribute to the achievement of the Fourth Millennium Development Goal (MDG4), whose target is to reduce the under-five mortality rate by two-thirds, by 2015.

2. Materials and Method

2.1. Setting

The study was carried out in the rural area of the health and social promotion center (CSPS) of Namsiguia. The CSPS depends on the health district of Ouahigouya, which is a town located 200 km north off Ouagadougou, the capital of Burkina Faso. The infrastructure of the CSPS included a dispensary, a repository of essential generic medicines and a maternity ward, which was under construction. The CSPS team comprised of two nurses and an auxiliary midwife. Two community health workers served as community relays. The CSPS covered nine villages, with a population estimated at approximately 9000 inhabitants. Accessibility to the CSPS was difficult during the rainy season owing to flooding in the lowland situated between the villages and the health center.

2.2. Method and Study Population

A descriptive and analytic study allowed inclusion of all cases of stillbirths and neonatal deaths that occurred in the health area of the CSPS of Namsiguia between January 2007 and December 2012, or a six year period. The method of the verbal autopsy was used. A proforma, adapted by the World Health Organization (WHO) standard No. 1 questionnaire of verbal autopsy, was designed for this study [5]. The interview respondents were the mother and/or the father of the stillborn or deceased newborn. Close family members who were present at the time of the death were also interviewed.

2.3. Data Collection and Management

Data collection unwound from February 1 to March 31, 2014. The main technique of data collection was a direct interview with individual or collective respondents, with their consent. If necessary, this technique was complemented by the review of files and records of the patients at the CSPS or at the regional hospital. Four health personnel and six investigators, who conducted the data collection, had been previously trained on the verbal autopsy technique and filling investigation proforma. The questionnaire was pretested, which allowed its revision. Births and neonatal deaths were identified before the beginning of the investigation by the two community health workers, who were well informed of these events in the villages. This allowed the investigators to go directly to the families where the death took place. Two doctors insured the supervision of the survey. After collection of the data, the audit was conducted by a team consisting of two pediatricians, two medical practitioners, and a nurse during a staff meeting. This allowed determination of the direct and indirect causes of the deaths and identified the factors associated with these deaths. Each sheet was reviewed and the causes of the death were set, depending on the algorithm used by Manandhar et al. [6]. A single cause of death and stillbirth was assigned per child. Causes of neonatal deaths were classified using the international classification of diseases of the WHO, tenth edition (ICD 10) [7]. The socioeconomic level of the surveyed family was classified as low, medium or high, according to the WHO classification [8]. To find the existence of a statistical significance associated with the studied factors, each deceased newborn was matched to a control, who was a living newborn. The matching
was made on date of birth, sex, and the village of birth of the deceased infants, with a ratio equal to 1. The matching on the date of birth was obtained more or less to a 15-day extent. Data were entered using the Sphinx™ version 5 software (the Sphinx development, 27, rue Cassiopée, Parc Atlais, Chavanod, France) and then analyzed using SPSS 16.0 (IBM SPSS Inc., Chicago, Illinois, USA). Chi-square and Fisher’s tests were used for comparisons between proportions. The odds ratio (OR) was computed to determine the significance of the association between variables, and the 95% confidence interval (CI) was calculated. Statistical tests yielding p-values < 0.05 were considered significant.

2.4. Ethical Considerations

During the preparatory phase of the investigation, we first obtained permission from the Ministry of Health. Furthermore, during a seminar, the community leaders (heads customary and religious, village development advisers) and the administrative authorities (mayor, prefect) of the study area were informed and sensitized on the verbal autopsy of neonatal deaths and its objectives. Populations that were the subject of the study were also informed on the project of study and it was with their consent that we conducted this investigation.

3. Results

3.1. Frequency of Stillbirths and Neonatal Deaths

Over the period of the study, a total of 55 stillbirths and neonatal deaths were identified consisting of 19 stillbirths and 36 neonatal deaths. During the same period, 1507 births were identified, demonstrating a rate of stillbirth of 12.6 per 1000 and a neonatal mortality rate of 28.8 per 1000. The state of stillbirths was specified in 16 cases and fresh stillbirths were 14 (87.5%), the other two (12.5%) were macerated stillborns. The sex ratio of the deceased newborns was 1.6 and the average age at death was 5.6 days.

3.2. Causes of Stillbirths and Neonatal Deaths

The direct causes of stillbirths were antenatal hypoxia and asphyxia at birth (eight cases), preterm birth (one case), and low birth weight (one case). The indirect causes found were related to maternal illness during pregnancy consisting of malaria (five cases), anemia (three cases), and hypertension (one case). The main direct causes of neonatal deaths were sepsis (41.7%), preterm birth (19.4%), and antenatal hypoxia and asphyxia at birth (11.1%). Sepsis was the most common cause of death in the late neonatal period (75.0%), whereas, antenatal hypoxia and asphyxia at birth (20.0%) and preterm birth (25.0%) were the most common causes of death in the early neonatal period, as shown in Table 1.

The indirect causes of neonatal deaths were maternal causes that were found in 19 cases out of 36 (52.8%). It was sepsis in 13 cases (68.5%) of which nine cases were of fever of unknown origin, three cases were of possible urinary tract infection, and one case was of malaria. Hypertension, prolonged labor, and anemia (two cases each) were the other maternal causes of neonatal deaths.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>ENNP* No. of deaths (%)</th>
<th>LNNP† No. of deaths (%)</th>
<th>Total No. of deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal sepsis</td>
<td>3 (15.0)</td>
<td>12 (75.0)</td>
<td>15 (41.7)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>5 (25.0)</td>
<td>2 (12.5)</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>Birth asphyxia</td>
<td>4 (20.0)</td>
<td>0 (0.0)</td>
<td>4 (11.1)</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>0 (0.0)</td>
<td>1 (6.25)</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>8 (40.0)</td>
<td>1 (6.25)</td>
<td>9 (25.0)</td>
</tr>
<tr>
<td>Total</td>
<td>20 (100.0)</td>
<td>16 (100.0)</td>
<td>36 (100.0)</td>
</tr>
</tbody>
</table>

*ENNP: Early Neonatal Period (0 - 6 days); †LNNP: Late Neonatal Period (7 - 28 days).
Table 2. Factors associated with neonatal deaths, Namsiguia, Burkina Faso, 2012.

<table>
<thead>
<tr>
<th>Putative risk factor for death</th>
<th>Deceased (n = 36)</th>
<th>Alive (n = 36)</th>
<th>OR [95% CI]*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of maternal education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30</td>
<td>20</td>
<td>4 [1.2 - 13.9]</td>
<td>0.01</td>
</tr>
<tr>
<td>No</td>
<td>6</td>
<td>16</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Precocious marriage (mother &lt; 18 years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25</td>
<td>8</td>
<td>8 [2.8 - 22.9]</td>
<td>0.00006</td>
</tr>
<tr>
<td>No</td>
<td>11</td>
<td>28</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Large multiparous mother (&gt;= 5 para)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9</td>
<td>3</td>
<td>4 [0.8 - 2.0]</td>
<td>0.5</td>
</tr>
<tr>
<td>No</td>
<td>27</td>
<td>33</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Poor follow-up of pregnancy (No. of ANC†s &lt; 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16</td>
<td>7</td>
<td>3 [1.0 - 10.9]</td>
<td>0.02</td>
</tr>
<tr>
<td>No</td>
<td>20</td>
<td>29</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Birth at home</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15</td>
<td>5</td>
<td>4 [1.2 - 16.6]</td>
<td>0.01</td>
</tr>
<tr>
<td>No</td>
<td>21</td>
<td>31</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Socioeconomic level of parents</td>
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<td></td>
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<tr>
<td>Low</td>
<td>32</td>
<td>20</td>
<td>6 [1.7 - 26.8]</td>
<td>0.001</td>
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<tr>
<td>Medium</td>
<td>4</td>
<td>16</td>
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<td>Lack of geographical access to the health center</td>
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<td></td>
</tr>
<tr>
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<td>30</td>
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<tr>
<td>No</td>
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<td>16</td>
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<td></td>
</tr>
</tbody>
</table>

*Odds ratio [95% Confident interval]; †Antenatal cares.

3.3. Factors Related to Neonatal Deaths

Deaths were early (55.5%) and more often occurred at home (58.3%). Factors significantly associated with neonatal deaths were, lack of maternal education (OR = 4), precocious marriage (OR = 8), poor follow-up of pregnancies (OR = 3), birth at home (OR = 4), low socioeconomic level (OR = 6), and lack of geographical access to the health center (OR = 4) (Table 2).

4. Discussion

Verbal autopsy aims at reduction of mortality. When it is implemented as a participatory process in a community, it can provide awareness of the factors that lead to deaths and can stimulate collective action. Despite the memory potential bias, owing to the retrospective collection of painful memories, questioning the mothers allowed us to obtain sufficient reliable information about stillbirths and neonatal deaths, which we have compared with data from the literature.

4.1. Stillbirths

With 12.6 per1000, the rate of stillbirths in our study was lower than the national rate, which is estimated to be 26 per 1000 [9]. This lower rate in our study is probably because of the small size of our sample, in a well-circumscribed health area, while the national rate is global and masks the disparity between regions. Antenatal hypoxia and asphyxia at birth were the main causes of stillbirths in this study. The discovery of a fresh stillbirth suggests that the child was viable during labor [6] and death dates back to less than 12 hours before birth [10]. In this study, as in those of other authors from countries with limited resources [11]-[13], the observed proportions of fresh stillbirths may reflect that women in labor had a delay in receiving care or there was lack of monitoring of the delivery by the care providers. This low capacity of the health care centers to provide quality rural perinatal care in Burkina Faso was already noted by Nikiema et al. [14], in the North East of the country. This high level of stillbirths is compounded by the fact that there are no skilled care providers in the community to take over deliveries or give neonatal care at home in accordance with our current national health policy. However,
according to several authors, community health workers do exist, who are trained to recognize the signs of danger and practice basic neonatal resuscitation to reduce deaths from asphyxia during labor [6] [15] [16].

### 4.2. Neonatal Deaths

The rate of 28.8 per 1000 of neonatal mortality in this study is comparable to the national neonatal mortality of 28 per 1000 [3]. Neonatal mortality remains a factor of worry in our country despite the efforts of giving a grant for obstetric and neonatal emergency care [17]. The causes of neonatal deaths were dominated by neonatal sepsis (41.7%) in this study and these deaths by sepsis were most frequent in the late neonatal period (75%). The high rate of deaths by sepsis after the first week was especially on account of the many deliveries that took place at home, which occurred in poor conditions of hygiene and traditional practices, harmful to the health of the newborn child during the section and the care of umbilical cord. These poor conditions of delivery and umbilical cord care had already been reported by Bagui et al. in India [11] and Manandhar et al. in the Nepal [6]. To reduce neonatal sepsis, awareness messages should be addressed to women and their families, to encourage deliveries at the health center and to abandon the traditional practices harmful to the health of the newborn.

This study has identified preterm birth (19.4%) as the second cause of neonatal death. Sombie [18] in the West of Burkina Faso, Edmond et al. [13] in Ghana, and Turnbull et al. [12] in Zambia had made the same observation, with the respective preterm death rates of 15%, 19.7%, and 34%. Poverty, hardship of field work and chores, the long walks on foot to look for firewood and water are situations experienced daily by women in the area of this study, which encourage preterm deliveries. In this study, preterm deaths were mainly related to the inadequacy of their management in a health center, however precarious this may be in a rural area of a developing country like Burkina Faso. However, the implementation of low-cost methods that have proven their effectiveness and that are adopted by poor countries, such as the Kangaroo method, can reduce neonatal mortality linked to preterm birth and low birth weight [19]. Actions that are aimed at improving the social economic status of women in developing countries, as well as the promotion of essential neonatal care in the context of a community health policy will reduce preterm-related morbidity and neonatal mortality.

Antenatal hypoxia and asphyxia at birth was the third cause of neonatal deaths in our study with a mortality rate of 11.1%; which is three times lesser than in the study of Manandhar et al. [6] in the Nepal and Edmond et al. [13] in Ghana. In sub-Saharan Africa, asphyxia at birth is responsible for 280,000 deaths per year, especially on the first day of life [9]. Poor quality of care, inadequate fetal monitoring, and lack of skills of the health personnel are frequently associated with asphyxia at birth [20]. The training and equipment of community health workers for basic neonatal resuscitation can combat neonatal asphyxia and death which are linked [6] [16].

### 4.3. Factors Associated with Neonatal Deaths

The occurrence of the death of a newborn is often the result of several factors, some of which are preventable. In this study, the factors associated with neonatal deaths were the social, cultural, economic, and environmental factors. The analysis of these factors allows us to classify them in three delays according to the conceptual model proposed by Thaddeus [21] and used by other authors [22] [23] to trace the path that leads to the death of a newborn. The first delay is relative to the decision to go to a health facility. It follows from a persistence of the harmful social cultural constraints to health, lack of knowledge of the signs of danger, and the weakness of the decision-making power of the woman, who is yet the center of care of the children. In this study the risk of neonatal death was multiplied four times in the absence of mother’s school education, five times in the event of precocious marriage, three times if pregnancy was poorly followed, and four times in the event of delivering at home. The second delay deals with access to the health facility. In this study, the risk of death was significantly associated with lack of geographical access to the health center (OR = 4) and the low socioeconomic level of parents (OR = 6). The third delay relates to the quality of care received once the newborn arrives in the health center. In this study, we observed the failing in the care of the newborn and the ignorance of pregnancies at risk by the health personnel. Beyond the social cultural constraints, delays seem to be interdependent. Indeed, going by the challenges for the transport and the cost of care in health facilities, the population often resigns to stay at home, abandoning themselves to fatalism. With the optimal implementation of a subsidy policy of obstetric and neonatal care emergency care, which has begun in Burkina Faso, since 2006, in particular in its section on transport and medical care, it is expected to accelerate the reduction of neonatal mortality.
5. Conclusion

Verbal autopsy permitted the identification of preventable causes of stillbirths and neonatal deaths in the health area of Namsiguia, Burkina Faso. The associated factors, in particular, were economic and social cultural. Improving school education, especially for women, reduction of extreme poverty, improvement of accessibility to high quality health services, promotion of essential newborn care, and adoption and implementation of a community health policy are essential for the reduction in neonatal mortality and for improving newborn survival in Burkina Faso, especially in the rural area.

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The authors thank the staff of the Regional Directorate of Health of the North and the Regional Directorate of the Health District of Ouahigouya. They express their gratitude to the members of the bereaved families who have accepted to talk about an event as painful as the loss of one of their own.

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References


Protecting all against tetanus

Guide to sustaining maternal and neonatal tetanus elimination (MNTE) and broadening tetanus protection for all populations
Protecting all against tetanus

Guide to sustaining maternal and neonatal tetanus elimination (MNTE) and broadening tetanus protection for all populations
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEAFI</td>
<td>Adverse event(s) following immunization</td>
</tr>
<tr>
<td>ANC</td>
<td>Antenatal care</td>
</tr>
<tr>
<td>CBK</td>
<td>Clean birth kit</td>
</tr>
<tr>
<td>CHD</td>
<td>Child Health Days</td>
</tr>
<tr>
<td>cMYP</td>
<td>Comprehensive multi-year plan</td>
</tr>
<tr>
<td>DHS</td>
<td>Demographic and Health Survey</td>
</tr>
<tr>
<td>HBR</td>
<td>Home-based records</td>
</tr>
<tr>
<td>HMIS</td>
<td>Health management information system</td>
</tr>
<tr>
<td>HPV</td>
<td>Human papillomavirus</td>
</tr>
<tr>
<td>ICC</td>
<td>Interagency Coordinating Committee</td>
</tr>
<tr>
<td>IEC</td>
<td>Information, Education and Communication</td>
</tr>
<tr>
<td>LQA-CS</td>
<td>Lot quality assurance – cluster sample</td>
</tr>
<tr>
<td>MCHD</td>
<td>Maternal and Child Health Days</td>
</tr>
<tr>
<td>M&amp;E</td>
<td>Monitoring and evaluation</td>
</tr>
<tr>
<td>MICS</td>
<td>Multiple Indicator Cluster Survey</td>
</tr>
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<td>MNTE</td>
<td>Maternal and neonatal tetanus elimination</td>
</tr>
<tr>
<td>NITAG</td>
<td>National Immunization Technical Advisory Group</td>
</tr>
<tr>
<td>Non-NT</td>
<td>Non-neonatal tetanus</td>
</tr>
<tr>
<td>NT</td>
<td>Neonatal tetanus</td>
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<tr>
<td>PAB</td>
<td>Protection at birth</td>
</tr>
<tr>
<td>PCV</td>
<td>Pneumococcal conjugate vaccine</td>
</tr>
<tr>
<td>PIRI</td>
<td>Periodic intensification of routine immunization</td>
</tr>
<tr>
<td>RCA</td>
<td>Root cause analysis</td>
</tr>
<tr>
<td>RED/REC</td>
<td>Reaching Every District/Reach Every Child</td>
</tr>
<tr>
<td>SBA</td>
<td>Skilled birth attendant</td>
</tr>
<tr>
<td>SIA</td>
<td>Supplementary immunization activity</td>
</tr>
<tr>
<td>Td</td>
<td>Tetanus-diphtheria toxoid</td>
</tr>
<tr>
<td>Tdap</td>
<td>Tetanus-diphtheria-acellular pertussis</td>
</tr>
<tr>
<td>TIG</td>
<td>Tetanus immune globulin</td>
</tr>
<tr>
<td>TTCV</td>
<td>Tetanus toxoid-containing vaccine</td>
</tr>
<tr>
<td>TTCV2+</td>
<td>Two or more TTCV doses at the time of last pregnancy</td>
</tr>
<tr>
<td>WRA</td>
<td>Women of reproductive age</td>
</tr>
<tr>
<td>2YL</td>
<td>Second year of life</td>
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About this guide

For the first time, this document pulls together in one place all the latest information, recommendations, and strategies that are required to both sustain maternal and neonatal tetanus elimination (MNTE) and broaden protection against tetanus for all people. It is a technical resource that is relevant not only for countries that have already successfully achieved elimination status, but also for those still working towards MNTE.

This guide is intended for use by national immunization programme managers and staff, and immunization partners involved in providing implementation support to countries.

The specific objectives of this guide are:

— to describe the strategies and activities required to (i) sustain the elimination of maternal and neonatal tetanus, and (ii) ensure long-term protection against tetanus for all people;
— to inform the policy discussions and operational decisions related to tetanus vaccination and sustaining MNTE at the country level;
— to provide up-to-date references on global policy recommendations as well as technical and strategic issues.

This document provides guidance and options to assist countries to decide and plan the policy changes and activities that are needed to successfully sustain MNTE and ensure long-term protection against tetanus for all populations.

Chapter by chapter, this guide explains how the core programmatic components for preventing MNT [antenatal care (ANC) vaccination of pregnant women and clean births with skilled health personnel] are interconnected with the implementation of routine tetanus vaccination (for both sexes with booster doses across the life course) to ensure elimination is sustained and that all populations are protected.
CHAPTER 1

Introduction
In this introductory chapter you will learn:

• Why there is a global goal for MNTE;

• How protection against tetanus and MNTE can be sustained;

• What are the recommended strategies for achieving and sustaining MNTE.

You can use this information to:

• Improve/refresh your technical knowledge and understanding of MNTE;

• Prepare briefing notes for policy and decision makers (including NITAGs);

• Develop training curriculum for health workers.
Why is there a global goal for maternal and neonatal tetanus elimination (MNTE)?

**Tetanus: quick facts**

- The causative agent of tetanus is the bacterium *Clostridium tetani*.
- Spores of *C. tetani* are found everywhere in the environment.
- Tetanus occurs when spores enter the human body through wounds and produce neurotoxin.
- Vaccination against tetanus is the main means of protection.

The burden of maternal and neonatal tetanus (MNT) is a health equity issue affecting those who are the most disadvantaged, poor, and without access to adequate health services. MNT has often been referred to as a “silent killer” since the victims often die without being officially recorded. A case of maternal and/or neonatal tetanus represents a triple failure of the public health system – failure of the routine immunization programme, failure of antenatal care, and failure of ensuring clean and safe birth practices.

Unlike polio and smallpox, tetanus cannot be eradicated as the spores are ubiquitous in the environment and there are animal reservoirs (tetanus spores in soil or fomites contaminated with animal and human faeces can contaminate wounds of all types). However, MNT can be eliminated through universal active immunization of children, mothers, and other women of reproductive age and improving maternity care with emphasis on hygienic birth and cord care practices, i.e. the number of cases can be reduced to an extent that it ceases to be a public health problem.

While considerable progress has been achieved, by end 2018, 14 countries in three regions1 still have not reached MNTE status. **Figure 1** shows the dynamic of progress made by the countries since neonatal tetanus (NT) was first declared a target in 1989.

The elimination of neonatal tetanus as a public health problem is defined as having less than one NT case per 1,000 live births in every district or similar administrative unit in the country each year. Maternal tetanus is assumed to be eliminated once NT elimination has been achieved.2

As more and more countries are validated3 as having achieved MNTE, attention and activities must shift towards ensuring that this accomplishment is sustained over the long term.

---

1 The priority countries where MNT is still a public health problem include: Afghanistan, Angola, Central African Republic, Chad, Congo DR, Guinea, Mali, Nigeria, Pakistan, Papua New Guinea, Somalia, Sudan, South Sudan and Yemen. Two countries have partially eliminated MNT: Pakistan (Punjab province) and Nigeria (south-east region).

2 The neonatal tetanus indicator acts as a proxy for maternal tetanus.

Maternal and Neonatal Elimination (MNTE) Goal: key details

When in the late 1980s WHO estimated that annual global neonatal tetanus (NT) mortality rate was approximately 6.7 NT deaths per 1000 live births, the global health community committed itself to decrease incidence of NT cases.

— In 1989: the 42nd World Health Assembly called for the elimination of neonatal tetanus in 59 priority countries by 1995.
— In 1990: the World Summit for Children listed neonatal tetanus elimination as one of its goals.
— In 1991: the MNTE goal was endorsed by the 44th World Health Assembly, but due to slow implementation of the recommended strategies for NT elimination, the target date for the attainment of elimination by all countries was postponed to 2000.
— In 1999: progress towards the attainment of the global elimination goal was reviewed by UNICEF, WHO, and UNFPA, and the Initiative was re-constituted. Elimination of maternal tetanus was added to the goal with a 2005 target date, which was later shifted to 2015.
— By the end of 2015, there were still 21 countries that had not yet attained elimination.
— Progress continues: today only 14 countries remain to eliminate MNTE.

Global Vaccine Action Plan (GVAP) goal 2: Achieve MNTE by 2020

— As a result of implementing recommended strategies in the period 1988–2015, the global estimate of NT deaths declined by 96%.
— Almost all the remaining priority countries will achieve MNTE by the GVAP target of 2020, if implementation challenges are addressed such as vaccinating high-risk populations due to geographical and/or security issues.
— Efforts must be made to ensure funding for activities and innovative approaches (e.g. TT Unject) to reach vulnerable populations.


**Figure 1**
Maternal and neonatal tetanus elimination progress since 1989: priority countries validated for elimination

<table>
<thead>
<tr>
<th></th>
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<td>NT elimination declared a goal at 42nd Health Assembly</td>
<td>World Summit for Children included NT elimination as a goal</td>
<td>Goal again endorsed at the 44th Health Assembly</td>
<td>Initial elimination target</td>
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Countries achieving MNTE validation

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<td>Egypt</td>
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<td>Burundi</td>
<td>Comores</td>
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New elimination initiative launched including maternal tetanus targeting 59 countries

<table>
<thead>
<tr>
<th>Year</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nepal</td>
<td>Togo</td>
<td>Vietnam</td>
<td>Egypt</td>
<td>Zambia</td>
<td>Bangladesh</td>
<td>Burundi</td>
<td>Comores</td>
<td>Congo</td>
</tr>
</tbody>
</table>

2nd elimination target

<table>
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<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Côte d’Ivoire</td>
<td>Gabon</td>
<td>Iraq</td>
<td>Laos</td>
<td>PDR</td>
<td>Sierra Leone</td>
<td>Madagascar</td>
<td>Cambodia</td>
<td>India</td>
</tr>
</tbody>
</table>

3rd elimination target

4th elimination target
How can protection against tetanus and MNTE be sustained?

The principal strategies for achieving MNTE focused on provision of tetanus toxoid (TT) immunization through routine and supplementary immunization activities (SIAs) to vaccinate women 15–49 years of age in areas with limited access to health services, strengthening of clean birth services, and effective surveillance to detect areas and populations at high risk for NT. Although these strategies have been very successful, once elimination status is achieved, the strategies used to reach it need to be adjusted to sustain elimination (see Table 1).

Table 1
Recommended strategies for achieving and sustaining MNTE

<table>
<thead>
<tr>
<th>Achieving MNTE</th>
<th>Sustaining MNTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strengthen antenatal care (ANC) immunization of pregnant women with tetanus toxoid-containing vaccine (TTCV).</td>
<td>Strengthen immunization of pregnant women and routine vaccination of all children/adolescents (both sexes) to receive 3 primary infant doses and 3 booster doses of TTCV before adolescence.</td>
</tr>
<tr>
<td>TTCV Supplementary Immunization Activities (SIAs) in selected high risk areas, targeting women of reproductive age (15–49 years) with 3 properly-spaced doses of the vaccine.</td>
<td>Antenatal screening of pregnant women to verify tetanus vaccination status (to ensure tetanus protection at birth – PAB) and vaccinate if required.</td>
</tr>
<tr>
<td>Promotion of clean birth and clean cord care practices and health education.</td>
<td>Increased access to skilled health personnel at birth and clean birth/cord care practices.</td>
</tr>
<tr>
<td>Reliable NT surveillance including case investigation and response.</td>
<td>Strong T/NT surveillance and regular review of data to identify districts at risk of re-emergence of MNT and needing corrective action.</td>
</tr>
</tbody>
</table>

Sustaining MNTE requires a comprehensive multi-pronged approach. In the short to medium term, key activities will continue to focus on women but plans need to begin to shift towards adjusting the national immunization schedule to provide long-term protection against tetanus for all people. This means achieving high coverage for both sexes with 6 doses of tetanus toxoid-containing vaccine (TTCV\(^4\)) – 3 primary infant doses and 3 booster doses through routine childhood and adolescent vaccination.\(^5\) Once high homogeneous vaccination coverage (≥90%) with the 6-dose child/adolescent schedule has been realized, a large share of future cohorts of women of reproductive age (WRA) will be fully protected against tetanus throughout their

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\(^4\) Since 1998 WHO has recommended that all countries replace tetanus toxoid (TT) with the combination tetanus-diphtheria (Td) vaccine, in order to sustain protection against diphtheria following waning immunity after the primary series.

As a result, antenatal care (ANC) contacts will increasingly be used to screen and verify the vaccination status of pregnant women, and less as the primary means to vaccinate them with TTCV. This will also make SIAs targeting WRA unnecessary.

Plans for achieving/sustaining MNTE should be included in the country’s comprehensive multiyear plan (cMYP) for immunization. The guidelines for developing/revising a cMYP are available online at: [http://www.who.int/immunization/programmes_systems/financing/tools/cmyp/en/](http://www.who.int/immunization/programmes_systems/financing/tools/cmyp/en/).

Figure 2 diagrammatically shows how this guide describes a comprehensive approach to sustaining MNTE and protecting all.
Figure 2
Overview of activities and strategies to sustain MNTE

Antenatal care
Chapter 3

Surveillance/Monitoring & Evaluation
Chapters 5+6

Routine vaccination
Chapter 2

Protection at birth
Chapter 4

Clean delivery with skilled personnel
Chapter 4
CHAPTER 2

Building routine immunization for long-term protection against tetanus

(3 primary infant and 3 booster doses of TTCV)
In this chapter you will learn:

• The WHO recommended routine vaccination schedule for TTCV;

• What vaccines to use, and when and why to use DT/Td rather than TT;

• Strategies to achieve high coverage for the primary series of TTCV;

• Strategies and opportunities for TTCV booster doses;

• Interim strategy for TTCV booster dose introduction using multi-age cohort vaccination schedules;

• Catch-up schedule for children >1 year old or adolescents with incomplete or unknown TTCV primary series vaccination status;

• Activities to ensure successful roll-out of a routine childhood 6 dose TTCV schedule.

You can use this information to:

• Plan the introduction of TTCV booster doses to help achieve and/or sustain MNTE, and so that all persons are protected;

• Decide the best delivery strategies for 3 booster contacts in your country;

• Develop an introduction plan with necessary activities.
What is the WHO recommended routine vaccination schedule for TTCV?

In 2017 WHO issued updated policy recommendations for tetanus vaccination. WHO recommends that all populations worldwide should be vaccinated against tetanus. In order to provide protection throughout adolescence and adulthood, national immunization programmes should provide a total of 6 doses consisting of 3 primary infant doses and 3 booster doses, preferably administered in childhood and completed by adolescence (Box 1).

**Box 1**

**WHO recommendation: routine vaccination schedule for TTCV**

**Primary series:** The primary infant series of 3 doses of TTCV is the foundation for building lifelong immunity, with the first dose administered from 6 weeks of age. Subsequent doses should be given with a minimum interval of 4 weeks between doses. If possible, the primary series should be completed by 6 months of age.

**Booster doses:** Three booster doses should be given at ages: 12–23 months, 4–7 years, and 9–15 years. Ideally, there should be at least 4 years between boosters.

Note: All HIV-infected children should be vaccinated against tetanus following the same schedule.

Data from serological studies suggest that a primary series of 3 TTCV doses in infancy plus a booster during the second year of life (12–23 months) will provide 3–5 years of protection. A further booster dose (e.g. in early childhood, or at school entry, 4–7 years) will provide protection into adolescence, and another booster during adolescence (9–15 years) will induce immunity that lasts through much of adulthood and which protects women through their childbearing years (Figure 3).

Within age limits specified above, countries can adjust or tailor their TTCV vaccination schedule based on local epidemiology, the objectives of the immunization programme, or any programmatic issues or opportunities (e.g. existing child health contacts), keeping in mind the optimal 4-year interval between boosters.

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What TTCVs can be used for the childhood vaccination schedule?

Tetanus toxoid is available in a single-antigen vaccine (TT) and in combination vaccines against other vaccine-preventable diseases such as diphtheria, pertussis, polio, hepatitis B, and *Haemophilus influenzae* type b.

Many different TTCVs are licensed worldwide. The choice of which TTCV to use and when depends on many factors such as price, supply availability, target age, programmatic simplicity, cold chain capacity, and other vaccines in the national immunization schedule.

National immunization programmes have considerable flexibility in the choice of TTCVs and given the above mentioned factors, it is expected that the same TTCV product may not be used for all six of the childhood doses. Table 2 provides a summary of the TTCV product options that currently exist.

TTCVs can be co-administered with other childhood vaccines. All vaccines that are age-appropriate and consistent with the child’s prior immunization history can be administered during the same visit. However, conjugate vaccines such as Hib (PRP–TT)

**Figure 3**

**WHO recommended vaccination schedule and duration of protection**
and MenA (PsA–TT), unless co-administered with TTCV (i.e. given at the same visit), should be administered at least one month before TTCV.

**WHO recommendations for childhood vaccination for tetanus and diphtheria are the same.**

It is important to note that WHO recommendation for diphtheria childhood vaccination follows the same schedule as tetanus (i.e. 3 primary infant doses of diphtheria toxoid-containing vaccine, plus 3 booster doses as 12–23 months, 4–7 years, and 9–15 years).

**WHO recommendations for childhood vaccination for tetanus and pertussis are aligned.**

After the primary infant series (3 doses), a booster dose of pertussis vaccine is recommended for children aged 1–6 years, preferably during the second year of life (± 6 months after last primary dose), unless otherwise indicated by local epidemiology. This schedule should provide protection for at least 6 years for countries using whole-cell pertussis vaccines (wP). For countries using acellular pertussis (aP) vaccine, protection may decline appreciably before 6 years of age.

Table 2
Tetanus vaccination schedule and TTCV product options

<table>
<thead>
<tr>
<th>Primary series (3 doses)</th>
<th>2\textsuperscript{nd} year of life (12–23 months) (1\textsuperscript{st} booster)(^2)</th>
<th>4–7 years (2\textsuperscript{nd} booster)</th>
<th>9–15 years (3\textsuperscript{rd} booster)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTwP or DTaP(^3)</td>
<td>DTwP or DTaP</td>
<td>DTwP or DTaP DT or Td(^4)</td>
<td>Td TdaP(^5)</td>
</tr>
<tr>
<td>Quadrivalent</td>
<td>Quadrivalent (DTwP-HepB, DTwP-Hib; DTaP-HepB, DTaP-Hib)</td>
<td>Quadrivalent (DTwP-HepB, DTwP-Hib; DTaP-HepB, DTaP-Hib)</td>
<td></td>
</tr>
<tr>
<td>Pentavalent</td>
<td>Pentavalent (DTwP-Hib-HepB; DTaP-Hib-IPV; DTaP-HepB-IPV)</td>
<td>Pentavalent (DTwP-Hib-HepB; DTPaP-Hib-IPV; DTaP-HepB-IPV)</td>
<td></td>
</tr>
<tr>
<td>Hexavalent</td>
<td>Hexavalent (DTaP-Hib-HepB-IPV)</td>
<td>Hexavalent (DTaP-Hib-HepB-IPV)</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) WHO-prequalified vaccine options in regular font, non-prequalified vaccines in italics.
\(^2\) WHO recommends that a pertussis containing combination vaccine is preferred for the TTCV booster administered in the second year of life (2YL).
\(^3\) In most countries the use of DTP for the primary series has been replaced by quadrivalent or pentavalent vaccines.
\(^5\) Only acellular pertussis (aP) should be used for persons ≥7 years of age.

For up-to-date product information on the different TTCVs that are prequalified\(^7\) by WHO check:

For up-to-date information on UNICEF Supply Division vaccine prices see:

**Why use tetanus-diphtheria containing combination vaccines (DT/Td) rather than TT?**

To avoid the threat of diphtheria outbreaks and to improve protection against diphtheria, since 1998 WHO has recommended that all countries replace TT with...
Td for vaccination of reproductive age/pregnant women, older children and adolescents. The WHO position paper on diphtheria vaccine provides the background for this recommendation.

Although simply replacing TT with Td vaccine provides dual protection with negligible programmatic shift and marginal increase in cost, globally, however, this replacement has been incomplete and somewhat slow. As of May 2018, 133 of 194 countries made the change from TT to Td, which has been proven to be safe and cost effective. Yet, there are still about 61 countries remaining to fully implement the recommendation in order to ensure longer lasting protection against diphtheria. In the light of the important public health benefits of replacing TT with Td, as of January 2020 UNICEF will no longer procure and/or supply TT vaccine.

**Box 2**

WHO/UNICEF Guidance on TT-Td replacement

**WHO/UNICEF Guidance Note on replacing TT with Td vaccine (12 September 2018)** – provides background, rationale and practical action steps to make change from TT to Td.


Are TTCVs safe?

TTCVs have an excellent safety record. Mild local reactions (e.g. redness, swelling, pain) and systemic reactions (e.g. fever ≥38°C, irritability, malaise) are common after both primary and booster TTCV administration. In general, combination vaccines do not result in increased frequency and/or severity of adverse reactions compared to the individual vaccines given alone. Serious reactions, for example anaphylaxis or brachial plexus neuritis are very rare or extremely rare respectively.

For further information on TTCV vaccine safety refer to [WHO position paper on tetanus vaccine](https://apps.who.int/iris/bitstream/handle/10665/258681/WER9231.pdf) and a WHO information sheet [Observed rate of adverse reactions for diphtheria, pertussis, and tetanus vaccines](https://www.who.int/vaccine_safety/initiative/tools/DTP_vaccine_rates_information_sheet.pdf).
What strategies can be used to achieve high coverage of the primary series of TTCV?

The first three primary doses of TTCV in the infant vaccination schedule are most commonly given at 6, 10 and 14 weeks, or 2, 3, 4 months, or 2, 4 and 6 months. These doses are the foundation for building long-term immunity to tetanus, and therefore it is essential that national immunization programmes strive to achieve the GVAP coverage goal of ≥90% (with at least 80% coverage in every administrative unit).

High vaccination coverage depends on well-functioning immunization programmes, strong health systems and acceptance/demand from the population. There exist many strategies and resources to assist countries to improve their infant vaccination coverage (see Box 3). Key among these is the Reaching Every District (RED) approach.

**Reaching Every District (RED) approach***

The RED approach highlights the following five operational components to increase vaccination coverage:

1. **Planning and management of resources** – for better managing of human, material and financial resources.
2. **Reaching all eligible populations** – for improving access and use of immunization and other health services by all children, adolescents and adults.
3. **Monitoring and using data for action** – for analyzing the data at all levels to direct the programme in measuring progress, identifying areas needing specific interventions and making practical revisions to plans.
4. **Supportive supervision** – for regular on-site capacity-building, feedback, and follow-up with health staff.
5. **Engaging with communities** – for partnering with communities to promote and deliver immunization services which best fit local needs.

*WHO Regional Office for Africa (2017). Reaching Every District (RED). Brazzaville: WHO Regional Office for Africa*
Box 3
WHO resources for increasing vaccination coverage

Global Routine Immunization Strategies and Practices (GRISP) – contains a comprehensive framework of strategies and practices for routine immunization, and nine transformative investments to achieve better immunization programme outcomes.

Available online at: https://apps.who.int/iris/bitstream/handle/10665/204500/9789241510103_eng.pdf.

Reaching Every District (RED), 2017 Edition – a guide to increasing coverage and equity in all communities in the African Region. Its purpose is to support countries to plan and implement the five components of the RED approach.


Reducing Missed Opportunities for Vaccination (MOV) – resource guides for reducing MOV by making better use of existing vaccination sites and existing health contacts.


Periodic Intensification of Routine Immunization (PIRI) – a paper which summarizes a wide array of PIRI experiences, based on a desk review of available documents and grey literature.

Available online at: https://www.who.int/immunization/programmes_systems/policies_strategies/piri_020909.pdf.
**Immunization in Practice (2015 revision)** – a practical guide targeted at district and health facility staff, building upon the experiences of polio eradication.

Available online at: https://apps.who.int/iris/bitstream/handle/10665/193412/9789241549097_eng.pdf.

**Guide to Tailoring Immunization Programmes (2013)**
– provides tools to identify susceptible populations, determine barriers to vaccination and implement evidence-based interventions in order to assist national immunization programmes design targeted strategies that increase uptake of infant and childhood vaccinations.


**Training for Mid-Level Managers (MLM)** – 8 modules on the operational components of the routine immunization programme.

What strategies and opportunities can be used for TTCV booster doses?

In addition to completing the primary series, WHO recommends that three booster doses of TTCV should be administered as follows:

(i) 1st booster: in the 2nd year of life (12–23 months of age)
(ii) 2nd booster: between 4–7 years of age
(iii) 3rd booster: between 9–15 years of age.

In many low-income countries, national immunization programmes do not have any booster doses of vaccines in their current schedules. Therefore, experience providing vaccination to older target age groups may be limited. While there is increasing attention of the need to vaccinate throughout the life-course, extending vaccination beyond the first year of life can be a challenging step which takes special effort and planning to be successful.

In many ways, introducing a booster dose can be similar to the introduction of a new vaccine – it requires all of the same processes such as decision-making, policy revision, supply forecasting, cold chain capacity assessment, training of health staff, revision of home-based records (child vaccination cards), adaptation of recording and reporting forms/systems, advocacy, communication and social mobilization, strengthened supervision, etc. (see What activities need to be undertaken to ensure successful roll out of a routine childhood 6-dose TTCV schedule?, page 35).

Deciding on the best age and strategy to deliver a TTCV booster dose involves careful review of the opportunities and challenges. Each country will have its unique context and synergies with other programmes/interventions to consider. The possible platforms to build upon for each of the TTCV boosters are highlighted below.

(i) 1st TTCV booster in the second year of life (2YL platform)

Providing a TTCV booster between 12–23 months aligns with other WHO childhood vaccination recommendations such as the 2nd dose of measles-containing vaccine (MCV2), meningitis A, and alternative 2+1 schedules for PCV10, as well as boosters of pertussis and diphtheria.11 Additionally, countries may have a well-child visit, vitamin A supplementation, and/or deworming contacts scheduled within this age range.

Importantly, a 2YL vaccination contact also provides the opportunity to catch up children on doses of any vaccines they may have missed earlier. In this way, the coverage levels of fully immunized children by 2 years of age (FIC2) can be increased and the individual/public health benefit of greater population immunity realized.

Comprehensive guidance documents already exist for introducing a routine second dose of measles vaccine, and for 2YL vaccination (see Box 4). These materials contain

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10 Alternative PCV 2+1 schedule: 2 doses of PCV before 6 months of age, plus booster dose at 9-15 months of age.
detailed information which is relevant and helpful for planning and implementing a 1st TTCV booster in the 2YL.

Regarding the options of the vaccine product that can be used for the 1st TTCV booster please refer to Table 2.

WHO recommends that both pertussis and diphtheria boosters should be given to children in the second year of life, so the use of TTCV combination vaccines that include these antigens is strongly encouraged.

For children who are 12–23 months of age, combined vaccines with diphtheria antigen should contain full strength paediatric formulation (i.e. capital “D”, not small “d”).

Box 4
WHO resources for planning the introduction of interventions in the routine immunization programme in the second year of life (2YL)

A Guide to Introducing a Second Dose of Measles into Routine Immunization Schedules (2013) – provides guidance to support policy discussions and operational aspects of the introduction of a second dose of measles vaccine into the routine immunization schedule.

Available online at: https://apps.who.int/iris/bitstream/handle/10665/85900/WHO_IVB_13.03_eng.pdf.

Establishing and strengthening immunization in the second year of life: Practices for immunization beyond infancy (2018) – provides practical guidance on how to improve vaccination coverage during a scheduled visit in the second year of life that may include other child health interventions.

Available online at: https://apps.who.int/iris/bitstream/handle/10665/260556/9789241513678-eng.pdf.
(ii) 2nd TTCV Booster at 4–7 years

For many national immunization programmes, providing vaccination between 4–7 years of age can be an entirely new endeavour. The same introduction processes described above for the 1st TTCV booster dose will need to be considered.

Depending on a country’s programme and capacity, reaching children 4–7 years of age may be challenging. If vaccination is to be delivered through fixed-site services (either clinic-based or outreach) then an investment in information, education, and communication (IEC) will be necessary to ensure mothers/caregivers understand the need to bring their older children back for vaccination. This IEC effort will need to be continued for many years in order to change behaviours and assure demand and ultimately high coverage.

A day-care/crèche- or school-based vaccination strategy is an option, as 4–7 years is the age when many children are in day-care or begin primary school. This may also be an opportunity to implement school entry vaccination screening at the time of enrolment, to determine if children of this age have been fully vaccinated. Children with incomplete vaccination must be referred to health services to determine eligibility and receive their missing vaccine doses. Such an approach will require strong collaboration with the Ministry of Education, policy directives, and possibly a legislative or legal framework to empower the implementation. Depending on the national context, issues of parental consent may also need to be addressed if vaccination is to take place in nurseries/day-care/crèches/primary school because children will be unaccompanied by their mothers/caregivers, unlike for infant vaccination. See Box 6 for WHO document on consent to vaccination.

There are multiple factors to consider when deciding to implement vaccination in schools or nurseries/day-care/crèches. These are further discussed in the section on the 3rd TTCV booster dose below.

(iii) 3rd TTCV Booster at 9–15 years

Reaching children/adolescents in the 9–15 year old age group with a booster dose of TTCV is particularly important because it is this age group which is approaching their reproductive years. Girls especially need to have their tetanus immunity strengthened.
by a 3rd booster dose to enable the transfer of antibodies to their newborn (protection at birth) during future pregnancies. For coverage equity, boys also need to be protected against tetanus to avoid any future risk of exposure through contamination of wounds from medical interventions, occupational risks or accidents.

Moreover, when both boys and girls are vaccinated, it can help avoid false rumours about female sterilization and contraception which have sometimes accompanied tetanus vaccination activities that targeted girls and women only.

For the 3rd TTCV booster between 9–15 years, there are two current platforms that can provide opportunities for integration. Within the immunization programme there is the provision of HPV vaccine (which targets roughly the same age group). More broadly, there is the global momentum for improving adolescent health (see Box 5).

**WHO recommendations for HPV vaccination* and tetanus 3rd booster dose overlap**

For girls 9–14 years, WHO recommends a 2-dose schedule of HPV vaccine with a 6-month interval between doses. An interval no greater than 12–15 months is suggested in order to complete the schedule promptly and before becoming sexually active. If the interval between doses is shorter than 5 months, a third dose should be given at least 6 months after the first dose.

A 3-dose schedule (0, 1–2, 6 months) should be used for all HPV vaccinations initiated ≥15 years of age. Three doses are also needed for those younger than 15 years who are known to be immunocompromised and/or HIV-infected.

**Opportunities should be sought to link the introduction of HPV vaccination to other vaccinations carried out at the same age (e.g. diphtheria and tetanus vaccination) and programmes targeting young people (e.g. through school and adolescent health services).**


The vast experience from pilot and/or nationwide HPV vaccine introductions can help to inform the decision, design, and planning for an adolescent TTCV booster (see Box 6). Where HPV vaccination activities are already part of the national immunization programme, the 3rd dose of TTCV can be integrated and delivered together with HPV, although for TTCV it is necessary to vaccinate both boys and girls. As of October 2018, more than 85 countries have introduced HPV vaccine, and in some Td and other vaccines are co-administered during the same visit. But many countries that have introduced HPV vaccine have not yet taken advantage of the opportunity to link HPV and Td vaccination.
Box 5

Global commitment to adolescent health

There are few interventions targeting young adolescents, and those that do exist are not adequately reaching them. This is because the number of contacts with adolescents in the health system is generally low.

For years, the unique health issues associated with adolescence have been little understood or in some cases, ignored. But this has now changed.

Adolescent health and development was made an integral part of the Global Strategy for Women’s, Children’s and Adolescents’ Health (2016-2030) (The Global Strategy) in support of the Sustainable Development Goals (SDGs).


The Global Accelerated Action for the Health of Adolescents (AA-HA!): Guidance to Support Country Implementation (2017) provides technical guidance to policy-makers and programme managers as they respond to the health needs of adolescents in their countries.

Available online at: https://apps.who.int/iris/bitstream/handle/10665/255415/9789241512343-eng.pdf.

A multimedia interactive report, Health for the World’s Adolescents: A Second Chance in the Second Decade (2014) provides global and regional overview of health-related behaviours and conditions among adolescents, pulls together WHO recommendations and guidance, and proposes key actions and approaches that would strengthen national responses to adolescent health issues.

This report is available online at: http://www.searo.who.int/indonesia/documents/health-for-world-adolescent-who-fwc-mca-14.05-eng.pdf.
Box 6
HPV vaccine introduction resources to inform planning and implementation of TTCV adolescent booster

**A guide to introducing HPV vaccine into national immunization programmes (2016)** – provides policy and operational aspects of HPV vaccine introduction and up-to-date references on global policy and technical and strategic issues.

Available online at: [https://apps.who.int/iris/bitstream/handle/10665/253123/9789241549769-eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/253123/9789241549769-eng.pdf).

Resources on delivery strategies:

**Scaling up HPV vaccine introduction (2016)** – provides a summary of country-reported experiences introducing HPV vaccine in their national immunization programme.

Available online at: [https://apps.who.int/iris/bitstream/handle/10665/251909/9789241511544-eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/251909/9789241511544-eng.pdf).

**HPV Vaccine Lessons Learnt** – comprehensive review of HPV vaccine delivery experiences across 46 low- and middle- income countries.


**HPV Vaccine Communication: Special considerations for a unique vaccine (2016 update)** – provides communication guidance for countries introducing HPV vaccine at the national or subnational levels.

There are several commonly used strategies for HPV vaccination which would be adaptable for TTCV booster delivery:
— vaccine delivery at health-care facilities (may be in conjunction with schools)
— vaccine delivery through outreach (including school-based outreach)
— vaccine delivery through campaigns.

**Vaccination at health facilities**

Adolescent vaccination at health facilities has been shown to achieve more coverage if offered as “vaccination days” with minor incentives for those who attend (such as short waiting times, music, discussion groups, or videos in the waiting areas).

However, a fixed-site, health-care facility delivery strategy may not be effective if there are barriers for adolescents to access the health-care facility, for example, if opening hours are not convenient, or if the health facility is far away.

Schools can have an active role in a facility-based delivery strategy. For example, in some countries, schools are notified on a specific day to bring children/adolescents for vaccination to the health facility or nearest scheduled outreach session.
Vaccination through outreach

In the context of vaccine delivery, outreach refers to any strategy that requires health workers to leave their facility in order to transport and deliver vaccination services to a variety of permanent or temporary sites close to large numbers of the target population. Some examples of outreach venues are community centres, school buildings, markets or places of worship, if appropriate.

School-based (outreach) strategy

In most countries, >90% of both boys and girls attend primary school. In countries where school health programmes exist and a designated healthcare worker provides regular health services either at the school or at the health facility, the operational costs of adding TTCV vaccine delivery to an existing and already funded school health programme infrastructure may be minimal, assuming the costs for salary and transport are already provided in the health budget.

If, however, a school health programme with designated staff does not exist, a school-based delivery strategy may require the health facility staff to travel away from the health centre to reach all the schools in the catchment area. This is likely to require additional resources and can be disruptive to delivery of regular services. It may also be inefficient if school enrolment is low. In this case, special complementary efforts to reach and vaccinate out-of-school adolescents with TTCV would be needed.

The learning from measles, polio and HPV vaccination is that school-based programmes can be highly successful. If implemented in a campaign mode they may be costly, however, a school platform can deliver benefits across interventions and presents an opportunity to share costs. It should be noted that school children are exposed to a tetanus risk by participating in various school activities (e.g. sports, gardening). Therefore, TTCV should be offered to school children of both sexes. Before initiating a school-vaccination programme, countries need to be able to assess the capacity, strengths, and weaknesses of their school and health systems to support such programmes (see Box 7).

Box 7
WHO publication for readiness assessment of schools to support vaccination programmes

School Vaccination Readiness Assessment Tool – provides methodology specifically designed to assess country-wide readiness to implement school vaccination. It also provides information useful for assessing and subsequently improving broader school health services.

Interim strategy: using schools to catch up and deliver three booster doses

A routine 6-dose TTCV childhood schedule is the preferred tetanus vaccination strategy because it offers continuous protection throughout childhood, elicits a stronger immune response, and results in early life-long protection for both boys and girls.

While countries work towards building a routine childhood 6-dose TTCV schedule, some interim strategies may be considered specifically targeting young children/adolescents so that they are fully protected against tetanus prior to entering their reproductive years. If high coverage can be achieved, this approach can contribute significantly to sustaining MNTE, thus reducing thus the need for vaccination through ANC clinics and SIAs. As an alternative interim strategy, the complete TTCV 3-dose booster series with Td vaccine could be delivered in primary school using the multi-age cohort schedule proposed below. After 3 years of implementation, the older grades will have been caught up and boosters will need to be administered only to grades A, B and C.

<table>
<thead>
<tr>
<th>Level of enrolment</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4 and beyond</th>
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</thead>
<tbody>
<tr>
<td>Grade A</td>
<td>1st booster dose</td>
<td>1st booster dose</td>
<td>1st booster dose</td>
<td>1st booster dose</td>
</tr>
<tr>
<td>Grade B</td>
<td>1st booster dose</td>
<td>2nd booster dose</td>
<td>2nd booster dose</td>
<td>2nd booster dose</td>
</tr>
<tr>
<td>Grade C</td>
<td>1st booster dose</td>
<td>2nd booster dose</td>
<td>3rd booster dose</td>
<td>3rd booster dose</td>
</tr>
<tr>
<td>Grade D</td>
<td>1st booster dose</td>
<td>2nd booster dose</td>
<td>3rd booster dose</td>
<td></td>
</tr>
<tr>
<td>Grade E</td>
<td>2nd booster dose</td>
<td>3rd booster dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade F</td>
<td>3rd booster dose</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

High enrolment and attendance, plus good record keeping in order to track doses and children who change or drop-out of school are essential for success.

Vaccination through campaigns

In some instances there may be benefits or opportunities to deliver a TTCV booster through a campaign. It may be possible to include a TTCV booster as part of another planned campaign such as Child Health Days/Weeks, measles-rubella vaccination campaigns targeting up to 15 year olds, or even invite the adolescent boys to attend tetanus supplementary immunization campaign planned for reproductive age women (preferably using Td). Provided that resources are available, countries may wish to organize a catch-up campaign for the 3rd TTCV dose booster targeting all 9–15 year old children, before reverting to a routine health-facility based vaccination strategy to deliver the booster dose to all future cohorts of 9 year olds.
In countries with very small and/or hard-to-reach populations (for example, island states) the use of a campaign strategy for TTCV adolescent booster may be the most practical and cost-effective. This strategy could be repeated every 5–6 years to ensure complete coverage of the next cohort of adolescents 9–15 years.

In order to boost routine coverage in all children, WRA, and pregnant women, countries may opt for a “hybrid” approach, referred to as periodic intensification of routine immunization (PIRI). PIRI activities are time-limited, and depending on local planning and flexibility to arrange outreaches, may be organized once or twice a year. During PIRI, routine services are intensified and expanded to include not only fixed and outreach strategies but also many additional vaccination posts and possibly house-to-house services.

Table 3 provides a summary of considerations for different TTCV 3rd dose booster delivery strategies which are also applicable to the 2nd booster for 4–7 year olds. In practice, a balance of the pros and cons will need to be made. Countries may need to consider trade-offs between strategies that maximize coverage and those that are most feasible, affordable and sustainable. Ultimately, a combination of strategies may be required to achieve high coverage while optimizing resources.

Regardless of the strategy applied, doses should be correctly tallied and recorded in facility-based administrative records and recorded on the appropriate home-based child or adolescent record. Long term retention of records should be ensured so that the history of tetanus vaccination can be verified. WHO has produced a number of resources that provide practical experience and guidance on the design and use of home-based records (see Box 8).

NOTE: During the transition period, as countries move away from the high-risk SIA approach of vaccinating women of reproductive age (except in selected hard-to-reach areas with limited health services) and work towards providing 3 childhood booster doses of TTCV, it may be necessary to catch up young children/adolescents who were not able to benefit from the provision of the first two TTCV boosters (i.e. at 12–23 months and 4–7 years). This is discussed in section Vaccination through outreach (page 26).
Box 8
WHO resources on home-based records

Practical Guide for the Design, Use and Promotion of Home-Based Records in Immunization (2015) — In response to a recognized need for more guidance on the content and design of home-based records, WHO has developed a practical guide to provide direction to immunization programme managers and national health programmes on how to improve the use and design of home-based records, and serve as a reference with developing or revising home-based records.


The home-based vaccination record repository — An online repository for home-based vaccination records, including national immunization or child health cards, is maintained by UNICEF to support the free and open exchange of information related to home-based record content and design, with the aim of improving child health outcomes.


WHO recommendations on home-based records for maternal, newborn and child health (2018) — This report summarizes the final recommendation and the process for developing the guideline on home-based records for maternal, newborn and child health. The primary audience for the guideline is policy makers and health programme managers of MNCH and immunization programmes in ministries of health where decisions are made and policies created on the use and implementation of home-based records.

<table>
<thead>
<tr>
<th>Considerations</th>
<th>Health facility</th>
<th>Outreach</th>
<th>Campaign</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Access</strong></td>
<td>Adolescents must come to health centre (may not be successful if the adolescents are shy; requires facilities to be “adolescent friendly”) May need coordination with schools to encourage and release adolescents to go to facility Parents may be present at time of vaccination Does not require health workers to leave Working hours may need to be adapted to be made more convenient if the health facility is far away</td>
<td>A variety of locations is possible May need special communications effort to make sure adolescents attend (e.g. through social media) Requires health workers to leave health facility but can be part of regular health facility outreach</td>
<td>Large number of adolescents can be vaccinated at the same time Requires health workers to travel to school Parental consent process Teachers can assist with vaccination sessions</td>
</tr>
<tr>
<td><strong>Equity</strong></td>
<td>Accommodates in- and out-of school adolescents</td>
<td>In- and out-of school adolescents</td>
<td>In- and out-of school adolescents</td>
</tr>
<tr>
<td><strong>Community mobilization</strong></td>
<td>May need intensive mobilization for adolescents to attend, partnering with communities</td>
<td>Using same outreach locations as for infant vaccination may make mobilization easier</td>
<td>Needs comprehensive strategy and intense community mobilization</td>
</tr>
<tr>
<td><strong>Frequency of vaccination</strong></td>
<td>Continuous, all year round</td>
<td>Only when outreach is planned/occurs</td>
<td>Annual or periodically, depending on the number of cohorts targeted</td>
</tr>
<tr>
<td><strong>Vaccine supply</strong></td>
<td>Requires continuous available supply with other routine vaccines (ensure planning and placement of orders)</td>
<td>Challenging to know exact number of adolescents who will attend outreach session</td>
<td>Large volume of vaccine needed over short duration Distribution challenges - must be able to redistribute/resupply quickly during campaign</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Delivery strategy</th>
<th>Community outreach</th>
<th>School-based outreach</th>
<th>Campaign</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Access</strong></td>
<td>A variety of locations is possible May need special communications effort to make sure adolescents attend (e.g. through social media) Requires health workers to leave health facility but can be part of regular health facility outreach</td>
<td>If enrolment is high, larger number of adolescents vaccinated at the same time Requires health workers to travel to school Parental consent process Teachers can assist with vaccination sessions</td>
<td>Large number of adolescents can be vaccinated at the same time Requires health workers to travel to school Parental consent process Teachers can assist with vaccination sessions</td>
</tr>
<tr>
<td><strong>Equity</strong></td>
<td>In- and out-of school adolescents</td>
<td>In-school adolescents only</td>
<td>In- and out-of school adolescents</td>
</tr>
<tr>
<td><strong>Community mobilization</strong></td>
<td>Using same outreach locations as for infant vaccination may make mobilization easier</td>
<td>Schools can help facilitate sensitization and mobilization of parents/communities</td>
<td>Needs comprehensive strategy and intense community mobilization</td>
</tr>
<tr>
<td><strong>Frequency of vaccination</strong></td>
<td>Only when outreach is planned/occurs</td>
<td>Requires regular visits to all schools (frequency will depend on the number of school classes targeted for vaccination)</td>
<td>Annual or periodically, depending on the number of cohorts targeted</td>
</tr>
<tr>
<td><strong>Vaccine supply</strong></td>
<td>Challenging to know exact number of adolescents who will attend outreach session</td>
<td>Enrolment lists can facilitate estimate of needed vaccine and related supplies</td>
<td>Large volume of vaccine needed over short duration Distribution challenges - must be able to redistribute/resupply quickly during campaign</td>
</tr>
<tr>
<td>Considerations</td>
<td>Health facility</td>
<td>Delivery strategy</td>
<td>Outreach</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Community outreach</td>
</tr>
<tr>
<td>Cold chain management</td>
<td>Cold chain available at health centre</td>
<td>Vaccine carriers must be prepared to maintain cold chain</td>
<td>Vaccine carriers must be prepared to maintain cold chain</td>
</tr>
<tr>
<td>Integration with other interventions</td>
<td>With HPV (and other vaccines); may help to strengthen Adolescent Friendly Health Services</td>
<td>With HPV; possible co-delivery with interventions of short duration</td>
<td>With HPV; possible co-delivery with short-duration interventions possible; synergistic opportunities Integration with school health platform may be possible</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Tally sheets and registers available, as well as home-based records (HBRs)</td>
<td>Tally sheets, registers and HBRs available and taken to the outreach Persons asked to bring their HBRs, as available</td>
<td>Tally sheets, registers and HBRs available and taken to the school Persons asked to bring their HBRs, as available School enrolment lists can facilitate identifying and recording vaccinated students.</td>
</tr>
<tr>
<td>Cost</td>
<td>Low, when supported by national health budget</td>
<td>Medium-High (depends on use of existing outreach sessions that are already planned and funded in health budget)</td>
<td>Medium-high (depends on school enrolment, and on use of existing outreach sessions that are already planned and funded or if additional resources are required for healthcare workers to travel to schools)</td>
</tr>
</tbody>
</table>

Note: A combination of strategies may be needed to achieve high coverage while optimizing resources and to include out-of-school/hard-to-reach/vulnerable targeted adolescents. Strategies may also vary throughout a country, based on local/provincial/district characteristics or opportunities.
Is it necessary to introduce all three TTCV booster doses into the immunization schedule together at the same time?

For sustainability, and to develop early long-term protection, countries should strive towards a routine childhood vaccination schedule that provides 6-doses of TTCV by adolescence. This will provide protection throughout the reproductive years thereby sustaining MNTE, and beyond.

**Benefit of vaccinating early**
- Studies show that children develop higher antibody levels than adults.
- The immune response to TTCVs tends to decrease with age.

However, it is recognized that it may be difficult for many national immunization programmes in low-income countries to rapidly introduce all three of the TTCV booster doses at the same time, particularly if their programmes do not already have policies and activities in place to vaccinate school-age children. Countries may build their tetanus schedules incrementally, one booster at a time, also considering other new vaccine introductions (e.g. MCV2, HPV) as platforms for efficiently adding a TTCV booster.

Each and every additional booster dose of TTCV in childhood is of benefit. Although tetanus antibody levels are high after 3 primary TTCV doses in infancy, levels decline over time. A booster dose in the 2nd year of life rapidly increases antibody levels. Repeat boosting with two more doses by adolescence elicits a robust humoral immune response lasting decades (Figure 4).

**Figure 4**
Antibody response to TT and duration of immunity after 6 properly spaced doses

What is the catch-up schedule for children >1 year of age or adolescents who missed or did not complete the primary series of TTCV?

If tetanus vaccination is started ≥1 year of age (i.e. no primary series received) then only 5 appropriately spaced doses of TTCV are required to obtain long-term protection. The 5-dose “catch-up” schedule for children >1 year of age, adolescents and adults (including pregnant women) with no previous immunization against tetanus is the same for males and females and is as shown in Table 4.

Table 4
Catch-up vaccination schedule for previously unvaccinated and vaccine options according to age

<table>
<thead>
<tr>
<th>Vaccine (age-appropriate)</th>
<th>Minimum interval from the most recent dose administered</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; dose</td>
</tr>
<tr>
<td>1–4 years: DTwP, DTaP, or DT</td>
<td>As early as possible</td>
</tr>
<tr>
<td>4–7 years: DTwP, DTaP, Td, or DT</td>
<td></td>
</tr>
<tr>
<td>&gt;7 years: Td or TdaP</td>
<td></td>
</tr>
</tbody>
</table>

The reason that older age groups need only 5 doses for catch up is because the third dose is given 6 months after the second dose, thereby eliciting a stronger antibody response. In infants (i.e. <1 year of age) the first three doses are given closer together (i.e. minimum interval of 4 weeks between doses), mainly to ensure immunity to pertussis and protect infants who are at risk for complications or death if they get pertussis at such a young age.

Generally, if the country is using a DTP-containing vaccine with a whole-cell pertussis (wP) component then children up to 7 years of age who are previously unvaccinated would benefit from receiving a catch-up vaccination with DTwP. Those who are 7 years or older can receive Td because vaccines containing wP component are not recommended for those ≥7 years.

For countries using aP combinations, these can be given to all age groups. Since the duration of protection of aP against pertussis is shorter than wP, more boosters of aP containing vaccines may be required.
In some countries of Eastern and Southern Africa, several cases of tetanus following male circumcision for the prevention of HIV infection have highlighted the tetanus immunity gap in adolescent and adult males.\(^\text{13}\) See Box 9 for vaccination opportunities and guidance specific for these situations.

**Box 9**

**Voluntary male circumcision (VMMC) for HIV prevention and tetanus vaccination for adolescent boys and adult males**\(^\text{14}\)

WHO/UNAIDS recommends male circumcision as an intervention for HIV prevention in countries and regions with heterosexual epidemics, where there is high HIV burden and low male circumcision prevalence, and where there is limited contact with the health services. VMMC service delivery provides an opportunity to reach adolescent boys and adult men with relevant services, including vaccination with TTCV.

Methods for male circumcision have different risks for tetanus which should be mitigated. Several surgical methods are available including conventional and device-based circumcision.

For **conventional surgical** male circumcision, depending on the country context and the individual’s vaccination record, a dose of TTCV may be added at the time of or prior to surgery. Another dose, with an interval of at least 4 weeks, could be given at the follow-up visit. The client should be referred to a health facility to receive a third dose 6 months later.

Circumcision using the **elastic collar compression (Day7)** method has the greater risk of tetanus compared to conventional surgery and should be undertaken only if the client has been adequately protected against tetanus prior to device placement.

- For those not previously vaccinated, 2 doses of TTCV should be administered at least 4 weeks apart, with the second dose at least 2 weeks before placement of the device.
- If an individual has documented evidence of 3 doses received in infancy, and 1 dose during adolescence or adulthood, a booster dose of TTCV should be given at least 2 weeks before the device placement.

Individuals should be provided with and educated to keep their vaccination record/card.

---


What activities need to be undertaken to ensure successful roll out of a routine childhood 6-dose TTCV schedule?

Expanding the TTCV schedule to include three booster doses requires comprehensive planning. In many ways, this effort will follow the processes and activities that countries use for introducing a new vaccine (see Box 10).

**Box 10**
**WHO guidance on new vaccine introduction**

**Principles and considerations for adding a vaccine to a national immunization programme: From decision to implementation and monitoring (2014)** – resource document for countries that explains the principles, issues and processes to be considered when introducing a new vaccine into a national immunization programme.


Rather than repeating in detail, some of the key activities and reference to additional resource materials is summarized below.

**Decision-making and policies:**
- Involve the National Immunization Technical Advisory Group (NITAG) or its equivalent.
- Review policies and legislation concerning vaccination of school children.
- Consider consent processes.
- Involve other ministries (e.g. education, finance, etc.).
- Obtain endorsement from inter-agency coordinating committee (ICC) where available, and engage key stakeholders, such as paediatricians’, midwives’ and nurses’ associations.
- Estimate costs, prepare detailed introduction plan, update cMYP, and secure financial resources (submit applications to donors for funding, if applicable).

**Forecasting and procuring supply:**
- Estimate target populations using population data from various sources [UN Population Division (see Annex 2) school enrolment, census, other programmes, etc.].
- Estimate number of doses and injection equipment needed.
— Verify cold chain capacity and distribution schedule.
— Procure vaccine and injection equipment (using UNICEF Supply Division Procurement Services if needed).
— Procure tally sheets, registers and home-based records as needed.

**Microplanning:**
— Complete district level microplanning.
— Prepare and compile budgets.
— Develop a plan for using the TTCV booster contacts to provide catch up of previously missed doses of other childhood vaccines and estimate the supply needs of these other vaccines.

**Recording and reporting:**
— Adapt/revise home-based records/immunization cards, recording forms and systems.

**Training and supportive supervision:**
— Develop training materials and job aids.
— Undertake training of health workers.
— Distribute/communicate any revised policy directives.
— Revise supervision checklist and strengthen supportive supervision.
— Incorporate revised TTCV schedule into training curriculum of academic programmes for doctors, nurses and other healthcare professionals.

**Communications/hesitancy:**
— Develop a communication plan\(^{15}\) including a crisis management plan\(^{16}\), following Knowledge, Attitude and Practice (KAP) studies where appropriate (see Box 11).
— Identify target audiences (including media, parents, school teachers, etc.).
— Develop and test key messages (see Box 12).
— Anticipate rumours and proactively address vaccine hesitancy and possible anxiety-related reactions (see Box 13).

**Monitoring and evaluation:**
— Adapt immunization coverage wall monitoring charts, and monthly coverage reporting processes to include booster doses of TTCV (see Chapter 5 for more information).
— Review monthly reporting of doses administered and coverage to assess performance and need for corrective action.

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Consider doing a special post-introduction evaluation (PIE)\(^\text{17}\), 6-months after implementation, or include in the next Immunization Programme Review.

**Box 11**

**Crisis communications plan and vaccine safety**

Countries should prepare crisis communication plans that allow for a rapid and effective response to adverse events following immunization (AEFI), anti-vaccine movements, and any allegation that can have a negative effect on public acceptance of TTCVs and trust in the immunization programme.

Countries should have in place the basic elements of a crisis plan, which may include:

- an AEFI committee at different levels which can meet immediately to discuss and plan action;
- clear channels of communication with various media;
- engaging with credible opinion and traditional leaders to address misconceptions and rumours;
- training of health workers on inter-personal communication and on how to communicate with the public about AEFI and safety concerns;
- an AEFI action plan with specific roles for immunization programme partners.

**Box 12**

**Examples of key communication messages on TTCV boosters**

- The organism that causes tetanus is present everywhere in the environment.
- Tetanus is deadly at any age and vaccination is the key method for protection.
- TTCV boosters for young children and adolescents are needed to give long-term protection to girls and boys against tetanus.
- Each additional booster vaccination against tetanus extends protection lasting for many more years.
- Everyone needs to be protected, but tetanus vaccination is especially important to prevent newborns and mothers getting tetanus during delivery (use local names for MNT).
- TTCV is safe and has been used around the world for many decades.
- TTCV boosters are available free of charge at (location) (date, time).
- Three boosters are needed for long-term protection at ages 12–23 months, 4–7 years and at 9–15 years.
- The government supports TTCV booster vaccination and has added it to the national immunization schedule.

\(^{17}\) Given the burden of multiple assessment and review exercises, WHO no longer recommends that a PIE should be conducted after every new vaccine introduction (unless the vaccine product or strategy is drastically different from current practice). All programmatic assessments should ideally be combined into one comprehensive EPI Programme Review and performed only every 3–5 years.
Box 13
WHO resources on vaccine safety and AEFI communication

**WHO e-Learning Course in Vaccine Safety (2013)** – remote training package developed as a course on Vaccine Safety Basics to help health workers understand the origin and nature of adverse events, the importance of pharmacovigilance, and risk and crisis communication.


**Vaccine Safety Events: Managing the Communications Response (2013)** – provides practical, informative strategies and tools to help plan and manage a communications response following a vaccine-related event in a local community, at the national level, or beyond.


**How to respond to vaccine deniers in public (2016)** – based on psychological research on persuasion, on research in public health, communication studies and on WHO risk communication guidelines, this document provides basic broad principles for a spokesperson of any health authority on how to respond to vocal vaccine deniers.


For more resources on building and restoring confidence in vaccines and vaccination in routine work and in crisis, see Vaccine safety communication library available online at: [http://www.euro.who.int/en/health-topics/disease-prevention/vaccines-and-immunization/publications/vaccine-safety-communication-library](http://www.euro.who.int/en/health-topics/disease-prevention/vaccines-and-immunization/publications/vaccine-safety-communication-library).
CHAPTER 3

Antenatal care (ANC) contacts and tetanus vaccination status of pregnant women
In this chapter you will learn:

• The role of vaccinating pregnant women and how this will change as countries establish the 6-dose routine child/adolescent schedule;

• The current WHO recommendations for antenatal care (ANC) contacts;

• How to screen and verify the tetanus vaccination status of pregnant women;

• What records/cards pregnant women need to keep;

• What “Protection at Birth” (PAB) means and why it is important;

• Routine administrative TTCV2+ coverage monitoring.

You can use this information to:

• Plan how the ANC and EPI programmes can work together to protect against tetanus;

• Train health workers to screen correctly to determine what dose(s), if any, a pregnant women needs;

• Improve the use and retention of home-based records/cards;

• Ensure PAB and TTCV2+ coverage monitoring is implemented and calculated correctly.
What is the role of vaccinating pregnant women and how will this change as countries establish the 6-dose routine child/adolescent schedule?

In order to achieve and sustain MNTE, countries must ensure that at least 80% of pregnant women in every district are fully vaccinated against tetanus. Pregnant women can contract tetanus during unclean miscarriage, abortion, and childbirth.

**Maternal tetanus:** Tetanus occurring during pregnancy or within six weeks after any type of pregnancy termination (birth, miscarriage, abortion).

Increasingly, as countries implement the routine 6-dose child/adolescent tetanus schedule, fewer and fewer pregnant women will require tetanus vaccination during their pregnancy because they will have already been fully protected as children/adolescents.

However, achieving at least 80% coverage of 6 TTCV doses by adolescence in every district will take time. Because it is essential that every mother and newborn is protected against tetanus, it will **always** be necessary for ANC programmes to screen pregnant women to check that they are fully protected against tetanus, and administer any TTCV doses needed for long-term protection. It is important that received doses are accurately recorded on the appropriate home-based card and that their long-term retention is ensured so that the history of tetanus vaccination can be verified and unnecessary vaccinations avoided.

TTCVs are safe for pregnant women. There is no evidence of adverse pregnancy outcomes or risk to the foetus from TTCV vaccination during pregnancy.\(^ {18} \) TTCVs are also safe to use in HIV-infected and immunocompromised persons.

Anyone who receives 6 doses of TTCV starting with the primary series in infancy (or 5 doses if first vaccinated after infancy) achieves long-term protection and is protected against tetanus throughout their adulthood and beyond.

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What are current WHO recommendations for antenatal care (ANC) contacts?

Following a comprehensive review of evidence in 2016, WHO issued new recommendations on ANC.¹⁹

WHO now recommends a **minimum of eight ANC contacts**, scheduled to take place as follows:

- the 1ˢᵗ contact in the first trimester (up to 12 weeks of gestation);
- two contacts scheduled in the second trimester (at 20 and 26 weeks of gestation); and
- five contacts scheduled in the third trimester (at 30, 34, 36, 38, and 40 weeks).

<table>
<thead>
<tr>
<th>2016 WHO ANC Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Trimester</strong></td>
</tr>
<tr>
<td>Contact 1:</td>
</tr>
<tr>
<td>up to 12 weeks</td>
</tr>
<tr>
<td><strong>Second Trimester</strong></td>
</tr>
<tr>
<td>Contact 2:</td>
</tr>
<tr>
<td>20 weeks</td>
</tr>
<tr>
<td>Contact 3:</td>
</tr>
<tr>
<td>26 weeks</td>
</tr>
<tr>
<td><strong>Third Trimester</strong></td>
</tr>
<tr>
<td>Contact 4:</td>
</tr>
<tr>
<td>30 weeks</td>
</tr>
<tr>
<td>Contact 5:</td>
</tr>
<tr>
<td>34 weeks</td>
</tr>
<tr>
<td>Contact 6:</td>
</tr>
<tr>
<td>36 weeks</td>
</tr>
<tr>
<td>Contact 7:</td>
</tr>
<tr>
<td>38 weeks</td>
</tr>
<tr>
<td>Contact 8:</td>
</tr>
<tr>
<td>40 weeks</td>
</tr>
<tr>
<td>Return for delivery at 41 weeks if not given birth.</td>
</tr>
</tbody>
</table>

It is important that all pregnant women attend an antenatal clinic or can be reached by health staff in the community. Starting from the first ANC contact, WHO recommends verifying the TTCV status of pregnant women and administering TTCV if needed.²⁰ See [How to screen and vaccinate pregnant women for protection against tetanus?](page 44) (page 44) for vaccination schedule for TTCV unvaccinated and partially vaccinated pregnant women.

For effective implementation, ANC health-care providers need to be trained to screen the vaccination status of pregnant women and if needed, either refer for appropriate vaccination, or administer the TTCV themselves. The vaccine, equipment and supplies (refrigerator, needles and syringes, safety boxes) need to be readily available for provision of ANC vaccination in the facilities and/or during community outreach.

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²⁰ Policy-makers in low prevalence/high-income settings may choose not to include tetanus vaccination among ANC interventions if effective tetanus immunization programmes and good post-exposure prophylaxis exist outside of pregnancy.
When a pregnant woman attends an ANC visit, the health worker has an opportunity to:

— explain the advantages and encourage delivery at a health facility;
— reinforce the importance of delivery with skilled health personnel (competent maternal and newborn health professional) if the childbirth will happen outside of health facility and provide information on how to access such services;
— explain the principles of clean cord care practices, especially if unsafe practices are likely;
— emphasize the importance of timely infant vaccination and communicate the infant/child vaccination schedule to pregnant women.

If these services are not available or affordable, or if women prefer to deliver at home (non-facility delivery) without skilled health personnel, health workers should make additional effort to instruct pregnant women and their family on:

— how to ensure clean and safe childbirth at home
— how to ensure clean and appropriate cord care
— how to avoid harmful cord care practices
— how to recognize complications, especially early signs of tetanus
— when and where to seek care in case of complications.

Additionally, if appropriate and available, provide these women with a clean birth kit (CBK) and instruct them on how to use it (see *What are clean birth kits and childbirth checklists?*, page 60).

Home-based records for pregnant women and their unborn child may be distributed during ANC contacts and the importance of their retention well explained.
Box 14
WHO resources focusing on a positive pregnancy experience through improved quality of antenatal care

WHO recommendations on antenatal care for a positive pregnancy experience (2016) – comprehensive guideline intended to reflect and respond to the complex nature of the issues surrounding the practice and delivery of ANC, in accordance with a human rights-based approach.

Available online at: https://apps.who.int/iris/bitstream/handle/10665/250796/9789241549912-eng.pdf.

Antenatal care infographics – part of innovative, evidence-based approaches to antenatal care, focusing on contacts as an active connection between a pregnant woman and a health care provider, to ensure an effective transition of a positive pregnancy experience to positive labour, childbirth and motherhood experience.


How to screen and vaccinate pregnant women for protection against tetanus?

At the first ANC contact the tetanus vaccination status of pregnant women should be verified by card or history.

If card and/or history confirm that the pregnant woman is fully protected against tetanus (i.e. has received 6 TTCV doses in childhood/adolescence, or 5 doses if first vaccinated after 1 year of age/during adolescence/adulthood, including during previous pregnancies), then no further vaccination is needed. Vaccination of a “fully protected” pregnant woman (or any individual) should be avoided in order to prevent the risk of increased local reactions caused by pre-existing high levels of tetanus antibodies. However, it is still very important to record this pregnant woman as “fully vaccinated with TTCV” on her home-based record or ANC card and in the immunization register, even though she did not receive any TTCV doses in the current pregnancy.
If the pregnant woman does not have a card and the history seems unreliable, her vaccination status is considered unknown. Pregnant women with unknown vaccination status and those who have not been previously vaccinated should receive at least 2 TTCV doses as early as possible, with an interval of 4 weeks between the doses. Administer the 2nd dose at least 2 weeks before birth to allow for adequate immune response. Further doses of TTCV should be administered as shown in Table 5.

If the pregnant woman has received 1–4 doses of TTCV in the past, administer one dose of TTCV before delivery (see Table 5). For various training scenarios see Annex 3.

If the pregnant woman can confirm by card that she has received some but not all the needed doses of TTCV, provide vaccination following the schedule for partially vaccinated women shown in Table 6. The last dose of TTCV must be administered at least two weeks before delivery.

If the woman underwent miscarriage or unsafe abortion, and if she is considered unprotected against tetanus, vaccinate her immediately as shown in Table 5, to protect her against future tetanus risks.21

Table 5
TTCV vaccination schedule for WRA and pregnant women with unknown vaccination status or without previous exposure to TTCV22

<table>
<thead>
<tr>
<th>Dose of TTCV</th>
<th>When to give</th>
<th>Expected duration of protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTCV 1</td>
<td>At first contact or as early in pregnancy as possible</td>
<td>None</td>
</tr>
<tr>
<td>TTCV 2</td>
<td>At least 4 weeks after TTCV1 (at the latest 2 weeks prior to birth)</td>
<td>1-3 years</td>
</tr>
<tr>
<td>TTCV 3</td>
<td>At least 6 months after TTCV2, or during subsequent pregnancy</td>
<td>At least 5 years</td>
</tr>
<tr>
<td>TTCV 4</td>
<td>At least 1 year after TTCV3, or during subsequent pregnancy</td>
<td>At least 10 years</td>
</tr>
<tr>
<td>TTCV 5</td>
<td>At least 1 year after TTCV4, or during subsequent pregnancy</td>
<td>For all childbearing age and much of adulthood</td>
</tr>
</tbody>
</table>

21 In addition, offer prophylaxis with human tetanus immune globulins (TIG) if the wound is large and possibly infected with soil or unclean instruments. A single intramuscular dose is recommended as soon as possible. TIG should be readily available in all countries.

Table 6
TTCV vaccination schedule for partially vaccinated pregnant women

<table>
<thead>
<tr>
<th>Age of last vaccination</th>
<th>Previous vaccinations (from vaccination record)</th>
<th>Recommended TTCV doses At present ANC contact/pregnancy</th>
<th>Later (with interval of at least one year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infancy</td>
<td>3 TTCV primary doses</td>
<td>2 doses of TTCV (minimum 4 week interval between doses)</td>
<td>1 dose of TTCV</td>
</tr>
<tr>
<td>Early childhood/school age</td>
<td>3 TTCV primary doses + 1 booster (total of 4 TTCV doses)</td>
<td>1 dose of TTCV</td>
<td>1 dose of TTCV</td>
</tr>
<tr>
<td>School age</td>
<td>3 TTCV primary doses + 2 boosters (total of 5 TTCV doses)</td>
<td>1 dose of TTCV</td>
<td>None (fully protected)</td>
</tr>
<tr>
<td>Adolescence</td>
<td>3 TTCV primary doses + 3 boosters (total of 6 TTCV doses)</td>
<td>None (fully protected)</td>
<td>None (fully protected)</td>
</tr>
</tbody>
</table>

All doses given should be properly recorded in the home-based record or ANC/maternal health card and in the standard facility register and tally sheet. Accurate recording by dose number (i.e. TTCV2, TTCV3, etc.) is important so that repeated unnecessary vaccinations can be avoided.

If a case of NT is identified, the mother should receive one dose of TTCV as soon as possible, and the infant should be treated according to national guidelines (see Annex 1 for more information). A second dose of TTCV should be given to the mother at least 4 weeks after the first, and the third dose at least 6 months after the second. Other un- or under-vaccinated women living in the same area should be identified and vaccinated as appropriate (see Table 5). All cases of NT should be recorded and reported to the district authority, and all NT cases from low-risk areas should be investigated.24

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Maternal and neonatal tetanus can be prevented if:

1. women of reproductive age are fully vaccinated against tetanus before they become pregnant;
2. pregnant women are screened for protection against tetanus and vaccinated with TTCV as appropriate;
3. clean practices are used during birth and in the care of infant’s umbilical cord.

In countries which have not achieved MNTE status, the “high-risk” approach should be part of the elimination strategy. This entails coordinating three rounds of vaccination campaigns and targeting all WRA in high-risk districts to provide 3 doses of TTCV, irrespective of previous vaccination status. The interval between rounds 1 and 2 (i.e. TTCV doses 1 and 2) should be at least 4 weeks, and between rounds 2 and 3 (i.e. TTCV doses 2 and 3) at least 6 months. Ensuring clean birth and cord care practices are essential complementary activities.

What records/cards do pregnant women need to keep?

In many countries, women are given their own home-based record (HBR) or case notes to carry during pregnancy. These may be paper (e.g. card, journal, handbook) or in electronic format (e.g. memory stick), and women are expected to safeguard and bring them to all health visits.

In maternal and child health, the HBR can take various forms such as antenatal care records, vaccination cards, child health booklets, and antenatal and child health books. HBR or case notes contain patient data which facilitates access to women’s medical records when needed (e.g. if women change health-care provider, in case of emergency, etc) and may serve as important data collection and surveillance tools. Depending on the design and content, they can also be an effective tool to improve health awareness and client– health care provider communication (e.g. reminders about next appointments). In some countries, TTCV vaccination of pregnant women is recorded in the same booklet/record used for the child’s vaccination. In these instances, the mother/child vaccination record is given to the mother at the first ANC contact and she is instructed to keep and use it for her newborn child’s vaccination history.

Promote lifetime vaccination records

Permanent, lifetime vaccination cards should be given to every woman who receives TTCV vaccination. The lifetime cards help health workers schedule vaccination appointments correctly and avoid giving women too many (or too few) vaccines. It is important that women understand that the record is valuable and should be kept safely. For example, make sure health workers ask women for their vaccination cards or home-based record every time they come for a health service as a means of reinforcing their importance.

For more information on HBR for maternal, newborn and child health and implementation recommendations see Box 8 and http://www.who.int/maternal_child_adolescent/documents/home-based-records-guidelines/en/.

What does “protection at birth” (PAB) mean and why is it important?

Maternal tetanus immunization leads to the production of antibodies and transplacental transfer of these to the developing foetus. Because this process of passively acquiring maternal antibodies is highly efficient, the infant usually has a serum tetanus antibody concentration at birth greater than, or equal, to that of the mother. In this way, through maternal vaccination, both mother and infant are protected from tetanus occurring during the first few months after birth.

Protection at birth (PAB) against tetanus: A birth is considered protected against tetanus when occurring during the period of protection conferred by the maternal immunization status.

Protection at birth (PAB) is a monitoring method to determine whether a birth was protected against tetanus, based on written maternal records and/or questioning the mother (mother’s recall) about the number and timing of TTCV doses she had previously received.

Only valid doses (at least two), or those given with the minimum required time intervals between doses, are to be counted. A birth is considered protected if it occurred within the duration of protection offered by the last valid dose (see Table 7). TTCV doses received by mothers during childhood are included only if documented in paper or electronic records (e.g. infant or school vaccination records).

Table 7
Protection at birth based on maternal vaccination history (birth is PAB or considered protected if it occurred within the duration of protection offered by the last tetanus vaccine dose)

<table>
<thead>
<tr>
<th>Cumulative number of TTCV doses administered to mother</th>
<th>Minimal interval between doses to be considered valid</th>
<th>Duration of protection from receipt of last dose (PAB status)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTCV2</td>
<td>4 weeks</td>
<td>3 years (PAB if birth within 3 years)</td>
</tr>
<tr>
<td>TTCV3</td>
<td>6 months</td>
<td>5 years (PAB if birth within 5 years)</td>
</tr>
<tr>
<td>TTCV4</td>
<td>1 year</td>
<td>10 years (PAB if birth within 10 years)</td>
</tr>
<tr>
<td>TTCV5</td>
<td>1 year</td>
<td>Much of adulthood (PAB for all subsequent births)</td>
</tr>
</tbody>
</table>

If a birth was assessed as unprotected, the mother should receive a dose of TTCV during that visit and should be followed up with a subsequent TTCV dose(s) if needed, thereby protecting future pregnancies. The same applies for mothers whose children were protected at birth but who remain eligible for additional TTCV doses in order to be fully vaccinated and protected.

**How is protection at birth (PAB) implemented, recorded, and coverage calculated?**

WHO recommends that PAB status is assessed and recorded to estimate protection against tetanus in pregnant women. Together with records on facility-based deliveries (if available), PAB coverage can be used as a proxy marker to assess the district level risk of MNT.

Traditionally, PAB has been assessed and recorded at the first vaccination contact for the new-born baby/infant, usually at the Penta1/DPT1 visit. However, all post-natal care visits (currently recommended at 24 hours, day 3, and between 7–14 days and 6 weeks after delivery) present an opportunity to check PAB. With the increased integration of maternal, post-natal and vaccination services there are other contact opportunities where PAB status could be assessed and recorded (see Table 8). PAB status can be recorded in the home-based record, ANC card, child’s vaccination card, and tally sheets.
### Table 8
**Opportunities to implement assessment and recording of PAB status**

<table>
<thead>
<tr>
<th>Contact to assess/record PAB</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At birth</strong></td>
<td>Best for countries with high proportion (%) of facility-based deliveries.</td>
</tr>
<tr>
<td></td>
<td>Requires collaboration between maternal and immunization services.</td>
</tr>
<tr>
<td></td>
<td>PAB could be recorded in mother’s ANC card, or integrated maternal and child card, or child immunization card, and recorded on facility registers/tally sheets.</td>
</tr>
<tr>
<td></td>
<td>Especially appropriate if Hep B and BCG are given at time of birth (along with vaccination card).</td>
</tr>
<tr>
<td><strong>1st postnatal contact – ideally 24 hours after birth</strong> (e.g. HepB birth dose)</td>
<td>Would capture all infants born (non-facility and facility) as mother is required to come to the health facility after birth, but requires strong postnatal programme implementation and access to services to achieve high coverage.</td>
</tr>
<tr>
<td></td>
<td>Requires collaboration between maternal and immunization services.</td>
</tr>
<tr>
<td></td>
<td>PAB could be recorded in mothers ANC card, or integrated maternal and child card, or child immunization card if it has been given, and recorded on facility registers/tally sheets.</td>
</tr>
<tr>
<td><strong>First vaccination contact of the infant (Penta1/DTP1)</strong></td>
<td>Vaccination services usually have high attendance (high Penta 1 coverage).</td>
</tr>
<tr>
<td></td>
<td>Easy to do and record (cards and registers and tally sheets available) both for facility-based and outreach vaccination sessions.</td>
</tr>
<tr>
<td></td>
<td>Does not require collaboration with other programmes.</td>
</tr>
</tbody>
</table>

PAB coverage is the proportion of births in a given year that can be considered as having been protected against tetanus as a result of maternal immunization. PAB coverage is calculated as follows:

\[
\text{%PAB} = \left( \frac{\text{Total number of infants who were protected against neonatal tetanus by their mother’s TTCV status}}{\text{Total number of live births}} \right) \times 100
\]

**Annex 4** provides an overview of how to implement the PAB method in practice and examples of tools (i.e. reporting form, NT protection calculator, etc.).

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What is routine administrative TTCV2+ coverage monitoring?

Experience has shown that aggregated administrative monitoring of the second or subsequent dose of TTCV (TTCV2+) coverage of pregnant women is difficult to do accurately, particularly at the national level, unless countries have electronic registers.

Emphasis should be on making sure that doses of TTCV are recorded on home-based records for maternal, newborn and child health, and that these records/cards are retained over the long term or at least through reproductive age for women.29

Good recording of maternal and infant TTCV doses will enable PAB to be accurately monitored (see What does “protection at birth” mean and why is it important?, page 48).

Immunization coverage surveys (e.g. DHS, MICS) can be used to periodically assess TTCV2+ coverage in mothers who had a pregnancy in the past 12 months, and can also be used to validate PAB coverage.

In countries that continue with routine administrative monitoring of TTCV2+ coverage, as a refinement WHO recommends that the numerator includes those pregnant women who are already fully protected through previous TTCV vaccination to avoid underestimation.

TTCV2+ coverage for pregnant women is the proportion of pregnant women in a given year who are fully vaccinated for this pregnancy (who received TT2, TT3, TT4, or TT5 dose), including those pregnant women already fully protected/vaccinated against tetanus prior to the pregnancy.

\[
\text{%TTCV2+ coverage of pregnant women} = \frac{\text{Total no.of women vaccinated with 2 or more doses of TTCV during pregnancy} + \text{pregnant women already fully protected, in a year}}{\text{Estimated number of pregnant women during the year}^{30}}
\]

ANC cards, immunization registers and tally sheets should be adapted to include a column for “Fully Immunized Prior to the Pregnancy”. For an example of a tally sheet see Annex 5.

CHAPTER 4

Ensuring clean birth and umbilical cord care practices
In this chapter you will learn:

- Why clean birth and umbilical cord care are important for MNTE;
- How can clean birth and clean cord care practices be achieved;
- What practices ensure a clean birth and cord care;
- What are clean birth kits (CBK) and childbirth checklists.

You can use this information to:

- Plan and improve birth practices so that there is no risk of tetanus and other causes of perinatal mortality;
- Train health workers;
- Develop information, education and communication (IEC) materials for women and communities.
Why are clean birth and umbilical cord care important for MNTE?

A clean birth, along with appropriate hygienic practices post-childbirth, can effectively reduce risks of tetanus, even if maternal TTCV coverage is suboptimal in a country. Clean birth can also reduce other causes of perinatal mortality such as infections other than tetanus that could result in neonatal sepsis.

A newly cut umbilical cord can be a pathway for local and invasive infections. Localized infection of the umbilical stump (omphalitis) may progress beyond the subcutaneous tissues, involve abdominal wall muscles, the umbilical and portal veins, and lead to systemic sepsis which, if untreated, has a high case-fatality rate.

In many cultures around the world there is a desire to actively care for the umbilical cord of the newborn, irrespective of whether they are born at home or in health-care facilities. These traditional practices vary by country or cultural groups within a country, and include application of a wide range of substances such as:

- Oils, herbs/spices/plants;
- Minerals and powders;
- Animal dung;
- Water;
- Bodily fluids;
- Food;
- Heat (e.g. hot knife, steam, burning);
- Personal care or medical substances (e.g. creams, ointments, toothpaste, alcohol, iodine, herbal medicines, etc.);
- Other substances (e.g. burnt cotton, shells, tar, fish bones, crushed wasp nests, etc.).

Application of substances to the stump is not indicated because it delays the physiological drying of the umbilical cord stump and can be harmful. In settings with poor hygiene, adequate cord care practices for the newborn, especially if provided by skilled health personnel, has the potential to avoid preventable neonatal deaths. Evidence suggests that clean birth practices can reduce the incidence of NT by 55–99%. See WHO recommendation for cord care in section What practices ensure a clean birth and cord care?, page 58.

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How can clean birth and clean cord care practices be achieved?

Having skilled health personnel is key to ensuring clean birth and cord care (see Box 15 for definition of skilled health personnel).

Increasing the number of deliveries with a competent maternal and newborn health professional in order to reduce maternal and neonatal deaths is a global goal of the Every Newborn Action Plan (ENAP)\textsuperscript{33}, the Global Strategy for Women's, Children's and Adolescent Health\textsuperscript{34}, the Sustainable Development Goals (SDGs)\textsuperscript{35}, and Ending Preventable Maternal Mortality (EPMM) Initiative\textsuperscript{36}.

At the community level, skilled health personnel will often be the only qualified and accredited health care workers with exclusive responsibility for the care of women during pregnancy, childbirth, and the immediate postnatal period. Others, ranging from traditional birth attendants (TBAs), nurses to specialist physicians, will certainly contribute to the care of women and newborns, but none of these will have either the wide-ranging competence or the mandate for all the tasks the skilled health personnel is required to perform.

Globally the proportion of women giving birth with a competent MNH professional has increased in the last two decades. However, there are great disparities in coverage and quality of care between and within countries. Countries are encouraged to ensure, without delay, that skilled health personnel providing care during childbirth are available to all pregnant women and newborn.

\begin{flushright}
\end{flushright}
Sustainable Development Goals and definition of by skilled health personnel

A critical progress indicator adopted by the Sustainable Development Goals (SDG) and the Global Strategy for Women’s, Children’s and Adolescents’ Health, 2016-2030 agenda is the “percentage of births delivered by skilled attendant at birth” (SBA).

WHO, UNFPA, UNICEF, ICM, ICN, FIGO and IPA proposed a revised definition of skilled health personnel providing care during childbirth (previously referred to as “skilled birth attendants” or SBAs) in order to standardize and improve the accuracy of measurement.37

Skilled health personnel are competent maternal and newborn health (MNH) professionals educated, trained and regulated to national and international standards. They are competent to:

i. provide and promote evidence-based, human-rights based, quality, socio-culturally sensitive and dignified care to women and their newborns;

ii. facilitate physiological processes during labour and delivery to ensure a clean and positive childbirth experience; and

iii. identify and manage or refer women and/or newborns with complications.

In addition, as a part of an integrated team of MNH professionals (including midwives, nurses, doctors, obstetricians, neonatologists, paediatricians and anaesthesiologists), they perform all signal functions of emergency maternal and newborn care to optimize the health and well-being of mothers and newborns within an enabling and supporting environment.

WHO publication on skilled health personnel

Definition of skilled health personnel providing care during childbirth (2018) — This 2018 joint statement by the World Health Organization (WHO), the United Nations Population Fund (UNFPA), the United Nations Children’s Fund (UNICEF), the International Confederation of Midwives (ICM), the International Council of Nurses (ICN), the International Federation of Gynecology and Obstetrics (FIGO) and the International Pediatric Association (IPA) presents the 2018 definition of skilled health personnel providing care during childbirth, which is revised and refined definition of the widely used term “skilled birth attendant” (SBA).


What practices ensure a clean birth and cord care?

A clean birth is a delivery using hygienic practices and attended by competent maternal and newborn health personnel in a health care facility or at home.

Knowledge about the importance of clean birthing practice has been available for a long time. In various regions/countries practices may be summarized differently (e.g. ‘three cleans’\(^ {38} \), ‘five cleans’\(^ {39} \), ‘six cleans’\(^ {40} \) but they all emphasize ensuring clean hands, clean birth surface and clean cord care (cut, tie and stump).

Clean birth practices should include:

— **Clean hands of birth attendant**: wash hands with clean water and soap, once before the delivery and once before cord cutting (see Annex 6).

— **Clean delivery surface**: use a clean plastic sheet for mothers to lie on during delivery to maintain clean birth canal and perineum, and to protect the newborn from potential sources of infection.

— **Clean cord cut**: use a new razor blade or other new sharp instrument from its original packing to prevent the transmission of tetanus-causing spores and other pathogenic organisms via the umbilicus to the infant.

— **Clean cord ties**: use clean or sterile thread or narrow tape to tie the umbilicus tightly and keep the stump healthy.

— **Clean cord stump care**: in high neonatal mortality settings and where locally recommended for newborns born outside of health facilities, apply chlorhexidine to the cord stump (see below). For those born in health facilities, dry cord care is recommended as per national protocol.

Standard precautions and cleanliness as principles of good care should be observed at all times. These principles are:

1. Wash hands with soap and water
2. Wear gloves (sterile when attending to woman in labour, delivery and immediate postpartum care; clean when dealing with handling and cleaning instruments, handling contaminated waste, blood and body fluid spills).
3. Protect yourself from blood and other bodily fluids (wear gloves, long apron, protect your eyes and mouth).
4. Practice safe sharps disposal.

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5. Practice safe waste disposal.
6. Deal with contaminated laundry (do not touch directly clothing or sheets stained with blood or body fluids).
7. Sterilize and clean contaminated equipment.
8. Clean and disinfect gloves.*
9. Sterilize gloves.*

* Reusing gloves is not recommended. If it is necessary because of limited supply, gloves can be disinfected by soaking overnight in bleach solution or sterilized by autoclaving.

For updated recommendations relevant to maternal and perinatal health refer to Pregnancy, Childbirth, Postpartum and Newborn Care: a guide for essential practice (see Box 17).

**WHO recommendations on cord clamping**

- **Late cord clamping** (performed after one to three minutes after birth) is recommended for all births while initiating simultaneous essential newborn care.
- **Early cord clamping** (<1 minute after birth) is not recommended unless the neonate is asphyxiated and needs to be moved immediately for resuscitation.

**WHO recommendations on cord care**

- Daily chlorhexidine (7.1% chlorhexidine digluconate aqueous solution or gel, delivering 4% chlorhexidine) application to the umbilical cord stump during the first week of life is recommended for newborns who are born at home in settings with high neonatal mortality (30 or more neonatal deaths per 1000 live births).
- Clean, dry cord care is recommended for newborns delivered in health facilities and at home in low neonatal mortality settings. Use of chlorhexidine in these situations may be considered only to replace application of a harmful traditional substance, such as cow dung, to the cord stump.

What are clean birth kits (CBK) and childbirth checklists?

Along with training of health workers, media and public health messaging, and community-based behaviour change and training, one of the approaches to increase uptake of clean childbirth practices includes the distribution of clean birth kits (CBK).

WHO established the contents of clean birth kits (CBK) and their correct use in the 1990s. They differ from country to country depending on local guidelines and regulations, and the contents will also vary depending on where it is intended to be used (i.e. home delivery without skilled health personnel, home delivery by skilled health personnel, essential newborn kits for health facilities, essential newborn kits for hospitals, see Table 9).

Mother-held CBKs are highly cost-effective and considered appropriate in conflicts or complex humanitarian emergencies, or in settings where there is low coverage of facility births, as long as they are not a disincentive for facility birth.

United Nations Population Fund (UNFPA), WHO and UNICEF have developed essential reproductive health kits for emergency situations designed to respond to three month’s need for various population sizes and intended for the use of:

— community: kits packaged for individual distribution to pregnant women and kits with equipment and supplies for skilled health personnel;
— primary health care level: kits with equipment and supplies for essential newborn care for uncomplicated births, newborn resuscitation, stabilizing newborns with serious infection prior to referral, and caring for preterm babies; and
— referral hospital level: kits with equipment and supplies to provide comprehensive emergency obstetric and newborn care at the hospital (e.g. complicated births, newborn infections, newborn resuscitation, care for preterm babies with complications).

For detailed information on the contents of the kits, guidance for their use and orders please see https://www.unfpa.org/resources/humanitarian-emergencies-procurement.

Antenatal care (ANC) contacts and tetanus vaccination status of pregnant women

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### Table 9
Example of essential supplies for clean birth and newborn care\(^{44,45}\)

<table>
<thead>
<tr>
<th>Where?</th>
<th>What is needed?</th>
<th>Who uses it?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clean birth kit for home delivery without skilled health personnel</strong></td>
<td>Plastic sheet, soap, disposable razor blade, cord tie, cotton cloth 'tetra', gloves, plastic bag for disposal of placenta, pictorial instruction for use leaflet, pictorial leaflet on maternal and newborn danger signs</td>
<td>The person attending birth when there is no skilled health personnel</td>
</tr>
<tr>
<td><strong>Essential newborn kit for home delivery by skilled home personnel</strong></td>
<td>The above, plus protective apron and mask, portable weighing scale, essential medicines, bulb syringe or portable suction unit</td>
<td>Skilled health personnel</td>
</tr>
<tr>
<td><strong>Essential clean birth and newborn kits for primary health facilities and referral hospitals</strong></td>
<td>Medical devices, delivery set, suture set, sterilization kit, lighting, medicines, treatment guidelines</td>
<td>Skilled health personnel and doctors</td>
</tr>
</tbody>
</table>

Where permitted by local regulations, individual clean birth kits for home delivery may also include:\(^{44}\)

- The antiseptic chlorhexidine for newborn skin washing and umbilical cord cleaning. In high mortality settings, chlorhexidine has been shown to reduce newborn deaths by as much as 23 percent when applied within the first 24 hours of birth.
- Misoprostol pills, a uterotonic drug which contracts the uterus, can help to prevent excessive bleeding after delivery.

To ensure a high-quality of care of births in health facilities, in 2016 WHO developed quality of care standards which define the requirements. Accompanying these standards are a WHO Safe Childbirth Checklist and an Implementation Guide which are designed as tools to improve the quality of care provided to women giving birth in health facilities (see Box 17). All of these materials support the implementation of clean birth and cord care practices.

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Box 17

Resources on pregnancy, childbirth and newborn care

**Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice (2015)** – compiles all the updated norms and standards that enable health care workers to provide high-quality, integrated care during pregnancy, childbirth and after birth to both mothers and newborns. The recommendations are specifically for skilled attendants working at the primary health-care level, either at the facility or in the community. The guide can be adapted to local needs and resources.

Available online at: [https://apps.who.int/iris/bitstream/handle/10665/249580/9789241549356-eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/249580/9789241549356-eng.pdf).

**Managing complications in pregnancy and childbirth: a guide for midwives and doctors (2nd edition, 2017)** – a manual for midwives and doctors at the district hospital who are responsible for the care of women with complications of pregnancy, childbirth or the immediate postpartum period, including immediate problems of the newborn.

Available online at: [https://apps.who.int/iris/bitstream/handle/10665/255760/9789241565493-eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/255760/9789241565493-eng.pdf).

**Early essential newborn care clinical practice pocket guide (2014)** – is a good example of a user-friendly guide providing evidence-based protocol to essential newborn care focusing on the first hours and days of life, developed in the WHO Western Pacific Region.

Available online at: [https://iris.wpro.who.int/bitstream/handle/10665.1/10798/9789290616856_eng.pdf](https://iris.wpro.who.int/bitstream/handle/10665.1/10798/9789290616856_eng.pdf).

**WHO recommendations: intrapartum care for a positive childbirth experience (2018)** – consolidated new and existing WHO recommendations, intended to inform the development of relevant national- and local-level health policies and clinical protocols, and to ensure good-quality and evidence-based care irrespective of the setting or level of health care.

Available online at: [https://apps.who.int/iris/bitstream/handle/10665/260178/9789241550215-eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/260178/9789241550215-eng.pdf).
WHO recommendations on postnatal care of the mother and newborn (2013) – guidelines that address timing, number and place of postnatal contacts, and content of postnatal care for all mothers and babies during the six weeks after birth. Primarily intended for health professionals who are responsible for providing postnatal care to women and newborns, but can be included in job aids and tools for both pre- and in-service training of health professionals.


The Safe Childbirth Checklist (2015) – an organized list of evidence-based essential birth practices targeting major causes of maternal and neonatal deaths and intrapartum-related stillbirths. The Checklist may need to be adapted to reflect the local context and/or national guidelines and protocols. An Implementation Guide for health facilities has been developed to help birth attendants and health-care leaders successfully launch and sustain use of the WHO Safe Childbirth Checklist.

Available online at: [http://www.who.int/patientsafety/implementation/checklists/childbirth/en/](http://www.who.int/patientsafety/implementation/checklists/childbirth/en/).

Standards for improving quality of maternal and newborn care in health facilities (2016) – include eight domains of quality of care that should be assessed, improved and monitored within the health system.


Inter-Agency Reproductive Health Kits for Crisis Situations (2011) – manual which provides information on procurement procedures and contents of standardized emergency kits designed for worldwide use, pre-packed and kept ready for immediate dispatch in crisis situations.


Available online at: https://www.healthynewbornnetwork.org/resource/newborn-health-humanitarian-settings-field-guide/.
CHAPTER 5

Tetanus surveillance
In this chapter you will learn:

- What is tetanus surveillance and why it is necessary;
- WHO recommended standards for tetanus surveillance.

You can use this information to:

- Establish reliable tetanus surveillance systems;
- Monitor that MNTE is achieved and sustained.
What is tetanus surveillance and why is it necessary?

Tetanus surveillance is the systematic, timely, and continuous collection, analysis and interpretation of epidemiological data on tetanus cases, linked with timely dissemination of the results so that appropriate action can be taken to control or prevent further cases of tetanus.

Many countries have regulations for mandatory reporting of a list of notifiable diseases, tetanus being one of these. Surveillance reports should distinguish and separately categorize cases of neonatal (aged 0–28 days) and non-neonatal (aged >28 days) tetanus (see Table 10 for case definitions).

Surveillance for neonatal tetanus

A key objective of neonatal tetanus surveillance is to detect cases of NT towards monitoring achievement and maintenance of MNTE, defined as less than one NT case per 1,000 live births annually in every district or equivalent administrative unit.

NT surveillance data (or a lack thereof) are used to identify areas and sub-populations at high-risk for NT and to guide an effective response. High-quality surveillance data, along with other key programme indicators, at the national and subnational (i.e. district) levels, enables monitoring of the impact of interventions, and are necessary to identify areas of increased risk for MNT and to target interventions to maintain elimination.

Surveillance for non-neonatal tetanus

The objective of surveillance for non-NT is to monitor disease burden and changing epidemiology over time in order to assess the impact of vaccination and to identify gaps in the immunization programme and health systems in general.

Information from non-NT surveillance should be used to tailor strengthening of routine immunization services and optimize strategies and vaccination schedules, including introduction and timing of booster doses. It can also be used to identify clustering of tetanus cases warranting investigation. Finally, rapid detection of cases can help save lives, i.e. through initiating receipt of proper treatment, including administration of antitoxin.
**Table 10**

**WHO case definitions for tetanus**

<table>
<thead>
<tr>
<th>Neonatal tetanus (NT), aged 0-28 days</th>
<th>Non-neonatal tetanus (non-NT), aged &gt;28 days</th>
<th>Maternal tetanus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suspected case:</strong></td>
<td><strong>Suspected case</strong></td>
<td><strong>Tetanus occurring during pregnancy or within 6 weeks after any type of pregnancy termination (birth, miscarriage or abortion).</strong></td>
</tr>
<tr>
<td>— any neonate who could suck and cry normally during the first 2 days of life and developed tetanus-like illness or death between 3 and 28 days of age; <strong>OR</strong> — any neonate who died of an unknown cause during the first month of life.</td>
<td>— any case with acute onset of at least one of the following signs: — trismus (lockjaw); — risus sardonicus (sustained spasm of the facial muscles); — generalized muscle spasms (contractions).</td>
<td>—</td>
</tr>
<tr>
<td><strong>Confirmed case:</strong> any suspected case found to have all three of the following: — normal ability to suck and cry during the first 2 days of life; AND — could not suck normally between 3 and 28 days of age; AND — developed muscle stiffness and/or spasms (jerking).</td>
<td><strong>Confirmed case:</strong> suspected case clinically confirmed as tetanus by physician/trained clinician.</td>
<td></td>
</tr>
</tbody>
</table>

46 It includes postpartum or puerperal tetanus resulting from septic procedures during delivery, postabortal tetanus resulting from septic abortion, and tetanus incidental to pregnancy resulting from any type of wound during pregnancy.
Importance of accurate and complete reporting of non-neonatal tetanus (non-NT) surveillance for MNTE

Surveillance for non-neonatal tetanus can detect cases of maternal tetanus. However, in most countries non-NT surveillance occurs through aggregate reporting which lacks specific information (i.e. age, sex, pregnancy status) to distinguish maternal tetanus. If country programmes decide that maternal tetanus is of special priority, reports of maternal tetanus should be handled similarly to those of neonatal tetanus.

What are the WHO recommended standards for tetanus surveillance?

In 2018, WHO published an updated second edition of *Surveillance standards for vaccine-preventable diseases* (see Box 18). This document provides surveillance standards (see Table 11) and performance indicators for both NT and non-NT surveillance, and detailed guidance for surveillance activities including:

— case detection
— case definitions and final classification
— case investigation, public health response and clinical case management
— data elements for collection, as well as reporting, analysis, and use
— surveillance performance indicators.

Countries may adapt these standards based on local epidemiology, policy, disease control objectives and strategies. Relevant extracts are provided in Annex 7 for NT surveillance and in Annex 8 for non-NT surveillance.


Making disease surveillance work (2008) – Module 8 of WHO training for mid-level managers series provides the basic concepts of surveillance and explains in practical terms how to manage a surveillance system for vaccine-preventable diseases.

Available online at: [http://apps.who.int/iris/bitstream/handle/10665/70184/WHO_IVB_08.08_eng.pdf](http://apps.who.int/iris/bitstream/handle/10665/70184/WHO_IVB_08.08_eng.pdf).


### Table 11
**WHO recommended surveillance standards for tetanus**

<table>
<thead>
<tr>
<th>Neonatal Tetanus (NT)</th>
<th>Non-Neonatal Tetanus (Non-NT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The <strong>minimal</strong> recommended standard: Nation-wide, case-based surveillance (meaning every suspected NT case should be investigated and classified as confirmed or discarded).</td>
<td>The <strong>minimal</strong> recommended standard: Nation-wide, surveillance with aggregate routine reporting from inpatient facilities and investigation of any unusual disease clusters.</td>
</tr>
<tr>
<td>NT surveillance is population-based and includes all neonates aged 0–28 days.</td>
<td>Non-NT surveillance is population-based and includes all persons aged &gt;28 days.</td>
</tr>
<tr>
<td>Laboratory confirmation is not an aspect of NT surveillance, as the basis of tetanus diagnosis is clinical rather than laboratory-based.</td>
<td>Laboratory confirmation is not an aspect of non-NT surveillance, as the basis of tetanus diagnosis is clinical rather than laboratory-based.</td>
</tr>
<tr>
<td><strong>Enhanced</strong> surveillance for non-NT:</td>
<td></td>
</tr>
<tr>
<td>• Case-based surveillance.</td>
<td></td>
</tr>
<tr>
<td>• Either nationwide or sentinel surveillance is advised depending on the local context (public and private referral hospitals with intensive care capacity located in areas with high non-NT burden).</td>
<td></td>
</tr>
<tr>
<td><strong>Linkages to other surveillance</strong></td>
<td><strong>Linkages to other surveillance</strong></td>
</tr>
<tr>
<td>• Ideally, NT surveillance is linked with active surveillance for AFP and measles-rubella, and routine aggregate surveillance for “zero reporting” as part of Integrated Disease Surveillance and Response (IDSR).</td>
<td>• Ideally, non-NT surveillance is linked with aggregate surveillance systems for other diseases through systems such as IDSR and Early Warning, Alert and Response Network (EWARN).</td>
</tr>
<tr>
<td>• Linkage to vital event surveillance and neonatal death surveillance(^47) may be useful for increasing NT surveillance sensitivity and helping to conserve resources.</td>
<td>• In some cases, HMIS reporting may be used for facility-based aggregate reporting of non-NT cases.</td>
</tr>
<tr>
<td></td>
<td>• Linkage to maternal death surveillance and response (MDSR) and other maternal child health post-partum surveillance systems may be relevant in some countries.</td>
</tr>
</tbody>
</table>

CHAPTER 6
Monitoring & Evaluation (M&E)
In this chapter you will learn:

- What monitoring and evaluation (M&E) is required for tetanus vaccination;
- How to periodically assess if MNTE status is sustained;
- What to do if M&E and/or periodic assessment of MNTE finds that elimination status is at risk.

You can use this information to:

- Design/adapt recording and monitoring tools for tetanus vaccination, including boosters;
- Plan and conduct a post-validation assessment of MNTE to ensure it is sustained.
What monitoring and evaluation is required for tetanus vaccination?

A successful monitoring and evaluation system for tetanus vaccination consists of:

1. continuous programmatic monitoring that provides information on implementation performance of tetanus vaccination (i.e. vaccine supply/stock, number of doses administered, coverage of 3 primary infant doses and 3 booster doses, TTCV2+, PAB, AEFI reporting, etc.), and

2. periodic assessment to check that MNTE status is maintained.

These two activities are interlinked and will be explained in this chapter. Reliable disease surveillance data (described in Chapter 5) provide an important complement to programmatic monitoring and evaluation, as it confirms the impact of the programme.

What is most important is that countries (especially those that achieved MNTE by conducting TTCV campaigns for women of reproductive age in high-risk districts) recognize that even though they validated MNTE, strong surveillance and constant attention to TTCV protection levels (i.e. high coverage) must continue so that elimination status is sustained.

Programmatic M&E: what monitoring tools need to be in place or revised?

Most national immunization programmes are already providing TTCV to pregnant women through ANC contacts, and have an M&E system in place for this. However, as discussed in Chapter 3, there may be a need to revise the ANC TTCV recording forms and monitoring processes in order to improve accuracy, particularly for tallying pregnant women who are already fully vaccinated with TTCV. Additionally, the ANC M&E system needs to monitor and report the doses, coverage, and other relevant information (e.g. stock, AEFI, etc.) for the TTCV administered through its services.

As additional child/adolescent TTVC boosters are added, the main recording and reporting tools that are used by the immunization programme will need to be adapted or developed to include the booster doses of TTCV vaccine. These are:

- vaccination register and defaulter tracking system
- tally sheet
- home-based record (vaccination card) defaulter tracking system
- stock record
- integrated monthly report.
Depending on the national schedule and delivery strategy for TTCV booster doses, and given that the administration of these boosters spans several age groups over time, it will likely be necessary to introduce several new monitoring tools and processes for the booster doses given to older children/adolescents.

When there is a pre-existing vaccination contact with the same age group, such as MCV2 or HPV vaccination, then the M&E tools can be adapted to include the TTCV booster. Likewise, if TTCV booster vaccination includes a 4–7 year old target group, then this opportunity (possibly at entry to day-care/creche/school) can be used to check the vaccination status of these children and catch up missed doses of other childhood vaccines (see Annex 9 for Job Aid).

Good coordination and collaboration between national ANC and EPI programmes is needed to obtain high-quality TTCV data (e.g. TTCV2+ and PAB coverage is correctly and accurately calculated) so that the TTCV performance information from both programmes can be shared and reviewed to inform any needed corrective actions.

Given the great diversity of approaches and country context, there are no generic M&E tools or processes to recommend for TTCV. Each country will need to design its own system according to its unique programme of service delivery. Those countries that have moved to electronic monitoring systems will have clear advantages as it will be much easier to retain and track the vaccinations given to individuals over the life course.

Helpful general information on immunization programme monitoring can be found in WHO publication Immunization in Practice: A Practical Guide for Health Staff, Module 6 – Monitoring and Surveillance (see Box 18) and also a forthcoming WHO resource Handbook on the use, collection and improvement of immunization data (see Box 20).
How to periodically assess if MNTE status is sustained?

It is a proud moment when a country is officially validated as having successfully achieved elimination of maternal and neonatal tetanus. This end to a major public health problem usually represents years of hard work and investment, and is accompanied by much national and international media attention and celebration.

How can we know that MNTE is being sustained?

— Periodically conduct a post-validation assessment exercise.
— Check on MNTE as part of regular programme review opportunities.

Unfortunately, given the ubiquitous nature of Clostridium tetani in the environment, if high coverage of vaccination with TTCV is not sustained, in the absence of high rates of clean birth and cord care practices, it is possible that a country could lose its MNT elimination status. For this reason, countries that have been validated need to periodically assess whether MNTE is being sustained. If weaknesses or concerns are identified, corrective actions must be planned and implemented swiftly.

A high-performing and reliable surveillance system for NT provides essential information for MNTE monitoring and is the best method for monitoring programme success and sustaining of MNTE status. However, as described in Chapter 5, vaccine preventable disease surveillance systems are not always sufficiently robust and/or adequately funded in some countries to be confidently relied upon.

As a consequence, countries that have validated elimination need to periodically conduct a post-validation assessment of MNTE (a standalone exercise) or include checking on MNTE as part of regular programme review opportunities (such as annual VPD data desk review, or national immunization programme review). There may also be other periodic opportunities, such as serosurveys (see Annex 10) or DHS/MICS/immunization coverage surveys, which can provide information for monitoring MNTE. Nevertheless, surveys rarely provide precise district-level coverage estimates and therefore, if MNTE status is to be reconfirmed as validated, special surveys may need to be designed for selected districts.


For further information on the method of validating MNTE see https://www.who.int/immunization/diseases/MNTE_initiative/en/index2.html.

49 Reliable NT surveillance: a) 0 cases notification functioning, b) completeness of district health facility surveillance reporting ≥80%, c) annual review of hospital records at least once a year. The needs: 1. Case definition of NT cases available and known in all health facilities, 2. Case investigation forms for suspected cases available and cases investigated, 3. If rural district, functional community level surveillance.
Countries themselves, with support from partners/stakeholders, can decide which approach(es) to use. The decision will depend on many factors such as overall performance of the immunization programme, consideration of risk factors that might affect MNTE status (e.g. emergencies, natural disasters, civil unrest/conflicts), available time and funding, and the unique opportunities that arise.

Table 12 describes and outlines the pros and cons of various options that countries may consider using to assess if MNTE is sustained after validation. It is possible that countries may use a combination of approaches over time. Guidance for each of the options is described in the following pages.

Table 12
Approaches to assessing if MNTE is sustained after validation

<table>
<thead>
<tr>
<th>Description</th>
<th>PROs</th>
<th>CONs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Option A. Annual VPD data desk review</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compile and review key MNTE indicators (fewer) as part of annual process of immunization programme VPD data desk review.</td>
<td>Conducted annually</td>
<td>Possible tendency to conduct in isolation (need to specifically invite other MCH/ANC programmes to join and share their data).</td>
</tr>
<tr>
<td>If quality district coverage data, especially PAB and health facility deliveries are available, this approach can avoid having to do the more resource-intensive post-validation assessment.</td>
<td>Integrated with performance review of other vaccines</td>
<td>Less focus on tetanus alone (diluted)</td>
</tr>
<tr>
<td></td>
<td>No special funds needed</td>
<td>Good quality data at district level is required for a valid assessment.</td>
</tr>
<tr>
<td></td>
<td>More likely to happen as being established as norm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linkage to cMYP and annual planning</td>
<td></td>
</tr>
<tr>
<td><strong>Option B. National immunization programme review</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MNTE sustainability included as a part of periodic national immunization programme review</td>
<td>Gives visibility to sustaining MNTE</td>
<td>Frequency every 3-5 years</td>
</tr>
<tr>
<td>This would require adapting the approach outlined in C below, and visiting the “at risk” districts as part of the fieldwork. The questionnaires/data collection variables used in Approach C could be adapted and imbedded into those used for the Immunization Programme Review.</td>
<td>Partner involvement</td>
<td>Availability of other programmes to join</td>
</tr>
<tr>
<td></td>
<td>Field visits</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Funded</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Findings linked to action through recommendations and work-plan</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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### Option A – Including MNTE sustainability in annual desk review of data

WHO and UNICEF encourage countries that have achieved MNTE to review their surveillance and other relevant datasets annually, with the purpose to identify if any districts are at risk of MNT re-emergence and if necessary, design and implement corrective actions quickly. When undertaken jointly, this annual data review can serve to further improve the synergy of EPI and MNCH programmes.

Beyond MNTE, for all programmes it is good management practice to carry out data desk reviews regularly and at all administrative levels so that data problems can be identified and addressed. The vision is that through the “use of data for action” all countries continuously improve the performance of their national immunization programmes (see Box 20 for guidance).

WHO recommends, that at a minimum, countries undertake an annual data review as an initial step in compiling and critically analyzing the available information needed for an annual programme performance review. A good time for such a review is after all annual data are collated and before the WHO/UNICEF Joint Report Form is prepared and submitted.

### Option C. Post-validation assessment of MNTE

<table>
<thead>
<tr>
<th>Description</th>
<th>PROs</th>
<th>CONs</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-step method to review core and surrogate MNT risk indicators which requires planning, and depending on the size of a country, may require 3-4 weeks preparation, a 3-day workshop, and field visits.</td>
<td>Very rigorous</td>
<td>Intensive</td>
</tr>
<tr>
<td></td>
<td>Involves EPI, MCH and surveillance programmes</td>
<td>Vertical approach (focus on MNTE only)</td>
</tr>
<tr>
<td></td>
<td>Linked to action</td>
<td>May be more costly (outsourcing for preparation, workshop and implementation, if no in-house expertise)</td>
</tr>
</tbody>
</table>

### Option D. Other opportunities

<table>
<thead>
<tr>
<th>Description</th>
<th>PROs</th>
<th>CONs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serosurvey</td>
<td>Accurate (if correctly implemented)</td>
<td>Irregular frequency</td>
</tr>
<tr>
<td>DHS/MICS surveys</td>
<td>Integrated</td>
<td>Usually implemented at national level, rather than focus on districts at high risk for MNTE</td>
</tr>
<tr>
<td>Vaccination coverage surveys</td>
<td></td>
<td>Costly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May require specialized external technical expertise</td>
</tr>
</tbody>
</table>

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A desk review can be performed by immunization programme staff alone or it can be done in collaboration with ANC and Health Management Information System (HMIS) staff. If MNTE is to be included, a collaborative approach is the preferred option because it will facilitate review of the non-immunization parameters, such as skilled birth delivery data. Full datasets should be reviewed (i.e. full national dataset in the case of a national level review).

In addition to vaccination coverage data, the desk review should include review of reported NT surveillance by district. Silent districts should be identified. The desk review of data does not require additional data collection. It is a review of existing data from routine information systems and selected reproductive health data which focuses on the following domains of data quality:

— completeness of administrative data;
— internal consistency of administrative data;
— external comparisons and consistency of administrative data (i.e. consistency with survey estimates);
— consistency of population data estimates (i.e. target population, the denominator for calculating coverage).

Normally, the desk review requires monthly or quarterly data by subnational administrative area for the most recent reporting year, and annual aggregated data for the last three reporting years, for the selected programmatic indicators.

Through analysis of the selected programme indicators, the desk review process quantifies problems of data completeness, accuracy and consistency, and thus provides valuable information on the adequacy of health-facility data to support planning and annual monitoring.

Increasingly, donors (such as Gavi) are making reviews of data and data quality along with a data quality improvement plan, a requirement for countries to receive funding (see Box 19). With very little additional effort, these can also be used as opportunities to verify the sustainability of MNTE.

Box 19

Gavi data quality requirements

Gavi requires that countries applying for all types of Gavi support:

1. Undertake routine monitoring of vaccination coverage data through an annual desk review.
2. Conduct periodic (once every five years or more frequently where appropriate) in-depth assessments of routine administrative vaccination coverage data.
3. Conduct periodic (at least once every five years) nationally representative vaccination coverage surveys.
4. Use 1 and 2 to develop a data quality improvement plan, that it is ideally integrated into other EPI plans.

WHO has developed a number of technical guides to support countries in the review of data and data quality (Box 20).

Box 20

WHO key resources for data and data quality assessments/reviews

Handbook on the collection, assessment and use of immunization data (to be published in 2020) – provides a framework for the systematic assessment and strengthening of national and subnational immunization data and information systems. This critical information is intended for country decision-makers to improve and use immunization and surveillance data, and enable them to:
1. decide what data are needed for programme improvement, and use them for action;
2. develop efficient tools and information systems to collect those data;
3. assess immunization data and systems, and implement data quality improvement plans.

Available online at: http://www.who.int/immunization/monitoring_surveillance/en/.

Data Quality Review Toolkit Module 2: Desk review of data quality (2017) – This toolkit is the result of collaboration between WHO, The Global Fund, Gavi, and (USAID)/MEASURE Evaluation and integrates and builds upon previous and current tools and methods designed to assess data quality at facility level. It proposes a unified approach to data quality, taking into account best practices and lessons learned from many countries.

Available online at: http://www.who.int/healthinfo/tools_data_analysis/dqr_modules/en/.
Option B – Integrating MNTE sustainability into a national immunization programme review

A national immunization programme review (also referred to as an EPI Review), is the comprehensive assessment of the strengths and weaknesses of an immunization programme at national, subnational and service-delivery levels. The purpose of this review is to provide evidence for the programme’s strategic directions and priority activities.

With this in mind, an EPI review should be conducted before the immunization programme’s strategic planning cycle, such as the cMYP. Review findings are presented formally to the Ministry of Health, other relevant ministries, and often the country’s Interagency Coordinating Committee (ICC) for their responses and endorsement for incorporation into the next strategic plan.

Because EPI reviews are comprehensive and look at all aspects of the immunization programme, it is only natural that they include the assessment of MNTE sustainability. WHO recommends that EPI reviews should be conducted every 3–5 years. In 2018 WHO published a new Guide for Conducting a National Immunization Programme Review (see Box 21).

Periodic post-validation assessment of MNTE could also be included in a VPD surveillance review as it is an exercise that may identify missed NT cases. Guidance on how to conduct a VPD surveillance review is also provided in the Guide for Conducting a National Immunization Programme Review (Box 21).

Box 21
WHO resource for conducting EPI reviews

A Guide for Conducting a National Immunization Programme Review (2018) – provides guidance to individuals and teams responsible for planning and implementing an EPI Review, with the main objectives to set a benchmark for conducting quality EPI reviews, share best practices in order to increase the efficiency and quality of reviews, including through the integration of assessments as feasible, and to emphasize that EPI reviews should be country-driven and part of a strategic planning process.


Assessment of MNTE sustainability could also be incorporated into Reproductive Health Programme reviews of ANC and skilled birth delivery, these reviews could assess the performance and missed opportunities for TTCV vaccination of pregnant women at ANC contacts and clean delivery practices.
Option C – Conducting a post-validation assessment of MNTE

Annex 11 provides the full details on the methodology for conducting a stand-alone post-validation assessment of MNTE. Use of MNTE risk assessment data sheet must be the starting point for the post validation assessment. WHO website contains the MNTE risk assessment data spreadsheet (Excel file format), sample tools, data tables and questionnaires that can be adapted to the local context (https://www.who.int/immunization/diseases/MNTE_initiative/en/).

A post-validation assessment comprises a desk-review of data to determine if MNTE indicator standards are being maintained and to identify any districts that are potentially at risk of not sustaining MNTE. It includes field visits and interviews at both the facility and community level, which in the poorer performing districts (particularly if there is any doubt about the quality of district level data), is critical to cross check the reported coverage of TTCV, ANC and skilled birth delivery. The assessment includes bottleneck analysis and development of a workplan and timeframe for implementing corrective actions, if needed.

The success of a post-validation assessment depends on good preparation and planning, as well as the participation of other relevant programmes (particularly MNCH and ANC).

Option D – Using serosurveys\(^{52}\) to assess MNTE sustainability

In 2016, WHO Strategic Advisory Group of Experts (SAGE) on immunization recommended that tetanus serosurveys be considered where feasible, to validate assessments of disease risk identified using other data sources, and to guide vaccination strategies. In 2018, WHO developed guidance for tetanus serosurveys\(^{53}\) that references the Guidelines on the use of Serosurveys in Support of Measles and Rubella Elimination\(^{54}\) and the updated WHO Vaccination Coverage Cluster Survey Reference Manual.\(^{55}\)

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52 Information on immunization coverage survey methods is available online at http://www.who.int/immunization/monitoring_surveillance/routine/coverage/en/index2.html.


**Serosurvey** — the collection and testing of blood specimens from a defined population over a specified period of time to determine antibodies against a given etiologic agent as a direct measure of the population’s immunity

**Seropositivity** — serologic evidence of the presence of an antibody of a specific type in the serum

**Seroprevalence** — the proportion of people in a population who test positive for serum antibodies against a specific disease or pathogen; it is often presented as a per cent of the total specimens tested

**Serosurveillance** — serosurveys conducted routinely or periodically

Natural tetanus infection is not a source of immunity, so immunity presents an attractive biomarker of vaccination coverage. Serosurveys provide objective measures for estimating population immunity. Tetanus serosurveys can be used by country programmes to provide an immunologic assessment of true protection of mothers and infants, and the correlation between maternal histories and their actual protection. This may be useful for monitoring of disease risk and when assessing the sustainability of MNTE. Routine serosurveillance programmes are however most common in higher-income countries.

**Use of tetanus serosurveys for monitoring achievement and maintenance of MNTE**

MNTE is defined as a district level goal of <1 neonatal tetanus case per 1,000 live births in every district per year. MNTE strategies include coverage with >80% of women with protective TTCV doses in every district. Conducting tetanus serosurveys in every district to evaluate this indicator would be resource-intensive, and is not recommended.

However, serosurveys performed at the national level or in designated high-risk districts that document >80% seroprotection can provide evidence compatible with elimination. Nationally representative serosurveys may indicate the presence of important immunity gaps, but may not confirm absence of immunity gaps in specific districts, required to validate the sustainability of MNTE status.

Because tetanus is not eradicable and many countries have achieved MNTE through time-limited campaigns, serosurveys should be considered where feasible to monitor population immunity and MNT risk and guide vaccination strategies, especially in high-risk districts.

Integrating the fieldwork with other surveys or laboratory testing efforts is recommended where possible to allow monitoring of impact and sharing of costs across public health programmes.
Before undertaking a tetanus serosurvey, programme-specific questions should be defined so that specific objectives would drive the design of the serosurvey. Table 13 provides possible objectives of serosurveys by target population.

Population-based cluster surveys are a method for obtaining estimates of seroprevalence representative of the target population. During the planning and design stages, a protocol is developed which defines preparation and implementation activities. More information on survey design and sampling methodologies are available in Annex 10 and the WHO Vaccination Coverage Cluster Survey Reference Manual, while considerations for protocol development, budgeting and implementation are included in the WHO Guidelines on the Use of Serosurveys in Support of MR Elimination.

Given the high cost of serosurveys, opportunities can be explored for integration with other activities and cost savings. These can be generated by integrating tetanus serosurveys implementation with other surveys such as Demographic Health Surveys (DHS), periodically conducted in many countries. DHS often include blood sample collection for children and WRA, and collect information on TTCV coverage, neonatal deaths, deliveries in health facilities and by skilled health personnel, ANC visits, parity, obstetric care, health care access, and socio-demographics that can inform interpretation of serosurvey results.

Table 13

Objectives of tetanus serosurveys by target population

<table>
<thead>
<tr>
<th>Target population</th>
<th>Objectives of tetanus serosurveys</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages and both sexes</td>
<td>Assess disparities in seroprotection (examples: adult males vs females, young vs school-age children). Determine duration of immunity and need for booster dose introduction or schedule optimization. Evaluate impact of catch-up vaccination or campaigns on tetanus immunity (including TT-conjugate vaccines).</td>
</tr>
<tr>
<td>Children (e.g. 6–23 months, 12–35 months, 6 months–5 years, 1–15 years)</td>
<td>Evaluate population immunity, compared with vaccination coverage (ages 6–11 and 12–23 months). Identify areas and subgroups needing targeted remediation (outreach, school-based immunization, etc.). Determine duration of immunity and need for booster doses (for example, at ages 12–23 months, 4–7 years, 9–15 years.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Target population</th>
<th>Objectives of tetanus serosurveys</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women of reproductive age before achieving MNTE</td>
<td>Evaluate population immunity, compared with vaccination coverage (e.g. TTCV2+/PAB).</td>
</tr>
<tr>
<td></td>
<td>Monitor impact of targeted campaigns in areas at high risk for neonatal tetanus.</td>
</tr>
<tr>
<td></td>
<td>Identify areas and subgroups needing targeted remediation through campaigns, outreach or another strategy.</td>
</tr>
<tr>
<td>Women of reproductive age after achieving MNTE</td>
<td>Monitor population immunity for maintenance of MNTE (e.g. in countries relying on campaigns to achieve MNTE).</td>
</tr>
<tr>
<td></td>
<td>Provide evidence needed for TTCV booster dose introduction as part of sustaining elimination.</td>
</tr>
<tr>
<td></td>
<td>Identify areas and subgroups for targeted remediation such as outreach vaccination or improved ANC and obstetric care.</td>
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</tbody>
</table>

AIDS Indicator Surveys (AIS) and Malaria Indicator Surveys (MIS) are other periodic surveys that almost always include collection of blood samples. Serosurveys for vaccine-preventable diseases (polio, measles, rubella, diphtheria, etc.) or other diseases (such as parasites, arboviral, or food- and water-borne diseases) may also be options for integration in some countries.

Another widely conducted periodic survey is the Multiple Indicator Cluster Survey (MICS), but it less often includes collection of blood samples.

An additional potential opportunity for integration and cost savings is through the use of multiplex laboratory testing such as bead-based immunofluorescence assays. Tetanus multiplex assays have been demonstrated to have good performance and cost saving compared to other laboratory tests. For more detail on options and cost see Annex 10.

Serosurvey findings should be interpreted in the context of current and historic data on immunization programme policies and performance, including any past supplementary immunization activities and disease incidence, if available. Tetanus survey results may differ from administrative vaccination coverage or coverage survey estimates. For interpretation of data, explanations of disparities between seroprotection rates and vaccinations coverage, and use of results see Annex 10.
Annexes
Annex 1.
What is tetanus?

Clinical features

Tetanus is an acute infectious disease caused by tetanospasmin, a toxin produced by the spores of bacterium Clostridium tetani (C. tetani) that grows in anaerobic conditions found in devitalized tissue and decaying matter. Tetanus toxin disseminates to nervous tissue via the blood and lymphatic system or enters the central nervous system along the peripheral motor neurons. The toxin blocks inhibitory neurotransmitters of the central nervous system, resulting in muscular rigidity and prolonged spasms.

Three clinical types of disease are often described.

1. **Localized tetanus** is uncommon and consists of spasms of muscles surrounding the site of injury. Although generally mild, localized tetanus may progress to generalized form of disease.

2. **Cephalic tetanus** is rare, associated with head or face lesions and/or with chronic ear infections. It presents as cranial nerve palsies and may progress to generalized tetanus.

3. **Generalized tetanus** is most common (>80% of cases) and presents as a generalized spastic disease. The common first sign is muscular stiffness in the jaw (trismus or lockjaw), followed by stiffness in the neck, difficulty in swallowing, rigidity of abdominal muscles, and spasms. Typical features are the facial expression resembling a forced grin known as “risus sardonicus”, and the position of backward arching of the head, neck and spine (ophisthotonus). Generalized spasms are initially induced by sensory stimuli, but they occur spontaneously as the disease progresses. During spasms the limbs are drawn up and flexed, fists are tightly clenched, and toes are hyper-flexed. Intense spasms can lead to convulsive fits. Ultimately, breathing becomes difficult as spasms become more frequent and prolonged, leading to respiratory failure. Spasm of the glottis can result in immediate death.

**Neonatal tetanus** (NT) is a form of generalized tetanus occurring in newborn infants, most often as a result of an infected umbilical cord stump. It is characterized by a newborn infant who sucks and cries for the first few days after birth, but who subsequently develops excessive crying and progressive difficulty to suck and breastfeed. Death occurs as a result of paralysis of the respiratory muscles and/or inability to feed.

Depending on age, quality of care available, and the length of the incubation period, the case-fatality rate of tetanus ranges from <1% for localized, 15–30% for cephalic, and 10–70% for generalized, including neonatal, tetanus. Higher mortality rates are associated with shorter incubation periods.

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1 The incubation period of non-neonatal tetanus usually varies 3-21 days, although it may range from 1 day to several months. The median interval to onset of symptoms is 7 days. In general, shorter incubation periods are associated with more heavily contaminated wounds, more severe disease, and a worse prognosis. For neonatal tetanus, the average incubation period is about 7 days, with a range from 3 to 14 days after birth in 90% of cases.
Tetanus can occur at any age and case-fatality rates are high. In the absence of medical intervention, the case-fatality rate approaches 100%. Even with intensive care, case-fatality rates are high (10–20%).

Reservoir and transmission
The spores of \(C.\text{ tetani}\) are found everywhere in the environment, particularly in soil, ash, intestinal tracts/faeces of animals and humans, and on the surfaces of skin and rusty tools like nails, needles, barbed wire, farm implements, etc. Being very resistant to heat and most antiseptics, the spores can survive for years.

Tetanus is not transmitted from person to person. Rather, \(C.\text{ tetani}\) enters the human body through contaminated wounds or tissue injuries, including those resulting from unclean deliveries, burns, dental extractions and surgical procedures such as abortions and circumcision performed under unhygienic conditions. Cases can occur in patients unable to recall a specific wound or injury and may follow inapparent wounds or those considered trivial.

Neonatal tetanus usually occurs through introduction of tetanus spores via the umbilical cord during the delivery through the use of an unclean instrument used to cut the cord or after delivery by ‘dressing’ the umbilical stump with substances contaminated with tetanus spores (see Chapter 4).

A person who recovers from tetanus does not develop immunity and must receive or complete a tetanus vaccination series to prevent future disease.

Risk groups
Anyone who has not received a complete vaccination series against tetanus and who has greater than usual risk of traumatic and puncture injury is at risk of contracting tetanus. This includes un- or under-vaccinated women of reproductive age and their newborn delivered by untrained birth attendant where delivery conditions and postpartum cord care practices are unclean.

Diagnosis
The diagnosis of tetanus is primarily based on clinical features, secondarily supported by epidemiologic setting, and does not depend on laboratory confirmation. There are no reliable confirmatory laboratory tests. WHO definitions for tetanus cases are summarized in the Table 11, Chapter 5.
Clinical case management of neonatal tetanus

NT is a medical emergency requiring hospitalization, immediate treatment with human tetanus immune globulin (TIG), agents to control muscle spasm (preferred choice benzodiazepines), and antibiotics (preferred choice metronidazole or penicillin G). A single intramuscular dose of human TIG is recommended as soon as possible to prevent further progression of the disease. If TIG is not available, equine-derived antitoxin tetanus serum (ATS) can be given in a single intravenous dose, after testing for hypersensitivity. Alternatively, intravenous immune globulin (IVIG) may be used. Supportive care should be provided including keeping patients in a dark and quiet environment to reduce the risk of reflex spasms, and nasogastric feeding for newborn infants. If muscle spasms are occurring, it is critical to maintain a safe airway. If mechanical ventilation is not available, patients should be carefully monitored in order to minimize spasm and autonomic dysfunction while avoiding respiratory failure.

Clinical case management of non-neonatal tetanus

Non-NT is a medical emergency requiring hospitalization and immediate treatment with TIG, drugs to control muscle spasm (preferred choice benzodiazepines), wound care, and antibiotics (preferred choice metronidazole or penicillin G). A single intramuscular dose of human TIG is recommended as soon as possible to prevent further progression of the disease. If TIG is not available, equine-derived antitoxin tetanus serum (ATS) can be given in a single intravenous dose after testing for hypersensitivity. Alternatively, intravenous immunoglobulin (IVIG) may be used.

Supportive care should be provided; patients should be kept in a dark and quiet environment to reduce the risk of reflex spasms. If muscle spasms are occurring, it is critical to maintain a safe airway. If mechanical ventilation is not available, patients should be carefully monitored in order to minimize spasm and autonomic dysfunction while avoiding respiratory failure. Finally, before discharge, age-appropriate tetanus toxoid containing vaccines (TTCV) should be administered to prevent future disease.

Health burden of tetanus

The health burden of tetanus is almost completely preventable through immunization with TTCV which are included in routine immunization programmes globally, and administered during antenatal care contacts (ANC) in many countries.

In many countries tetanus disease surveillance is not well established and its incidence is not known accurately. WHO estimates that in 2015, the latest year for which estimates are available, approximately 34 000 newborns died from NT, which represents a 96% reduction from the situation in the late 1980s. However, in 2017, a total of 12 476 tetanus cases including 2266 neonatal cases were reported through the WHO/UNICEF Joint Reporting Form indicating the low reporting sensitivity and uncertainty about the true disease incidence. However, WHO/UNICEF global and regional summary data reflect the changing picture of tetanus with decreasing NT and persistent burden of non-NT.

In settings where high TTCV coverage has not been achieved, immunity gaps exist. The immunity gaps in women of reproductive age (WRA) and in their newborn infants who

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are not protected against birth-associated tetanus contribute to continuing maternal
and neonatal tetanus burden in low-income countries. Immunity gaps have also been
identified in school-aged children and adolescents and notably adolescent/adult males
in low income countries who did not receive booster doses following the primary series
given in infancy,\(^3\) and who also need sustained protection against tetanus following
injuries and surgical procedures (e.g. motorbike accidents, voluntary male circumcision
as part of the programme for HIV/AIDS prevention, etc.). Because non-NT is beginning
to predominate globally, further reductions in disease incidence can be gained as
countries are able to ensure and maintain high coverage of the complete vaccination
series (3 primary and 3 booster doses prior to adolescence). Ultimately, the most
equitable and sustainable approach is to ensure tetanus protection over the life course
for all members of the population.

Annex 2.
Estimating target populations using UN Population Division estimates and projections

Official United Nations population estimates and projections have been prepared by the UN Population Division and are available in the series of Excel files that can be downloaded from the following link: https://population.un.org/wpp/ . A new Revision is issued every two years and the 2017 Revision provides population projections for the period 2015-2100. The next Revision is due in the first half of 2019.

To obtain the single age cohort estimates, do the following:


2. Under Major topic/Special Groupings select ‘Annual and single age data’ and the subgroup and files you are interested in (e.g. in ‘Age composition’ subgroup select file ‘Annual Population by Age - Both Sexes’).
3. Download the Excel file and filter the year and the country you are looking for.
Annex 3.
Determining the number of TTCV doses to be administered to a pregnant woman at ANC contact or health facility – health worker training scenarios

At a pregnant woman’s first contact with the health facility, health personnel enquire about her previous vaccination history and examine her vaccination cards/records to determine the number of Td doses required. A pregnant woman is deemed fully protected against tetanus upon receipt of 6 doses of a tetanus-containing vaccine, with the last dose being received in the adolescent period.

The following scenarios are used to determine the number of doses of tetanus-containing vaccines to be administered to pregnant women when they visit the health facility.

If a pregnant woman visits the health facility for the first time and this is NOT her first pregnancy her vaccination status must be reviewed against the schedule to ensure that she has been appropriately vaccinated. Efforts are usually made by health workers to complete vaccination schedules post-pregnancy.
If a pregnant woman received:

- **No TTCV doses or has unknown vaccination status**
  - she will need
  - a) 1 Td dose as early as possible
  - b) 1 Td dose at least 4 weeks later
  - c) 1 Td dose at least 6 months later
  - d) 1 Td dose at least 1 year later
  - e) 1 more Td dose at least 1 year later (to obtain long-term protection)

- **Only 3 TTCV doses in childhood**
  - she will need
  - a) 1 Td dose at the first ANC visit
  - b) Another Td dose 4 weeks later (to be protected for that pregnancy)
  - c) 1 more Td dose at least 1 year later (to obtain long-term protection)

- **4 TTCV doses in childhood**
  - she will need
  - a) 1 Td dose at that visit (to be protected for that pregnancy)
  - b) 1 more Td dose at least 1 year later (to obtain long-term protection)

- **3 TTCV doses in childhood and 1 Td or 1 DT dose later**
  - she will need
  - a) 1 Td dose at that visit (to be protected for that pregnancy)
  - b) 1 more Td dose at least 1 year later (to obtain long-term protection)

- **4 TTCV doses in childhood and 1 Td dose later**
  - she will need
  - a) 1 Td dose at that contact (no further doses required)

- **4 TTCV doses and 2 Td boosters**
  - she will need
  - No vaccination, the woman is fully protected
Annex 4.
How to implement the protection at birth (PAB) method in practice?

Introduction of the PAB method may require a modification of vaccination cards/home-based records, tally sheets, and immunization registers as well as an inclusion of this indicator in the HMIS at all levels, along with quality training and supervision of workers at immunization sites for it to be successful.

Mothers need to bring their ANC or maternal immunization card to facilitate the process, otherwise the health worker will have to rely on the mother’s recall to assess the number of TTCV doses received in the past and their timing.

Materials required:

— revised child vaccination cards/home-based records with space to record PAB;
— revised immunization tally sheets that include a space for recording PAB status;
— revised immunization reporting forms adapted to include PAB totals;
— the PAB calculator (Figure 1), available from WHO, can facilitate the process for health workers when they assess infants until they are confident with the method;
— availability/retention of long lasting immunization cards for mothers and children to prevent the need to take and rely on mother’s recall of TTCV doses (which can be difficult given other injections received by the mother during pregnancies or outside of pregnancies).

Method to assess PAB:

When mothers bring their children for their first vaccination of Penta/DTP1:

1) If the mother has a card

a. Ask to see it and check the number of Td doses given during the last pregnancy and during previous pregnancies if indicated on the card (1 to 5 doses).

b. Note when the last Td dose was administered.

c. Tally PAB (birth protected against tetanus) if the mother has received:
   — 2 properly spaced Td doses while pregnant with the child, OR
   — 1 Td doses while pregnant with the child and 1 TT/Td doses at any time before the pregnancy in the past, OR
   — NO dose of Td while pregnant with the child BUT 3 or more doses at any time during her reproductive years before that pregnancy.
   — NO dose of Td while pregnant BUT 5 (if tetanus vaccination started during adolescence or adulthood) or 6 TTCV doses previously which provides long-term protection.

1 There are other contacts that can be used to assess PAB. Refer to Table 8 for implementation options.
2) If mother does not have a card ask her questions about her Td immunization history:

a. How many doses of Td did she receive while pregnant with the child? If she received 2 doses, the birth was protected (PAB).

If she received one dose or no Td doses ask:

b. Did she receive any doses of Td before this pregnancy? If yes, how many doses of Td did she receive while not pregnant during Td/TT SIAs (special event when all women of reproductive age, including pregnant and non-pregnant, received an injectable vaccine)?

c. Did she have previous pregnancies? If yes, ask her the number of Td/TT doses she received during last 3 pregnancies.

Estimate if the infant was PAB based upon number of doses received and timing of last Td/TT doses and tally accordingly (PAB or not PAB) using criteria listed above.

How to introduce the PAB method at district and health facility level

— Start implementing the PAB method in 1–2 districts or in health centres with high coverage ANC1 (over 80%) to understand and optimize the process of implementing this new method. Training, vaccination cards/home-based records, recording and reporting forms are required.

— Prepare materials for training health staff to use the PAB method.

  — Adapt vaccination cards/home-based records, tally sheets, recording and reporting forms and make enough available for use during the training

  — Distribute the list of questions to ask mothers to each trainee. Adapt question to local context if needed.

— Prepare training agenda topics for each category of staff to be trained, district supervisors and health facility staff.

— Make sure health facilities use the recommended 5-dose Td schedule for maternal vaccination.

— Conduct practical training for supervisors, vaccinators, and other health facility staff with hands-on skills that are required, such as history taking, correctly assessing PAB, and correctly recording on the tally sheet, etc.

— Make sure district supervisors master the method, and can effectively detect and correct mistakes.

— After 2–3 months compare administrative maternal Td coverage rates and the coverage assessed by PAB method. Determine if you can extend the method nationally.
Example of reporting form for assessing protection at birth  
(adapted from Ghana reporting form)

**Section A: Health facility information**

1. Health Facility/District/Region: ________________________________

2. Type of service:  
   a) Health facility ☐   b) Community outreach ☐

3. Date of visit: ________________________________

**Section B: Mother information**

1. Age of mother in years ________________________________

2. Gravida (total pregnancies so far) ________________________________

3. Parity (total deliveries of number of children so far) ________________________________

4. Have you ever received any TTCV vaccination (before or during last pregnancy)?  
   ☐ a) Yes  
   ☐ b) No        If No, skip to question 9.

5. If Yes in question 4, total number of TTCV vaccinations

6. Source of information:  
   ☐ a) Maternal health record  
   ☐ b) History/recall (___)

7. Did you receive TTCV vaccination in last pregnancy (this child)  
   ☐ a) Yes  
   ☐ b) No        If No, skip to question 9.

8. If Yes in question 7, what is the total number of TTCV vaccinations received? _______

**Decision point (use NT protection calculator if available)**

Was the child protected from tetanus at birth?

   ☐ a) Yes  
   ☐ b) No  
   Decision rule:  
   If mother received 2 or more valid doses of TTCV – tick ‘yes’  
   If mother received less than 2 doses of TTCV – tick ‘no’
An easy to use tool for assessing PAB can be developed and used at the health facility, like the NT protection calculator featured in Figure 1. It is used to assess PAB at the Penta1/DTP1 contact as indicated in the instructions below.

**Figure 1**

**NT protection calculator**

Instructions for use of NT protection calculator:

**Question 1:** Ask the mother how many years ago she received her last dose of TTCV vaccine. Check her vaccination card if available. Rotate the disk until it points to the indicated number of years. If the answer is less than one year, assume one year.

**Question 2:** Ask the mother how many doses of TTCV vaccine she has received in her life. Check her vaccination card if available. Look at the colour in the window corresponding to the number of doses received.

**Answer:** If the colour in the window is green, the child was protected at birth by maternal antibodies. If the colour in the window is red, the child was not protected by maternal antibodies at birth, but may have been protected by clean birth practices. If the mother is eligible for TTCV vaccination, vaccinate her.
Annex 5.
Example of national tally sheet for TTCV2+ (or Td2+) for pregnant women

Proper recording of TTCV2+ coverage in pregnant women is important for NT prevention and should be emphasized to health workers. When assessing vaccination status, health workers must check whether a pregnant woman was fully vaccinated prior to pregnancy and vaccinate her if needed. Such monitoring of TTCV vaccination status prevents the unnecessary vaccinations of pregnant women. The example below is a national aggregate tally sheet for TTCV2+ vaccination coverage in pregnant women, and can be adapted to the specific country context.

<table>
<thead>
<tr>
<th>Region/ District</th>
<th>Target</th>
<th>Inadequately vaccinated</th>
<th>Fully vaccinated for this pregnancy</th>
<th>Fully vaccinated prior to the pregnancy</th>
<th>Total TTCV2+ g=b+c+d+e+f</th>
<th>%TTCV2+ coverage for pregnant women = g/target x 100</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>a (1st dose)</td>
<td>b (2nd dose)</td>
<td>c (3rd dose)</td>
<td>d (4th dose)</td>
<td>e (5th dose)</td>
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<td>Region/ District 1</td>
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<td>Region/ District 12</td>
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<td>Region/ District 13</td>
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<td>Private Sector</td>
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Annex 6.
Five moments for hand hygiene

Hand hygiene is the primary measure to reduce infections. Cleaning hands at the right times and in the right way makes most health care-associated infections preventable. In 2009, WHO developed guidelines for hand hygiene in health care which provides a thorough review of the evidence on hand hygiene in health care and specific recommendations to improve practices and reduce transmission of pathogenic microorganisms to patients and health care workers. These guidelines are complemented with a guide for implementation and an implementation toolkit which contain many ready-to-use and field-tested practical tools (see http://www.who.int/gpsc/5may/tools/en/).

The approach ‘My 5 Moments of Hand Hygiene’ explains five situations when cleaning the hands properly is recommended.

<table>
<thead>
<tr>
<th></th>
<th>When?</th>
<th>Why?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Before touching a patient</td>
<td>Clean your hands before touching a patient when approaching him/her. To protect the patient against harmful germs carried on your hands.</td>
</tr>
<tr>
<td>2</td>
<td>Before clean/aseptic procedure</td>
<td>Clean your hands immediately before performing a clean/aseptic procedure. To protect the patient against harmful germs, including the patient’s own, from entering his/her body.</td>
</tr>
<tr>
<td>3</td>
<td>After body fluid exposure risk</td>
<td>Clean your hands immediately after an exposure risk to body fluids (and after glove removal). To protect yourself and the health-care environment from harmful patient germs.</td>
</tr>
<tr>
<td>4</td>
<td>After touching a patient</td>
<td>Clean your hands after touching a patient and her/his immediate surroundings, when leaving the patient’s side. To protect yourself and the health-care environment from harmful patient germs.</td>
</tr>
<tr>
<td>5</td>
<td>After touching patient surroundings</td>
<td>Clean your hands after touching any object or furniture in the patient’s immediate surroundings, when leaving – even if the patient has not been touched. To protect yourself and the health-care environment from harmful patient germs.</td>
</tr>
</tbody>
</table>
Annex 7.
WHO Recommended Surveillance Standards for Neonatal Tetanus (NT)

Effective NT surveillance is a key component of the MNTE strategy.

Rationale and objectives of surveillance
Every NT case is an event that marks the failure of multiple levels of the health system. The key objective of NT surveillance is to detect cases of NT towards monitoring achievement and maintenance of MNTE, defined as less than one NT case per 1 000 live births annually in every district. NT surveillance data (or a lack thereof) are used to identify areas and subpopulations at high-risk for NT and guide effective public health response for MNTE. High-quality surveillance data and other key programme indicators should be used at the national and subnational (district) levels to monitor the impact of interventions and achievement and maintenance of MNTE.

Type of surveillance recommended
The minimal recommended standard for NT surveillance is nationwide, case-based surveillance, meaning that every suspected NT case should be investigated and classified as confirmed or discarded. NT surveillance is population-based and includes all neonates aged 0–28 days. Laboratory confirmation is not an aspect of NT surveillance, as the basis of tetanus diagnosis is clinical rather than laboratory-based.

Case detection

— Facility-based. Conduct facility-based surveillance by sensitizing surveillance focal points and key clinical staff (such as paediatric ward and special care nursery staff) at designated reporting sites to immediately report every suspected NT case to the designated surveillance staff. The network of reporting sites should include both public and private facilities.

— Passive surveillance. Report the number of suspected NT cases seen at designated reporting sites at a specified frequency (weekly or monthly) to the next higher level, even if there are zero cases (referred to as “zero reporting”). Health facility reports should be regularly monitored and verified by surveillance staff.

— Active surveillance. Make regular visits to reporting sites that are most likely to admit NT patients (weekly at major health facilities), or as part of active search for acute flaccid paralysis (AFP) and measles-rubella. During visits, review facility registers for unreported NT cases and ask key clinical staff whether any new NT case has been identified since the previous visit. At a minimum, every facility should review registers for NT cases annually. Active surveillance can also be conducted in the community during outreach visits, SIAs or case investigations.

— Community-based surveillance. Community-based surveillance should be done in high-risk areas through a network of traditional birth attendants, community leaders, traditional healers or other community members that are sensitized to report suspected NT cases and deaths to health authorities. In these cases, lay case definitions may be used in order to ensure that all suspected NT cases and deaths are detected and reported.

Linkages to other surveillance

Ideally, NT surveillance is linked with active surveillance for AFP and measles-rubella and routine aggregate surveillance for zero reporting as part of the Integrated Disease Surveillance and Response (IDSR). Linkage to vital events surveillance and neonatal death surveillance may be useful for increasing NT surveillance sensitivity and helping to conserve resources.

Case definitions and final classification

All suspected NT cases should be investigated. The basis for case classification is entirely clinical and does not depend on laboratory confirmation.

**Suspected NT case**

A case that meets either of the following two criteria:
- any neonate who could suck and cry normally during the first two days of life and developed tetanus-like illness or death between 3 and 28 days of age;
- any neonate who died of an unknown cause during the first month of life.

**Final case classification**

<table>
<thead>
<tr>
<th>Confirmed</th>
<th>Discarded</th>
<th>Not investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any suspected NT case found to have all three of the following:</td>
<td></td>
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<tr>
<td>— normal ability to suck and cry during the first two days of life;</td>
<td></td>
<td></td>
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<tr>
<td>AND</td>
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<tr>
<td>— could not suck normally between 3 and 28 days of age;</td>
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<td></td>
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<tr>
<td>AND</td>
<td></td>
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<tr>
<td>— developed muscle stiffness and/or spasms (jerking).</td>
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<td></td>
</tr>
<tr>
<td>The suspected NT case that has been investigated and does not satisfy the clinical criteria for confirmation or has an alternate diagnosis.</td>
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</tr>
<tr>
<td>Any suspected NT case not investigated or without information available on age and symptoms to confirm the case.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Case investigation

— Ideally, every NT case should be investigated. However, before achieving MNTE, the emphasis should be on implementing SIAs and community interventions to reduce NT burden in known high-risk areas.

— Once MNTE has been achieved, each suspected NT case or death should be investigated by trained staff to confirm or discard the case, ideally within seven days of notification. The sooner the mother and persons who attended the birth are visited, the more likely they are to be available and remember relevant details.

— All reported cases or deaths should be investigated using a standard case investigation form to confirm the NT diagnosis based on case history and symptoms. The investigation should determine why the infant contracted tetanus, such as lack of maternal vaccination, birth unattended or attended by unskilled staff, use of unhygienic cutting tools or application of substances to the umbilical stump. A simplified algorithm can be used to determine if the mother and infant were
protected at birth (PAB) against tetanus, based on maternal vaccination history (see Box 1 below).

— As NT diagnosis is entirely clinical, misdiagnosis can occur due to lack of training or lack of exposure to NT cases in low-incidence settings. Misdiagnosed cases of NT are most commonly meningitis, sepsis (including umbilical sepsis) or birth defects. Trismus (lockjaw) is absent in these illnesses. In addition, there is no bulging of the fontanelle in NT. During tetanus spasms, the child is conscious, and the spasm is often brought on by stimuli such as light and sound, unlike other convulsions from other causes such as high fever where the child is unconscious. In addition to clinical presentation, details from the case investigation (such as lack of maternal vaccination, unskilled birth attendant or application of unhygienic substances to the cord) may support the NT diagnosis.

Ensure that the filled case investigation form details the findings and actions taken or recommended, and is sent to the next level. Also give written feedback to the reporting facility and community.

Box 1

**Simplified protection at birth (PAB) method**

During case investigations, surveillance staff can use a simplified PAB method to determine whether a birth is protected against tetanus based on written maternal immunization records and questioning the mother about the number TTCV doses she received during the last pregnancy and the number of doses she received during school-age, previous pregnancies, or campaigns/outreach occurring any time before the last pregnancy. A birth is protected if the mother received:

— two TTCV doses while pregnant with the last child (with second dose delivered at least two weeks before birth); OR

— one TTCV dose while pregnant with the last child (delivered at least two weeks before birth) and one or more doses at any time before that pregnancy; OR

— no dose while pregnant with the last child and three or more adolescent/adult doses at any time before that pregnancy.

**Public health response**

— The mother of the suspected NT case and any other unprotected woman of reproductive age in the community should receive TTCV as indicated (two doses separated by four weeks) to protect her and infants during future births. If possible, the mother should be provided a TTCV dose before leaving the hospital, as part of outreach vaccination organized in conjunction with case investigation, or within six months of confirming the NT case.
Identification of a confirmed NT case may indicate a more systematic problem. A rapid community assessment should be conducted to determine the need for interventions.

- Starting from the house where the confirmed NT case occurred, move house to house to interview 10–15 other mothers of the community who delivered in the last two years about their vaccination status, delivery place and attendant, application of substances to the umbilical cord, and the survival and vaccination status of their last born child.

- If at least 80% of mothers are protected (either through clean birth, including delivery by a skilled birth attendant and hygienic cord practices, or PAB status), the response can be limited to vaccination of the mother of the NT case and promotion of hygienic cord care practices.

- If less than 80% of mothers are protected, determine the cause of non-protection and formulate an appropriate intervention. If less than 80% of mothers are protected through vaccination, assure that this community is added to the microplan for routine vaccination sessions, including outreach sessions that should include vaccination of pregnant women with TTCV. Make a return visit with a basket of interventions, including providing TTCV to pregnant women.

- If less than 90% of last-born children received DTP3, strengthen routine immunization services in the area (e.g. incorporate community in outreach microplans, reduce missed opportunities at outreach sessions, ensure vaccination at antenatal care visits and sick child visits).

- Complete corrective actions based on the factors that placed the infant at risk for NT. Corrective actions may include maternal vaccination, education on correct delivery or cord care practices and better coordination with maternal and child health services.

**Specimen collection**

No specimens are collected for NT cases, as there is no laboratory diagnosis of NT.

**Laboratory**

Tetanus diagnosis is entirely based on clinical features and does not depend on laboratory confirmation. C. tetani is recovered from microbiologic culture of wounds in only about 30% of cases, and the organism is sometimes isolated from patients who do not have tetanus. As non-toxigenic strains of C. tetani also exist, definitive laboratory diagnosis is not currently possible.

**Data collection, reporting and use**

**Recommended data elements**

(* designated core variable required to be completed as part of an adequate case investigation)

**Case notification**

- Name (if confidentiality is a concern the name can be omitted so long as a unique identifier exists)*
- Unique case identifier
- Date of notification*
- Source of notification (health facility location, name of person)
- Date of case investigation*
Geographic information
- Place of residence (city, district, and province)
- Reporting health facility

Demographics
- Date of birth*
- Sex*

Clinical
- Age of baby in days at onset of symptoms
- Date of onset (date of onset of lockjaw/inability to suck)*
- Date of hospitalization
- Signs and symptoms, including at minimum:
  - Ability to suck and cry during the first 2 days of life*
  - Between 3 and 28 days of age, cannot suck normally*
  - Muscle stiffness and/or spasms (jerking)*

Neonatal outcome
- Final outcome of child’s illness: alive, dead, unknown*
- Final classification: confirmed, discarded, not investigated, unknown
- Date of discharge/death

Maternal and perinatal risk factors
- Age of mother
- Ethnic group
- Migrant status
  (mother’s length of residency in locality where delivery took place)
- Number of live births delivered (including this most recent one) by the mother
- Number of previous births with similar symptoms and whether child(ren) survived
- Number of antenatal care (ANC) contacts the mother had with a trained healthcare worker during this last pregnancy
- Location of ANC (for follow-up regarding missed vaccination opportunity)
- PAB status of last birth (see Box 1)*
- Place of birth: hospital, health centre, home, other, or unknown*
- Assistance during childbirth: health staff (skilled birth attendant), traditional birth attendant, family member/alone, other, or unknown*
  - If not health staff, ask if clean surface and hands were used for delivery
- Tool(s) used to cut umbilical cord and sterilization of tool (cleaned and boiled)*
- Substance put on umbilical cord*
- Maternal outcome (dead, alive; cause of death)

Public health response
- Mother given TTCV (such as Td) dose(s) at the time of case detection/investigation, or as soon as possible afterwards (yes, no, not needed/already protected, unknown/unavailable)
  - If given protective dose, record date that TTCV dose was given
Reporting recommendations and requirements

The number of NT cases should be reported separately from non-NT cases by designated reporting sites weekly, monthly or at another specified frequency, even if there are zero cases (zero reporting). Copies of case investigation forms or electronic data from these forms should be forwarded to the national level.

Cases of NT (0–28 days of age) should be reported annually to WHO-UNICEF, and separately from non-NT (>28 days of age), through the WHO/UNICEF Joint Reporting Form available online at [http://www.who.int/immunization/monitoring_surveillance/routine/reporting/en/](http://www.who.int/immunization/monitoring_surveillance/routine/reporting/en/). Reporting of NT is not required by International Health Regulations (IHR).

Recommended data analyses

— Number and incidence of confirmed NT cases per 1,000 live births, by month, year, sex, and district
— Percentage of confirmed NT cases that were PAB by maternal vaccination (see Box 1)
— Percentage of confirmed NT cases whose mother received ANC, and among those who received ANC, those not vaccinated (for analysis of missed opportunities)
— Percentage distribution of confirmed NT cases by
  • Place of birth (health facility or home delivery)
  • Type of birth assistance
  • Type of cord-cutting tools used
  • Type of umbilical cord dressing used
  • Mother’s age
  • Mother’s parity (first birth vs. multiple births)
— Distribution of outcomes (death, left against medical advice, survived, unknown) among confirmed NT cases
— Percentage of confirmed NT cases whose mother received a TTCV dose(s) after the NT case occurred, as a result of the case detection/investigation or soon after
— Percentage of neonatal deaths attributable to NT (if part of neonatal death surveillance)
— Risk assessments (see section *Using data for decision-making* below)

As with other diseases, surveillance data should be triangulated with data from the immunization programme, such as vaccination coverage, history of SIAs, ANC coverage, and skilled birth attendance (SBA) coverage to understand the entire picture of the disease when formulating conclusions and new policies or strategies.
Using data for decision-making

— Monitor achievement and maintenance of MNTE (<1 NT case per 1 000 live births in every district) and document evidence towards validation and /or sustainability of elimination.

— Input data such as NT rates, TT protection, ANC and SBA coverage into annual risk assessments to identify high-risk geographical areas for targeting improvements in antenatal, obstetric, and vaccination services and conducting targeted SIAs for women of reproductive age.

— Identify with results of case investigations NT risk factors such as place/type of delivery, cord care, age and parity of mother, migrant status and ethnicity, in order to design appropriate messaging and interventions.

— Monitor impact of interventions, including SIAs.

— Identify missed opportunities for maternal immunization with TTCV, such as ANC visits, child visits and outreach vaccination sites.

— Document evidence needed for immunization policy or strategy change (for example, introduction of WHO-recommended booster doses and school-based immunization if first-time mothers are not being reached with vaccination at ANC visits).

— Rapidly identify cases for appropriate case management (refer NT cases for medical care and provide TTCV dose to mother).

— Monitor surveillance performance indicators and identify areas that need targeted surveillance reviews or strengthening (this may be needed when surveillance data appears unreliable when compared with NT risk).

Surveillance performance indicators

— Evaluate NT surveillance through periodic national reviews approximately every five years, integrating with other VPDs and including triangulation of aggregate and case-based NT reports as well as a review of facility records for missed cases.

— Conduct retrospective review of facility registers in hospitals and large health clinics at least annually to identify previously unreported NT cases alongside other VPDs and other diseases.

— As part of the quarterly EPI data review meetings, review surveillance, coverage, and programme performance data at national and subnational level to help identify potential areas where surveillance gaps might exist or surveillance needs to be strengthened.

— At least annually, review the indicators listed in Table 1.
## Table 1
### Neonatal tetanus surveillance performance indicators

<table>
<thead>
<tr>
<th>Surveillance indicator</th>
<th>Description</th>
<th>Target</th>
<th>Formula</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completeness of reporting</td>
<td>Percentage of designated sites reporting NT data, even in the absence of cases (zero reporting)</td>
<td>≥ 90%</td>
<td># sites reporting NT/# designated reporting sites for NT surveillance x 100 (for given time period)</td>
<td></td>
</tr>
<tr>
<td>Timeliness of reporting</td>
<td>Percentage of designated sites reporting NT data on time, even in the absence of cases (zero reporting)</td>
<td>≥ 80%</td>
<td># of surveillance units in the country reporting by the deadline/ # of designated reporting sites for NT surveillance x 100</td>
<td>At each level reports should be received on or before the requested date.</td>
</tr>
<tr>
<td>Completeness of investigation</td>
<td>Proportion of neonatal tetanus suspected cases that have been investigated (only among cases reported from health facilities)</td>
<td>≥ 90%</td>
<td># of NT case investigations/ # of suspected NT cases reported x 100</td>
<td>If case-based database only includes data on case investigations performed, this indicator can be calculated as: # suspected cases in the case-based dataset/# suspected cases in the aggregate report x 100. This indicator will reflect the representativeness of case-based surveillance and efficiency of case investigations.</td>
</tr>
<tr>
<td>Timeliness of investigation</td>
<td>Percentage of all suspected cases investigated within 7 days of notification</td>
<td>≥ 80%</td>
<td># suspected NT cases investigated within 7 days of notification/ # suspected NT cases investigated x 100</td>
<td></td>
</tr>
<tr>
<td>Adequacy of investigation</td>
<td>Percentage of investigated suspect cases with complete information for all core variables</td>
<td>≥ 80%</td>
<td># of suspected NT cases for which an adequate investigation was completed with collection of 12 core variables/ # of suspected NT cases investigated x 100</td>
<td>1) The core variables are: case identification, date of birth, sex, place of usual residence, date of illness onset, date of notification, date of investigation, symptoms in case definition, outcome (alive/dead), maternal vaccination history, place/type of delivery, tool for cutting cord, and material applied to cord. 2) For any case, if information on any of the core variables is missing, the investigation will be considered inadequate.</td>
</tr>
<tr>
<td>Achievement and maintenance of MNTE</td>
<td>Percentage of districts with &lt;1 NT case per 1 000 live births</td>
<td>100%</td>
<td># districts with &lt;1 NT case per 1,000 live births/ total # districts x 100</td>
<td>Ideally, this indicator should be calculated using confirmed NT cases. If the completeness of investigating suspect cases is &lt;90%, the indicator can be calculated using suspect cases to highlight districts needing targeted interventions and programme strengthening.</td>
</tr>
<tr>
<td>Adequate case response</td>
<td>Percentage of confirmed NT cases for which the mother received a TTCV dose in conjunction with case detection or investigation</td>
<td>100%</td>
<td># of mothers of NT cases that received a TTCV dose in conjunction with case detection or investigation/total # of NT case investigations x 100</td>
<td></td>
</tr>
</tbody>
</table>
Contact tracing and management
As tetanus is not contagious, no contact tracing is needed.

Surveillance, investigation and response during outbreaks
Tetanus is not considered an outbreak-prone disease. In general, NT outbreaks do not occur, but clusters linked to a single source of substandard clinical care have been observed. For disease clusters occurring in countries where MNTE has already been achieved, every case should still be investigated and there should be no change in the surveillance process. Before achieving MNTE, disease clusters should be investigated to determine risk factors, but the primary emphasis should be on implementing SIAs in known high-risk areas to reduce NT burden.

Special considerations in surveillance of neonatal tetanus
— Risk assessments. NT risk assessments are used to identify high-risk areas for targeted SIAs, programme improvement, and field evaluation during MNTE validation. For countries yet to achieve MNTE, NT risk assessments should be performed at least every one to three years, triangulating district-level data on NT cases and rates, skilled birth attendance (SBA), TT/PAB coverage from routine and SIAs, and other proxy indicators. For countries that have already achieved MNTE, regular risk assessments using the same inputs should be done (Annex 11).

— Ethical and equity issues. Discussion of neonatal deaths may be a sensitive topic, especially among some cultures and ethnic groups. NT may occur most frequently among marginalized groups missed by the immunization programme, such as migrants, the homeless and residents in urban slums, who may be sensitive to questioning by outside government officials. Use guidance from local health staff on how best to address these challenges.

— Neonatal death surveys. The relative contribution of NT to neonatal mortality can be assessed through audits of neonatal deaths at health facilities or in community settings, as described in the document called Making every baby count: audit and review of stillbirths and neonatal deaths¹ and implemented in some countries as part of the Every Newborn Action Plan. In some countries, activities in sentinel communities may approach or achieve real-time reporting of neonatal deaths and attempts should be made to link NT case detection to investigation through case-based surveillance. Of note, neonatal mortality cluster surveys (with verbal autopsies) are also conducted in the districts determined to be of highest risk for NT during MNTE validation exercises.²

— Serological surveys or serosurveillance. Where feasible, serosurveys of tetanus IgG among adult women should be considered as a complementary tool for monitoring MNT risk and guiding vaccination strategies. Because immunity does not result from natural infection, tetanus seroprotection reflects population immunity from vaccination. Close attention should be paid to the survey objective, sampling strategies and laboratory methods to ensure that results are valid and interpretable. Serosurveillance should not replace NT surveillance.

Annex 8.
WHO Recommended Surveillance Standards for Non-NT

Rationale and objectives of surveillance

The need for improved tetanus surveillance is underscored by the absence of reliable global estimates of non-NT cases and deaths, including maternal tetanus (see Box 1). A key objective of surveillance for non-NT is to monitor disease burden and changing epidemiology over time in order to assess the impact of vaccination and to identify gaps in the immunization programme. This information should be used to inform targeted strengthening of routine immunization services and optimize strategies and immunization schedules, including introduction and timing of booster doses. Another key objective is detecting and investigating unusual disease clusters. Finally, rapid detection of cases can help save lives and allow for proper treatment, including antitoxin, to begin.

Box 1

Maternal tetanus

Maternal tetanus is defined as tetanus occurring during pregnancy or within 6 weeks after pregnancy ends (with birth, miscarriage or abortion) and has the same risk factors and means of prevention as neonatal tetanus. For this reason, NT elimination (<1 case per 1 000 live births) is considered a proxy for maternal tetanus elimination.

If country programmes decide that maternal tetanus is of special priority, reports of maternal tetanus could be handled similar to reports of neonatal tetanus, including case investigation, rapid community assessments and public health response (see Annex 7). When feasible, serosurveys of tetanus immunity among women of reproductive age can be a complementary tool for monitoring MNT risk and guiding vaccination strategies (see Annex 10).

Type of surveillance recommended

The minimal recommended standard for non-NT surveillance is nationwide, aggregate surveillance with routine reporting from inpatient facilities and investigation of any unusual disease clusters. Non-NT surveillance is population-based and includes all persons ≥28 days of age. Laboratory confirmation is not an aspect of non-NT surveillance, as the basis of tetanus diagnosis is clinical rather than laboratory-based.

Enhanced surveillance for non-NT consists of case-based surveillance to aid understanding the epidemiology of the disease and causes of infection and to allow monitoring of treatment practices and disease outcomes. Either nationwide or sentinel surveillance would be advised, depending on the burden of disease, health-seeking behaviours and resources available in the country (sentinel surveillance requires fewer resources).

Case detection

— Establish a formal surveillance network of inpatient facilities designated for non-NT reporting and sensitize surveillance focal points and key clinical staff (such as ICU staff) to recognize and report non-NT cases per national guidelines.

— Report the aggregate number of inpatients with a final diagnosis of non-NT at designated reporting sites at a specified frequency (weekly or monthly), even if there are zero cases (referred to as zero reporting). Health facility reports should be regularly monitored and verified by surveillance staff. Unusually high numbers reported in a given month may represent a data entry error that needs to be corrected, or a disease cluster that needs investigation.

— For countries deciding to establish case-based surveillance for non-NT, public and private referral hospitals with intensive care capacity located in areas with high non-NT burden should be prioritized as sentinel sites to capture the majority of non-NT cases. Later, surveillance can be expanded to include additional sites that represent a larger extent of the population.

Linkages to other surveillance

Ideally, non-NT surveillance is linked with aggregate surveillance systems for other diseases through systems such as IDSR and EWARN. In some cases, HMIS reporting may be used for facility-based aggregate reporting of non-NT cases. Linkage to maternal death surveillance and response (MDSR) and other maternal child health post-partum surveillance systems may be relevant in some countries.

<table>
<thead>
<tr>
<th>Suspected non-NT case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any person &gt;28 days of age with acute onset of at least one of the following:</td>
</tr>
<tr>
<td>- trismus (lockjaw)</td>
</tr>
<tr>
<td>- risus sardonicus (sustained spasm of the facial muscles)</td>
</tr>
<tr>
<td>- generalized muscle spasms (contractions).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Final case classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed</strong></td>
</tr>
<tr>
<td>A suspected non-NT case</td>
</tr>
<tr>
<td>clinically confirmed as</td>
</tr>
<tr>
<td>tetanus by a physician/</td>
</tr>
<tr>
<td>trained clinician.</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Note:** The basis for case classification is entirely clinical and does not depend on laboratory confirmation. In low incidence settings, many clinicians may have never seen a tetanus case, making clinical diagnosis more challenging. During tetanus spasms, the patient is usually conscious, and the spasm is often brought on by stimuli such as light and sound, unlike other convulsions where the patient may be unconscious. Although tetanus diagnosis usually includes a history of injury or wound, tetanus may also occur in patients who are unable to recall a specific wound or injury. The most common differential diagnoses for tetanus are hypocalcemic tetany, drug-induced dystonias (from drugs such as phenothiazines), meningoencephalitis, strychnine poisoning, and trismus due to dental infections.
Case investigation

In countries conducting aggregate surveillance, information should be collected at designated health facilities from inpatient records for cases with a final diagnosis of non-NT, and reported to the next higher level based on national surveillance guidelines. No further investigation is needed except in the case of unusual disease clusters.

In countries conducting case-based surveillance, each suspected tetanus case should be investigated using a standard case investigation form, ideally within seven days of notification, to confirm the diagnosis and determine the cause of infection. Send filled case investigation forms detailing findings and actions taken or recommended to the next level and give written feedback to the reporting facility and community.

Tetanus immunoglobulin (TIG) or antitoxin tetanus serum (ATS) should be given immediately, even if investigation cannot be performed in a timely manner.

Specimen collection

No specimens are collected for non-NT cases, as there is no laboratory diagnosis.

Laboratory

Same as for NT, non-NT diagnosis is entirely based on clinical features and does not depend on laboratory confirmation.

Data collection, reporting and use

Recommended data elements

Aggregate surveillance

— Age group (optimal for tetanus epidemiology are 29 days–4 years, 5–14, 15–44, 45–64 and 65+ years, but can be aligned with needs of integrated surveillance system)
— Sex
— Month
— Geographical area
— Immunization status (if possible)

Case-based surveillance

— Case notification
  • Name (if confidentiality is a concern the name can be omitted so long as unique identifier exists.
  • Unique case identifier (such as EPID number)
  • Date of notification
  • Source of notification (health facility location, name of person)
  • Date of case investigation
Demographics
— Sex
— Date of birth (or age if date of birth not available)
— Race/ethnicity (if relevant)
— Migrant status
— Educational status
— Place of residence (city, district, province)

Clinical
— Date of onset
— Date of hospitalizations
— Signs and symptoms (at a minimum)
  • Trismus
  • Risus sardonicus
  • Muscle spasms

Vaccination status
— Number of tetanus vaccine doses (preferably by documentation, by recall if documentation not available)
— Date of vaccine doses, especially the last dose
— Receipt of tetanus conjugate vaccines (such as Hib, MenA, MenC, Pneumo, Typhoid, depending on formulation)

Risk factors
— Occupation
— History of wound or injury (including chigger/jigger infestation and intravenous drug use)
— History of surgery or medical procedure (e.g. male circumcision)
— History of dental or ear infection
— Maternal tetanus
  • Current or recent pregnancies (within the last 6 weeks)
  • Number of antenatal care (ANC) contacts during pregnancy
  • Pregnancy outcome (live birth/healthy child, live birth/NT case, still birth, miscarriage, or abortion)
  • Information on birth/pregnancy termination (date, location, who attended, clean surface/hands/tools)
  • Parity
— Application of unhygienic substances to wounds
Treatment
  — Tetanus immunoglobulin (TIG), antitoxin tetanus serum (ATS), intravenous immune globulin (IVIG) given
    • Date of administration
  — Antibiotics given (type)
    • Date of administration (starting date)

Outcome
  — Outcome (patient survived, died, unknown)
  — Final classification (confirmed, probable, discarded)
  — Date of discharge/death

Reporting recommendations and requirements
The number of non-NT cases should be reported separately from NT cases by designated reporting sites weekly, monthly or at another specified frequency, even if there are zero cases (zero reporting). Case investigation forms or electronic data from these forms should be forwarded to the national level.

For the purpose of case counts, tally only confirmed inpatient cases for national reporting because non-NT is managed on an inpatient basis. Including outpatients would likely result in overestimation because of problems like misdiagnosis, reporting errors from smaller facilities or double-counting of outpatients referred for inpatient admission.

Cases of non-NT should be reported annually to WHO-UNICEF and separately from NT, through the JRF (http://www.who.int/immunization/monitoring_surveillance/routine/reporting/en/). Reporting of NT is not required by International Health Regulations (IHR).

Recommended data analyses are:
  — number of non-NT cases and incidence rates by month, year and geographical area;
  — incidence rates by sex and age group (29 days–4 years, 5–14, 15–44, 45–64, and 65+
    years);
  — trends in the sex ratio of non-NT cases over time;
  — proportion of cases protected against tetanus (see Table 1);
  — proportion of cases by risk factor;
  — proportion of cases receiving TIG/ATS/IVIG;
  — case-fatality ratio (number of non-NT deaths / number of non-NT cases x 100);
  — proportion of maternal tetanus cases.

As with other diseases, surveillance data should be triangulated with data from the immunization programme, such as coverage and historic vaccination schedules, to understand the entire picture of the disease when formulating conclusions and new policy.
Table 1
Expected duration of protection provided by valid tetanus toxoid containing vaccine (TTCV) doses

(A valid dose is defined as a dose administered after the minimum time interval required. TTCV doses received by adolescents and adults during childhood are only included if verified by reviewing written records such as infant or school vaccination records.)

<table>
<thead>
<tr>
<th>Cumulative no. of TTCV doses if vaccination began in infancy</th>
<th>Cumulative no. of TTCV doses if vaccination begun 1 year of age</th>
<th>Minimum interval between doses to be considered valid</th>
<th>Duration of protection from receipt of last dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTCV1</td>
<td>TTCV1</td>
<td>—</td>
<td>None</td>
</tr>
<tr>
<td>TTCV2/TTCV3</td>
<td>TTCV2</td>
<td>4 weeks</td>
<td>3 years</td>
</tr>
<tr>
<td>TTCV4</td>
<td>TTCV3</td>
<td>6 months</td>
<td>5 years</td>
</tr>
<tr>
<td>TTCV5</td>
<td>TTCV4</td>
<td>1 year</td>
<td>10 years</td>
</tr>
<tr>
<td>TTCV6</td>
<td>TTCV5</td>
<td>1 year</td>
<td>20–30 years</td>
</tr>
</tbody>
</table>

Using data for decision making

— Monitor disease burden and impact of vaccination, including TTCV campaigns targeting women of reproductive age or wide-age range campaigns for both sexes with TT-conjugate vaccines such as MenA.

— Identify and investigate non-NT disease clusters to determine risk factors and appropriately design risk mitigation strategies such as provision of vaccine and improved hygiene practices.

— Identify gaps in the immunization programme (areas with low coverage, cold chain issues resulting in frozen TTCV, etc.) to inform targeted strengthening of routine immunization services or need for catch-up vaccination.

— Identify groups at higher risk for tetanus infection (women of reproductive age, school-age children, male adults, elderly) to inform changes in policy or strategy such as introduction of booster doses or optimization of schedule.

— Monitor maternal tetanus to strengthen MNTE strategies and reduce missed opportunities for vaccination such as ANC, sick visits, and outreach.

— Periodically assess tetanus risk factors (occupation, road accidents, unclean deliveries/surgeries, migrant status, ethnicity) to appropriately design and implement messaging and interventions.

— Rapidly identify cases for appropriate case management, including provision of TIG/ATS/IVIG.

— Monitor surveillance reporting to identify areas that need targeted surveillance reviews or strengthening, where surveillance data appear unreliable.
Surveillance performance indicators

Evaluate non-NT surveillance through periodic national reviews approximately every five years, integrating with other VPDs and including triangulation of aggregate and case-based NT reports as well as a review of facility records for missed cases. Targeted subnational reviews and data quality assessments can be conducted more frequently. As part of the quarterly EPI data review meetings, review surveillance, coverage and programme performance data at national and subnational level to help identify potential areas where surveillance gaps might exist or surveillance needs to be strengthened. Regular monitoring of surveillance indicators could help identify specific areas of the surveillance system and reporting network that should be targeted for improvement (Table 2).

Contact tracing and management

As tetanus is not contagious, no contact tracing is needed.

Surveillance, investigation and response in outbreak settings

Definition of outbreak

For non-NT, traditional communicable disease outbreaks do not occur because there is no person-to-person transmission, but cases may cluster together in time and space as a result of the same environmental exposure. A specific threshold has not been defined for the number of non-NT cases that should trigger investigation, but any substantial increase compared with previous reporting from the same area within a comparable timeframe should be investigated. A cluster of non-NT cases could include those occurring within the same geographic and time proximity, or multiple cases determined to be linked to the same source or event. Clusters of non-NT cases have been documented after natural disasters (earthquakes, tsunamis, typhoons), after male circumcision and from injection drug use.

Changes to surveillance in an outbreak setting

Even in countries with aggregate surveillance, data should be regularly monitored to identify potential clusters of non-NT disease. Clusters should be followed up with investigation to determine if there is a common cause. If a cluster is identified, consider line listing of cases with a limited set of variables so that more detailed analysis of cases can be performed (by age, sex, vaccination status, risk factors, treatment, etc.). This information can be used to inform risk mitigation efforts, including provision of vaccine and promotion of improved hygiene practices, both for individuals and for healthcare settings.

Special aspects of investigation

If there is a non-NT cluster, it is important to identify environmental exposure risk factors (nosocomial, occupational, accident).
<table>
<thead>
<tr>
<th>Surveillance attribute</th>
<th>Indicator</th>
<th>Target</th>
<th>How to calculate (numerator/denominator)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completeness of reporting</td>
<td>Percentage of designated reporting sites reporting non-NT data, even in the absence of cases</td>
<td>≥90%</td>
<td># designated sites reporting non-NT / # designated reporting sites for non-NT surveillance x 100 (for given time period)</td>
<td>Designated reporting sites for non-NT surveillance might only include hospitals or referral hospitals, rather than all health facilities.</td>
</tr>
<tr>
<td>Timeliness of reporting</td>
<td>Percentage of designated sites reporting non-NT data on time</td>
<td>≥80%</td>
<td># designated sites reporting non-NT on time / # designated reporting sites for non-NT surveillance x 100</td>
<td>At each level reports should be received on or before the requested date.</td>
</tr>
<tr>
<td>Completeness of investigation (case-based surveillance only)</td>
<td>Percentage of suspect-ed non-NT cases that have been investigated, only among cases reported from health facilities included in case-based surveillance</td>
<td>≥90%</td>
<td># of non-NT case investigations / # of suspected non-NT cases reported x 100</td>
<td>If case-based database only includes data on case investigations performed, this indicator can be calculated as: # suspected cases in the case-based dataset/# suspected cases in the aggregate report x 100. This indicator will reflect the representativeness of case-based surveillance and efficiency of case investigations.</td>
</tr>
<tr>
<td>Timeliness of investigation (case-based surveillance only)</td>
<td>Percentage of all suspected non-NT cases investigated within 7 days of notification</td>
<td>≥80%</td>
<td># suspected non-NT cases investigated within 7 days of notification / # suspected non-NT cases investigated x 100</td>
<td></td>
</tr>
</tbody>
</table>

Table 2
Performance indicators for non-NT surveillance
Special considerations in surveillance for non-neonatal tetanus

— **Serological surveys or serosurveillance.** Serological assessments of tetanus IgG antibody levels in a survey setting may be useful for evaluating protection against tetanus. Because immunity does not result from natural infection, tetanus seroprotection reflects population immunity from vaccination. However, the role of serological investigations should always be complementary to surveillance and other assessment methods, and the survey objective and outcomes should be well defined (see **Annex 10**).

— **Immunity gaps resulting from lack of booster doses.** Investigations have documented immunity gaps and higher burden of disease in school-aged children and adult men in countries not providing the WHO-recommended six TTCV doses to both sexes. All immunization programmes should review programme data and adjust routine immunization schedules to ensure tetanus protection over the life course (three primary doses in infancy and three booster doses in childhood/adolescence).²

— **Humanitarian emergencies.** Non-NT should be considered for inclusion in surveillance systems set up during humanitarian emergencies because of the documented outbreaks after earthquakes and tsunamis.³

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Annex 9.
Illustrative example of job aid on screening for vaccine eligibility

Example from Establishing and strengthening immunization in the second year of life guidance, available online at http://apps.who.int/iris/bitstream/handle/10665/260556/9789241513678-eng.pdf, adapted from Timor Leste and based on their vaccination schedule (up to 2 years of age). This example can be adapted to match local vaccination schedules.

<table>
<thead>
<tr>
<th>WHICH VACCINES CAN BE GIVEN TODAY?</th>
<th>WHEN TO GIVE</th>
<th>WHEN TO NOT GIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIRTH</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HepB (0, 1)</td>
<td>As soon as possible after birth, ideally within 24 hours, and up to 6 weeks</td>
<td>Not after 6 weeks</td>
</tr>
<tr>
<td>BCG</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **6 WEEKS**                        |              |                 |
| OPV 1                             | At 6 weeks (or as soon as possible thereafter) | Not after 2 years of age |
| PCV 1                             |              |                 |
| Penta 1                           |              |                 |
| IPV                               |              |                 |
| RSV                               |              |                 |

| **10 WEEKS**                       |              |                 |
| OPV 2                             | At 10 weeks (or as soon as possible thereafter), and at least 4 weeks after dose 1 | Not before 4 weeks has passed since previous dose |
| PCV 2                             |              |                 |
| Penta 2                           |              |                 |
| RV 2                              |              |                 |

| **14 WEEKS**                       |              |                 |
| OPV 3                             | At 14 weeks (or as soon as possible thereafter), and at least 4 weeks after dose 2 | Not before 4 weeks has passed since previous dose |
| PCV 3                             |              |                 |
| Penta 3                           |              |                 |
| RV 3                              |              |                 |
| IPV                               |              |                 |

| **9 MONTHS**                       |              |                 |
| MCV 1                             | At 9 months (or as soon as possible thereafter) | Not before 9 months of age (except where indicated) |

| **18 MONTHS**                      |              |                 |
| DTP 4                             | At 18 months (or as soon as possible thereafter), and at least 4 weeks since previous dose | Not before 4 weeks has passed since DTP 1 |
| MCV 2                             |              |                 |
| MenA                              |              |                 |

| **2 YEARS**                        |              |                 |
| Even if a long time has passed between doses, there is no need to restart the series from the beginning. | There is no upper age limit for most vaccines (except rotavirus <2yrs and hepatitis B birth dose <6 weeks) |
Annex 10. Serosurveys

Background and rationale

Tetanus is not eradicable because tetanus spores persist in the environment. Continued high and uniform vaccination coverage is needed to protect the population. Tetanus immunity from infant vaccination wanes with age, so booster doses are given at optimal ages to provide continuous protection across the lifespan (at 12–23 months, 4–7 years, and 9–15 years). In countries where childhood booster doses are not provided and maternal and neonatal tetanus is a public health problem, five TTCV doses (preferably tetanus-diphtheria vaccine, or Td) are provided to women of reproductive age (WRA) through campaigns in high-risk areas and pregnant women through routine services. In some countries, the provision of tetanus-toxoid conjugate vaccines (such as Hib, meningococcal, pneumococcal and typhoid conjugate vaccines) may boost tetanus immunity, but these vaccines are not counted towards the TTCV doses required in the schedule.

Coverage with three doses of diphtheria, tetanus and pertussis containing vaccine (TTCV3) is a key performance indicator of the routine immunization system. However, countries may encounter challenges with monitoring TTCV3 coverage through administrative methods due to inaccurate recording and reporting of vaccination doses and outdated target populations, significant migration from rural areas or through surveys with limited documentation of vaccination history or other biases associated with the survey methods (see Figure 1).

Countries that have yet to introduce the recommended three TTCV booster doses beyond infancy may desire evidence to make the decision for introduction. Some countries have achieved or will achieve MNTE through TTCV campaigns without accompanying health systems improvements such as routine immunization, antenatal care (ANC) or obstetric care. Continued monitoring is needed to ensure that MNTE is sustained. Even in countries that include six TTCV doses in their vaccination schedules, evidence may be needed to optimize schedules and close immunity gaps.

Figure 1

Tetanus vaccination coverage and seroprotection among children 12–23 months in linked coverage and serosurveys in three districts in Ethiopia, 2013

<table>
<thead>
<tr>
<th>District</th>
<th>Administrative DTP3 coverage</th>
<th>DTP3 coverage by survey (card + recall + facility register)</th>
<th>Seroprotection (≥0.15 IU/ml by in-house indirect ELISA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hintalo Wajerate</td>
<td>100%</td>
<td>80%</td>
<td>60%</td>
</tr>
<tr>
<td>Arbegona</td>
<td>80%</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>Assaieta</td>
<td>60%</td>
<td>40%</td>
<td>20%</td>
</tr>
</tbody>
</table>

In general, serosurveys provide objective biological measures for estimating population immunity and monitoring disease risk. Data from serosurveys are increasingly desired to guide policy and strategy, from supporting vaccine introduction to verifying disease elimination. Periodic cross-sectional serosurveys, or serosurveillance, can help document challenges with suboptimal programme implementation and changes in epidemiology resulting from accelerated disease control efforts. Routine serosurveillance programmes are most common in higher-income settings, such as Australia, the Netherlands and UK, but a case has been made for greater use of serological data for vaccination decision-making in lower and middle-income settings.

A limitation of serosurveys is that they cannot discriminate the number of vaccine doses received (for example, two or three doses) or the source of the immunizing event (natural infection for most diseases, routine vaccination or campaign vaccination). Unlike other vaccine-preventable diseases, a natural tetanus infection is not a source of immunity for tetanus, so immunity is an attractive biomarker of vaccination coverage.

Tetanus serosurveys are helpful in assessing population immunity resulting from cumulative coverage from vaccine doses, vaccine effectiveness (for example, reduced effectiveness due to freezing TTCV) and waning immunity over time (see Figure 2). Assessment of tetanus vaccination history for older children and adults is particularly challenging due to missing documentation, inability to recall infant doses and other doses received, and doses from sources not recorded on cards (such as during campaigns or after injury). In fact, tetanus serosurveys among adult women have shown vaccination coverage to be underestimated compared with tetanus seroprotection (see Table 1).

As immunization programmes mature and increasing proportions of adult women receive protective TTCV doses during infancy, school, campaigns and other places outside antenatal care, the disparity between seroprotection and maternal vaccination coverage is expected to grow. Indicators for maternal vaccination coverage include a second or subsequent TTCV dose (TTCV2+) or protected at birth (PAB). As part of broader tetanus prevention efforts, the Strategic Advisory Group of Experts (SAGE) on Immunization recommended that, where feasible, tetanus serosurveys should be considered to validate assessments of disease risk identified by other data sources, and to guide vaccination strategies, especially in high-risk districts.

Protection at birth (PAB) is a supplementary method of determining tetanus vaccination coverage, particularly where TT2+ is unreliable. PAB can be routinely monitored by surveying maternal vaccination status during infant DTPCV1 visits, and can also be assessed during vaccination coverage surveys that ask about maternal vaccination status during the last pregnancy occurring with a specified time period (1, 2, or 5 prior years). PAB is defined as having received 2 TTCV doses during the last pregnancy, ≥2 total TTCV doses with the last dose ≥3 years prior to the last birth, ≥3 doses with the last dose ≥5 years prior, ≥4 doses with the last dose ≥10 years prior, or ≥5 prior doses. A simplified PAB definition has also been proposed as mothers who received: (i) 2 TTCV doses while pregnant with the last child (with second dose delivered at least 2 weeks before birth), or (ii) 1 TTCV dose while pregnant with the last child (delivered at least 2 weeks before birth) and 1 or more doses at any time before that pregnancy, or (iii) no dose while pregnant with the last child and 3 or more adolescent/adult doses at any time before that pregnancy.

Figure 2
Tetanus seroprotection among individuals at district level in Kenya, Tanzania and Mozambique

Seroprotection was defined as ≥0.01 IU/ml by a tetanus bead-based immunofluorescence assay. Immunity gaps in older children and adult males exist because of waning immunity and provision of booster doses only to women of reproductive age. Of the three countries, only Mozambique provides two TTCV boosters to both sexes in first and second grades.

Table 1
Summary of vaccination coverage and seroprotection results of nationally representative tetanus serosurveys among reproductive-age women

<table>
<thead>
<tr>
<th>Survey</th>
<th>Population</th>
<th>PAB coverage</th>
<th>Seroprotection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burundi, 1989</td>
<td>Women giving birth in past year</td>
<td>73%</td>
<td>67%*</td>
</tr>
<tr>
<td>Central African</td>
<td>Women giving birth in past year</td>
<td>76%</td>
<td>89%**</td>
</tr>
<tr>
<td>Republic, 1996</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cambodia, 2012</td>
<td>Women aged 15–39 years</td>
<td>—</td>
<td>88%**</td>
</tr>
<tr>
<td></td>
<td>Parous women aged 15–39 years</td>
<td>83%</td>
<td>97%**</td>
</tr>
</tbody>
</table>

PAB = protected at birth
* ≥0.01 IU/ml in competition ELISA
** ≥0.01 IU/ml in Double Antigen ELISA

Survey setting and population

Globally, surveillance for neonatal and non-neonatal tetanus has been documented to be suboptimal. Serosurveillance complements disease surveillance but does not replace it. Tetanus serologic data can provide helpful information for monitoring population immunity and disease risk. It should be considered, where feasible, to guide vaccination strategies. Tetanus serosurveys can be useful in settings where reported vaccination coverage is high or where vaccination coverage data is known to be unreliable and independent verification of population immunity is desired. However, serosurveys are resource-intensive and not recommended for every country.

Across a broad age range, tetanus serological data can be used to assess immunity gaps and inform evidence-based remediation (catch-up vaccination or campaigns, optimization of schedules or addition of booster doses, etc.). In children, tetanus immunity has been identified as a potential biomarker for monitoring TTCV coverage. In WRA, sufficient tetanus immunity can be used to help monitor achievement and maintenance of MNTE (see Box 1 below). Depending on the country, WRA may be defined as 15–39 years, 15–45 years, 15–49 years or another similar age range. Women giving birth in the last year, two years or five years may be specifically targeted in order to assess recent changes in maternal vaccination programme performance. Restricting the survey population to include individuals targeted for vaccination within the last one to two years may improve recall of vaccination doses received and comparability between vaccination coverage and seroprotection. However, the number of household visits required to identify an eligible survey cohort with a narrow age range or birth period (such as one year) will be larger than the number of households required for a wider age range or birth period (such as five years). This has important resource implications.

Box 1

Use of tetanus serosurveys for monitoring achievement and maintenance of MNTE

MNTE is defined as a district level goal of <1 neonatal tetanus case per 1 000 live births in every district per year. MNTE strategies include coverage with >80% of women with protective TTCV doses in every district. Conducting tetanus serosurveys in every district to evaluate this indicator would be resource-intensive, and is not recommended. However, serosurveys performed at the national level or in designated high-risk districts that document >80% seroprotection can provide evidence compatible with elimination.

Because tetanus is not eradicable and many countries have achieved MNTE through time-limited campaigns, serosurveys should be considered where feasible to monitor population immunity and MNT risk and guide vaccination strategies, especially in high-risk districts. Integration of fieldwork for surveys or laboratory testing is recommended where possible to allow monitoring of impact and sharing of costs across public health programmes.

Objectives of tetanus serosurveys

Serosurveys assess population immunity rather than directly assessing vaccination coverage. For tetanus, the proportion of the population with demonstrated seroprotection is related to vaccination coverage as well as vaccine effectiveness and duration of vaccine-induced immunity. Before undertaking a tetanus serosurvey, it is
important to define the questions the programme hopes to answer and how the data will be used to guide policy, strategy or programme improvement. The specific objectives should drive the design of a tetanus serosurvey (see Table 2).

Usually, nationally representative estimates of seroprotection are desired, but subnational estimates in high-risk areas may suffice depending on the objective and the country situation. Inclusion of age, sex or regional/subnational strata in national surveys allows greater insight into variation in seroprotection, but can greatly increase the cost of the survey. Surveys of residual sera from ANC clinics or other convenience surveys are the most economical option, but the results of these surveys are not generalizable to the rest of the population and are subject to selection bias. For example, ANC coverage is low in many countries and those attending ANC are more likely to receive tetanus vaccination.

Table 2
Objectives of tetanus serosurveys by target population

<table>
<thead>
<tr>
<th>All ages and both sexes</th>
<th>Assess disparities in seroprotection (examples: adult males vs females, young vs school-age children)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Determine duration of immunity and need for booster dose introduction or schedule optimization</td>
</tr>
<tr>
<td></td>
<td>Evaluate impact of catch-up vaccination or campaigns on tetanus immunity (including TT-conjugate vaccines)</td>
</tr>
<tr>
<td>Children (e.g. 6–23 months, 12–35 months, 6 months–5 years, 1–15 years)</td>
<td>Evaluate population immunity, compared with vaccination coverage (ages 6–11 and 12–23 months)</td>
</tr>
<tr>
<td></td>
<td>Identify areas and subgroups needing targeted remediation (outreach, school-based immunization, etc.)</td>
</tr>
<tr>
<td></td>
<td>Determine duration of immunity and need for booster doses (for example, at ages 12–23 months, 4–7 years, 9–15 years)</td>
</tr>
<tr>
<td>Women of reproductive age before achieving MNTE</td>
<td>Evaluate population immunity, compared with vaccination coverage (for example, TTCV2+/PAB)</td>
</tr>
<tr>
<td></td>
<td>Monitor impact of targeted campaigns in areas at high risk for neonatal tetanus</td>
</tr>
<tr>
<td></td>
<td>Identify areas and subgroups needing targeted remediation through campaigns, outreach or another strategy</td>
</tr>
<tr>
<td>Women of reproductive age after achieving MNTE</td>
<td>Monitor population immunity for maintenance of MNTE (for example, in countries relying on campaigns to achieve MNTE)</td>
</tr>
<tr>
<td></td>
<td>Provide evidence needed for TTCV booster dose introduction as part of sustaining elimination</td>
</tr>
<tr>
<td></td>
<td>Identify areas and subgroups for targeted remediation such as outreach vaccination or improved ANC and obstetric care</td>
</tr>
</tbody>
</table>
Survey methods

Population-based cluster surveys are a method for obtaining estimates of seroprevalence that are representative of the target population. General considerations for protocol development, budgeting and implementation of serosurveys are included in the WHO Guidelines on the Use of Serosurveys in Support of Measles and Rubella (MR) Elimination (2018), while details on cluster survey design and sampling methodologies are found in the WHO Vaccination Coverage Cluster Survey Reference Manual. Close attention should be paid to survey sampling and laboratory methods to ensure that results are valid and interpretable.

During survey implementation, provide adequate training, supervision, and monitoring to ensure that survey staff follow the established protocol for selection of survey participants. Consent should be collected from all survey participants and parents of selected children; assent may also be needed for older children. The most important variables to collect for detailed analysis of seroprotection across subpopulations are age, sex, area of residence, education and vaccination status. For WRA, it is also important to collect data on parity, ANC attendance, clean birth and cord care for the last pregnancy.

Care should be taken to document the history of all received TTCV doses on home-based and health facility records, and by recall of doses received. TTCV doses may be documented on infant/child, school, maternal and campaign vaccination cards. Questions for recall of vaccination history should prompt survey participants about receipt of vaccines from all relevant sources (clinic/outreach, school, military, campaigns, etc.), and such questions should be asked of every participant in case the recorded history is incomplete. In settings where TT-conjugate vaccines are given (such as MenAfricvac campaigns), those doses should also be recorded separately (see sample questionnaire).

Sample collection

Serum or dried bloodspots (DBS) are the specimens of choice for serosurveys. Serum specimens prepared from whole blood (5 mL for older children and adults, 2.5 mL for infants and young children) are used most widely in serosurveys. DBS prepared from fingerprick blood may be more acceptable for participants and have the advantage of not requiring immediate cold storage and cold shipment. However, drying DBS completely may be challenging in humid climates, and the additional step required to elute serum from filter papers increases the labour required in the laboratory. Oral fluid specimens have been used for research, but are not recommended for regular use in tetanus serosurveys. Protocols for specimen preparation and storage are summarized elsewhere.

Serologic testing of tetanus immunity

The accepted minimum level of IgG antibody required for protection against tetanus is 0.01 IU/mL, as measured by the in vivo neutralization assay (gold standard). However, the antibody level required to achieve absolute protection against tetanus disease has been shown to vary based on individual exposure, including anatomical site and severity of infection. In vitro tests currently validated as accurate at the threshold for

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seroprotection (≥0.01 IU/mL) include modified ELISAs, such as competition ELISA, double-antigen ELISA (DAE), and toxin-binding inhibition (ToBI), as well as bead-based immunofluorescence assays such as multiplex bead assay (MBA). Though not commercially available, DAE, ToBI and MBA have all been successfully established in developing country settings and used in large serosurveys. Before serosurvey use, newly established tetanus assays should be validated against a reference test and calibrated with the tetanus international reference serum (TE-3).

A number of commercial options exist for tetanus indirect ELISAs, making these tests the most commonly used. However, indirect ELISAs have issues with non-specific binding in the low seroprotective range (≥0.01–0.20 IU/mL) requiring a higher cut-off; antitoxin concentrations of ≥0.1–0.2 IU/mL are usually defined as seroprotective when indirect ELISA is used (ideally determined by validation against reference test). None of the commercial indirect ELISAs have been validated against in vivo or in vitro tests accurate at the 0.01 IU/mL threshold for seroprotection. In addition to concerns of misclassification bias related to using a higher cut-off for indirect ELISA, documented variation in the sensitivity and accuracy of individual tests leads to important disparities in final results. For these reasons, use of indirect ELISAs is not generally recommended for tetanus serosurveys without confirmatory testing of samples with ELISA results <0.2 IU/mL by in vivo neutralization, DAE, ToBI or bead-based assays. Point of care tetanus IgG testing is also not recommended for serosurveys.

Opportunities for integration and cost savings
The largest cost savings for tetanus serosurveys can be generated by integrating field implementation with other planned vaccination coverage or serosurveys. Demographic Health Surveys (DHS) are periodically conducted in many countries and often include blood sample for children and WRA, in addition to collecting information on TTCV coverage, neonatal deaths, deliveries in health facilities and by skilled birth attendants, ANC visits, parity, obstetric care, health care access and socio-demographics that can inform interpretation of serosurvey results. The Multiple Indicator Cluster Survey (MICS) is also a widely conducted periodic survey, but less often includes collection of blood samples. AIDS Indicator Surveys (AIS) and Malaria Indicator Surveys (MIS) are other periodic surveys that almost always include collection of blood samples. Serosurveys for vaccine-preventable diseases (polio, measles, rubella, diphtheria, etc.) or other diseases (such as parasites, arboviral or food- and water-borne diseases) may also be options for integration in some countries.

Another potential opportunity for integration and cost savings is through multiplex laboratory testing. Bead-based immunofluorescence assays can be multiplexed to measure antibodies to multiple viral, parasitic or bacterial antigens simultaneously from the same small volume of serum (1–5 µL, or <1/10 of the volume required for ELISA). Tetanus multiplex assays have been demonstrated to have good performance with a relative cost savings over other laboratory tests. In one serosurvey, the cost of adding tetanus to a multiplex assay with 19 other antigens was 0.30 USD per sample, and the total cost of the 20-plex assay was less than the reference tetanus test (DAE) at 30 USD per sample. In costing of other serosurveys, the marginal cost of a 20-plex bead assay performed in-country is less than 20 USD per sample — similar in cost to separate ELISAs for measles and rubella.

Suggested data analyses
During data analysis, survey methods should be used to account for cluster survey design elements including strata, cluster and survey weights. Survey methods should also be used to calculate point estimates and 95% confidence intervals for the overall target population and survey strata. When estimating within subpopulations
not included in the original survey design (for example, those with three or more documented doses), the analyst should first evaluate whether the available sample size for each subpopulation is adequate, and whether the subsample is spread across many clusters or is from only a few clusters representing a narrow segment of the overall sample. The analyst should also consider the impact of the survey weights if the subsample is small. The following data analyses and visualizations are suggested if sufficient data is available:

— Proportion of target population with tetanus seroprotection (binary outcome using defined antibody level threshold, ≥0.01 for modified ELISAs, and bead-based immunoassays)
  
  • When reporting tetanus IgG results, the test method and cut-off used should be stated, as well as the correlation with a neutralization assay or other validation process, if known.

— Proportion of tetanus seroprotection by vaccination status (number of doses received) and data source (card, recall or card + recall).

— Proportion of tetanus seroprotection by subpopulation, such as age, geographic area, parity or education.

— Statistical comparisons of differences in seroprotection across subpopulations, noting that sample size may be insufficient to detect true differences among subpopulations.

— Median antibody levels by vaccination status and subpopulation.

— Proportion by antibody level category (0.01–0.09 IU/mL, 0.1–0.9 IU/mL, ≥1.0 IU/mL, with higher antibody levels generally correlating with higher probability and duration of tetanus protection).
  
  • It is unnecessary and technically inaccurate to give a qualitative assignment of duration of protection such as “short” or “long”. Instead, report the numeric category ranges.

— For parous women unprotected by vaccination, proportion with clean birth with skilled health personnel and clean cord care for last birth.

— Suggested data visualization:
  
  • stacked bar chart of proportions of antibody level categories by subpopulation (Figure 3);
  
  • if geographic strata are included, a choropleth map of seroprotection by subnational area;
  
  • for wide age range surveys, bar chart of proportion seroprotected (primary y-axis) and line chart of median antibody level (secondary y-axis) by age cohort (x-axis) (Figure 3).
Tetanus antibody levels were assessed using a tetanus bead-based immunofluorescence where seroprotection was defined as ≥0.01 IU/ml. The proportions of individuals by age groups and antibody level categories (<0.01 IU/ml, 0.01-0.09 IU/ml, 0.1-0.9 IU/ml, ≥1.0 IU/ml) are depicted with stacked bars and the geometric mean concentrations as a black line with 95% confidence intervals. Higher antibody levels generally correlate with higher probability and duration of tetanus protection and are noted following tetanus vaccination opportunities (depicted above the graph). The “MenC mass campaign” was a meningococcal C tetanus-toxoid conjugate catch-up vaccination campaign that occurred in 2002 as part of vaccine introduction into the routine immunization program at 14 months of age.

**Interpretation of results**

Tetanus antibody levels generally correlate with the robustness and duration of immunological protection against tetanus resulting from vaccination. Serosurvey findings should be interpreted in light of current and historic data on immunization programme policies and performance (schedules, coverage, etc.), including any past supplementary immunization activities and disease incidence, if available. This approach will give context to serosurvey results and may help highlight areas for potential improvement.

Limitations of the serosurvey should be included in any presentation of results, including selection bias (exclusion or non-random selection of participants), information bias (systematic bias from misclassification error of test or vaccination history) and non-response bias. Considerations for the use of serologic data to assess vaccination history have been summarized elsewhere. It is important to recognize that serological data are not necessarily a gold standard for assessing vaccination.

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status, and that serosurveys performed using tests with poor accuracy (inability to correctly classify seroprotection) have a substantial limitation.

Tetanus serosurvey results may differ from reported vaccination coverage or coverage survey estimates (Figure 1), and have the potential to indicate that immunization services are more or less effective than previously appreciated. Possible explanations for these differences are summarized in Table 3. Administrative TTCV2+ coverage of pregnant women is known to underestimate true protection against tetanus, as it excludes women unvaccinated during their current pregnancy but already protected through previous vaccination, or who received one dose in pregnancy and had undocumented previous doses. PAB coverage can also be underestimated due to residual immunity from infant doses in some women, or from booster doses provided outside routine services and misclassification of PAB status due to poor availability of documented vaccination history and recall bias.

**Table 3**
Possible explanations for differences in tetanus seroprotection and vaccination coverage

<table>
<thead>
<tr>
<th>Result</th>
<th>Possible explanations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus seroprotection higher than vaccination coverage</td>
<td>inaccuracies in reported TTCV coverage data (numerator and/or denominator)</td>
</tr>
<tr>
<td></td>
<td>immunity from TTCV doses not documented/recalled (examples: infant/childhood doses for adult participants, TTCV and MenAfriVac campaigns doses, doses following injury)</td>
</tr>
<tr>
<td></td>
<td>partial series of multidose vaccine (such as TTCV2) results in immunity</td>
</tr>
<tr>
<td></td>
<td>suboptimal specificity of laboratory testing, especially in areas with low immunity</td>
</tr>
<tr>
<td>Tetanus seroprotection lower than vaccination coverage</td>
<td>inaccuracies in reported TTCV coverage data (numerator and/or denominator)</td>
</tr>
<tr>
<td></td>
<td>reduced vaccine effectiveness from substandard vaccine administration or freezing of TTCV</td>
</tr>
<tr>
<td></td>
<td>age-group affected by waning tetanus immunity</td>
</tr>
<tr>
<td></td>
<td>suboptimal sensitivity of laboratory testing, especially in areas with high immunity</td>
</tr>
</tbody>
</table>

**Use of results**

Results from tetanus serosurveys have important potential use for monitoring population immunity and disease risk, as well as guiding policy, strategy and targeted improvements for the immunization programme. Triangulation of serosurvey results with current and historic immunization schedules and policies, coverage data, past campaigns and available data on disease incidence will help highlight any challenges with data quality as well as areas for potential improvement. For broader tetanus control, serosurveys can be used to:

— document evidence needed for tetanus immunization policy or strategy change (Td campaigns, introduction of recommended booster doses, school-based immunization, etc.);
— monitor impact of tetanus vaccination programmes, including changes in policy and strategies for greater effectiveness, such as catch-up vaccination, vaccination campaigns and strengthening ANC;

— verify adequate tetanus population immunity needed for disease control goals, and compare with other programme data (such as coverage and surveillance) as a means of independent validation;

— identify areas and subgroups (sex, age group, parity status, migrant status, ethnicity) with low tetanus seroprotection to appropriately design interventions (outreach, catch-up vaccination, campaigns, school-based vaccination).
Annex 11.
Methodology for a post-validation assessment of MNTE

(The forms/questionnaires are available to be downloaded from WHO website https://www.who.int/immunization/diseases/MNTE_initiative/en/)

A post-validation assessment of MNTE is an in-depth exercise to check that elimination status is being maintained. It can be undertaken periodically in any country that has achieved MNTE elimination status, but in particular, it is relevant for those who have concerns about the sustainability of their programme performance (e.g. declining EPI immunization coverage, implementation and management problems, humanitarian crisis or natural disaster, etc).

A post-validation assessment of MNTE requires sufficient time to plan and complete the following:
— conduct a comprehensive desk review;
— synthesize the findings of the desk review;
— undertake district risk categorization;
— complete a root cause analysis or field assessment (if needed);
— identify corrective actions and develop/endorse a MNTE priority action plan and budget for the implementation of proposed activities.¹

It is essential that the national EPI, MNCH and surveillance managers, together with partner representatives, are involved throughout the post-validation assessment of MNTE. Regional and district EPI, MNCH and surveillance managers participate once the districts are identified.

In order to conduct the post-validation assessment of MNTE, it is critical that reliable NT surveillance, vaccination and SBA coverage data, along with expert knowledge, are available to enable the accurate district categorization of potential risk for NT. Data for the past three years need to be compiled so that coverage trends can be reviewed.

There are five steps to complete a post-validation assessment of MNTE which are described below.

Five steps to complete a post-validation assessment of MNTE:
Step 1: Determine risk indicators (core, surrogate, additional).
Step 2: Collect and compile data for each district. Review data and adjust risk cut off points if needed.
Step 3: Review each district and classify them into risk categories (‘low risk’, ‘high risk’, or ‘at risk’) based on their level of performance and expert input.
Step 4: Conduct in-depth analysis for selected districts to identify corrective actions.
Step 5: Create a MNTE action plan for implementation of proposed activities.

¹  All activities should be detailed and budgeted in country annual plans, which can then form the basis for local plans of action.
²  Reliable NT surveillance: a) 0 cases notification functioning, b) completeness of district health facility surveillance reporting 80%, c) annual review of hospital records at least once a year. This requires the following: 1. Case definition of NT cases is available and known in all health facilities, 2. Case investigation forms for suspected cases are available and cases are investigated, 3. In rural districts, there is functional community level surveillance.
The approach uses core and surrogate risk indicators for MNT (see Table 1) over the past three years which are compiled and reviewed to identify and classify districts at risk. Additional indicators of interest may be added to extend the review of district performance beyond MNT.

The review process is complemented by the use of expert knowledge of the potential risk for NT before the final classification of the districts' risk status. The assessment exercise can be completed as a desk review or it may include field assessments to selected districts.

**STEP 1 (2 to 3 weeks):**

**Determine risk indicators, collect and compile data for each district**

Using Table 1 the post-validation assessment team leader should gather all the administrative data, as well as from surveys (e.g. MICS, DHS, coverage surveys) to cross-check reported coverage data and guide any adjustments that need to be made (see Step 2). Data for each district over the past three years should be compiled in a concise and easy to read format. An example template spreadsheet is available at WHO website (https://www.who.int/immunization/diseases/MNTE_initiative/en/).

<table>
<thead>
<tr>
<th>Core indicators</th>
<th>Surrogate indicators</th>
<th>Additional indicators of interest (examples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>reported number of NT cases</td>
<td>ANC1 coverage</td>
<td>urban vs. rural district</td>
</tr>
<tr>
<td>reported NT rate/1000 LB per district</td>
<td>ANC 4 coverage</td>
<td>geographic accessibility</td>
</tr>
<tr>
<td>skilled birth attendance (SBA) coverage</td>
<td>DTP1/Penta1 coverage</td>
<td>health infrastructure</td>
</tr>
<tr>
<td>district level data for coverage TTCV2+ and PAB</td>
<td>DTP3/Penta 3 coverage</td>
<td>other human development indicators</td>
</tr>
<tr>
<td>TTCV2+ coverage (for calculation see Chapter 3):</td>
<td>MCV1 coverage</td>
<td>percentage, absolute number and clustering of un- or under- vaccinated infants</td>
</tr>
<tr>
<td>— For pregnant women (routine EPI)</td>
<td>TTCV booster coverage</td>
<td>% pregnant women never attending ANC1, and/or delivering in absence of a SBA</td>
</tr>
<tr>
<td>— For WRA (age group as defined by the country) by TTCV SIAs and year of implementation</td>
<td>survey based coverage estimates (EPI-CES/MICS/DHS) by years, for comparison with reported data (HMIS or EPI or WUENIC data)</td>
<td></td>
</tr>
</tbody>
</table>

Data can be found from the following sources:

- **Health management information system (HMIS)**
  - HMIS data may show an over- or underestimate of performance indicators compared to survey data due to incomplete and/or untimely reporting, inaccurate numerators and denominators (e.g. outdated census, internal migrations, etc.), and the classic under- or over- reporting of NT cases (i.e. not reaching reporting sites and/or cases not confirmed by case investigation).
WHO and UNICEF Estimates of National Immunization Coverage (WUENIC)

WUENIC estimates\(^3\) which are revised annually, can serve to assess if reported national coverage data are under- or overestimated. Local knowledge or coherence between ANC coverage and reported TTCV2+, as well as DTP3/Penta3 coverage, may provide additional information for the review of district performance.

Recent (within the past 3 years) population health surveys (vaccination coverage surveys, MICS, DHS, etc.)

Although population health surveys assess national/regional and rarely district coverage performance, information obtained from these surveys, along with expert knowledge, may be helpful for the review and adjustment of under- or overestimated reported coverage for TTCV2+, other antigens, PAB, and SBA.

**STEP 2 (1 day workshop):**

Review and adjust risk cut-off points if needed

In a one-day workshop, the collected data compiled in the spreadsheet should be carefully reviewed and analysed by the assessment team. If there is a discrepancy between any very recent MICS/DHS/immunization coverage surveys and WUENIC data, the cut-off points for indicators in districts can be adjusted if supported by evidence and upon consensus of all team members.

Practical experience conducting post-validation MNTE assessment has found that it is often necessary to make cut-off adjustments in order to make the exercise manageable and focus on the districts likely at highest risk. Some further explanation and guidance regarding possible adjustments is provided below.

---

**NT rate cut-off point adjustment**

By definition, if there is <1 NT case per 1 000 live births reported in a district\(^4\) in the presence of reliable NT surveillance system, the district will be classified as ‘low risk’. In the presence of unreliable/weak NT surveillance, the cut-off point may be lowered to 0.5 cases per 1 000 live births or as agreed.

**SBA coverage cut-off point adjustment**

To attain MNTE status, the MNTE validation survey uses a Lot Quality Assurance Cluster Sample (LQA-CS)\(^5\) to assess that at least 70% of reported deliveries were in the presence of a SBA. However, for the post-validation assessment exercise, if needed this risk cut off-point can be adjusted to 60%. This is because reported SBA coverage remains a conservative estimate of the extent of clean birth practices due to the following reasons:

1. Deliveries in private clinics and home deliveries in presence of a SBA are often not accounted for in the HMIS reports. This underestimates urban SBA coverage.
2. A portion of home deliveries may not be attended by SBA (as defined by the country), but still adhere to the principles of Six Cleans (see Chapter 4).

---


\(^4\) In very large districts it may be necessary to consider sub-district analysis to verify clustering.

— TTCV2+ coverage cut-off point adjustment

Major differences may be noted in some countries between administrative reported TTCV2+ coverage (e.g. included in the WHO/UNICEF Joint Reporting Form) and TTCV (PAB) protection from coverage surveys. These coverage surveys take into account all TTCV doses ever administered through routine or SIAs and not just TTCV2+ of a given year. However, TTCV (PAB) protection from coverage surveys may still underestimate the true level of protection, as it excludes routine doses of TTCV administered during infancy.

When compared with survey results (EPI-CES, DHS, MICS), TTCV2+ administrative coverage at national and subnational levels can differ. This may be due to the following reasons:

- Pregnant women who completed the five-dose schedule are not eligible for another TTCV dose and often are not accounted for in the TTCV2+ coverage in the administrative reports (see Chapter 3 for correct formula to be used for TTCV2+ calculation)
- Pregnant women often receive a dose of TTCV vaccine in each pregnancy without taking previous history into account, especially in the absence of documented history such as through vaccination cards (as a result TTCV1 doses are de facto TTCV 2, 3, 4 or 5).
- TTCV doses administered during TTCV SIAs are not counted in the routine administration of TTCV doses at ANC contacts (i.e. history of past TTCV SIA doses is rarely asked at ANC, therefore these doses are not included in the routine administrative reporting of TTCV2+ coverage).

For the above reasons, although the TTCV2+ coverage of at least 80% is compatible with MNTE status, the TTCV2+ district coverage cut-off point to be used in the post-validation assessment may be adjusted to 70% if agreed/justified. However, the rationale for making this adjustment should be based on country and district specificities.

STEP 3 (same 1 day workshop):
Review each district and classify them into the following risk categories ‘low risk’, ‘high risk’, or ‘at risk’, based on their level of performance.

Following the WHO algorithm (Figure 1):
— Review the NT rate for each district, based on the agreed cut off point (1/1 000 LB or adjusted 0.5/1 000 LB):
  - If reported NT rate is higher than the cut-off point, classify the district as ‘high risk’.
  - If the reported rate is lower than the cut-off point, further evaluate the district, based on the reliability of the NT surveillance system.
— Evaluate the reliability of the NT surveillance:
  - If the surveillance system is reliable, classify the district as ‘low risk’.
  - If deemed unreliable, continue evaluation of the district using SBA coverage.
— Review the district for SBA coverage:

- If SBA coverage in the district is equal to or greater than the agreed upon cut-off point (i.e. ≥60%), classify the district as ‘low risk’.
- If the district SBA coverage is lower than the cut-off point, evaluate the district further for TTCV2+ or PAB coverage.

— Review TTCV2+ or PAB coverage:

- If the TTCV2+ coverage in the district is equal to or greater than the agreed upon cut-off point (i.e. ≥70%), classify the district as ‘low risk’.
- If the district TTCV2+ coverage is lower than the cut-off point, classify the district as ‘at risk’.

— Review ‘at risk’ districts and further classify them into ‘medium risk’ or ‘high risk’.

- Classify ‘at risk’ districts into ‘medium risk’ if any of these criteria apply:
  - Reported SBA coverage: 40–60%, or
  - Reported TTCV2+ coverage: 50–70%, or
  - Reported both ANC1 and DTP/Penta3: 60%–85%.
- If none of the above applies, classify remaining ‘at risk’ districts as ‘high risk’.

Where risk is unidentified because of lack of data (i.e. silent areas) the district should be deemed as ‘high risk’ as it is likely to have unreported NT cases.

---

6 Delivery by a skill health personnel or as defined by the national policy (see Chapter 4)
Antenatal care (ANC) contacts and tetanus vaccination status of pregnant women

Figure 1
WHO algorithm to classify potential risk of NT in districts
(Step 3 of MNT risk assessment)

NT rate <1/1000 LB?

NO

HIGH RISK

Reliable NT surveillance?*

NO

NO

AT RISK

SBA 40-60% or TTCV2+ in pregnant women 50-70%
ANC1 and DTP/ Penta3 >60%

MEDIUM RISK

YES

YES

LOW RISK

TTCV2+ or PAB coverage ≥70%?

NO

SBA <40% or TTCV2+ in pregnant women <50%
ANC1 and DTP/ Penta3 <60%

HIGH RISK

YES

LOW RISK**

* Reliable NT surveillance:
  a) 0 cases notification functioning,
  b) completeness of district health facility surveillance reporting ≥ 80%, c) annual review of hospital records at least once a year. This requires the following: 1. Case definition of NT cases is available and known in all health facilities, 2. Case investigation forms for suspect ed cases are available and cases are investigated, 3. In rural districts, there is functional community level surveillance.

** Delivery by skilled health personnel or as defined by the national policy.
STEP 4 (1 week):
Conduct in-depth analysis for selected districts to identify corrective actions

Based on findings from the desk review and district classifications, two approaches can be undertaken to conduct in-depth analysis for selected districts.

1. Conduct field assessment using standardized tools

The field assessments should be conducted using standardized tools (e.g. district assessment forms, available at WHO website https://www.who.int/immunization/diseases/MNTE_initiative/en/) in one ‘low risk’ (e.g. high performing) district, to document best practices, and two ‘at risk’ (e.g. lower performing) districts, to document possible weaknesses and recommendations for improvement.

The standardized tools for the field visits are designed to confirm if the districts have been able to sustain MNTE status since the country achieved its elimination. The field assessment evaluates the current risk of MNT through visits to district health offices; referral hospitals; health facilities, and communities with women who had a child in the previous two years.

Activities during field assessments include:

— review of registers, microplans, vaccine stock records to assess whether TTCV2+ is over or underestimated;
— examination of reports of NT cases to see if there have been misdiagnoses, or if the cases belonged to other districts (e.g. referral cases);
— review of the NT surveillance procedures, including if and how referral hospitals record reviews are performed, if there is active/community-based surveillance and community sensitization in rural areas;
— discussions with local health workers and authorities, including hospital paediatric ward staff, to get an impression of the general state of health services in the area and to obtain any additional reports and information;
— review of earlier reports on district performance (surveys, service or surveillance evaluations, etc.);
— interviews with a sample of women who had a child in the previous two years to assess their level of TTCV2+ protection based on history of all TTCV doses ever administered during past TTCV SIAs and during past pregnancies, their frequency of missed opportunities for TTCV administration, use of ANC services, PAB, typical delivery conditions, cord care practices, and perceptions about service availability and reliability.

All evidence gathered from the field assessments should be compiled and analyzed, with findings summarized, including key indicators: number of women interviewed, TTCV2+, TTCV5+ coverage, proportion of births in health facilities, proportion putting traditional substance on cord, proportion of women and deliveries protected against tetanus by combined TTCV and skilled birth attendance.

The assessment team, comprising of EPI, MNCH, surveillance managers and partner representatives, should consider again whether it is likely that MNTE elimination has been sustained, and if weaknesses have been identified, how they should be addressed (see Step 5).

7 Debriefing slide set example available online at: https://www.who.int/immunization/diseases/MNTE_initiative/en/
2. Root-cause analysis (RCA)

As an alternative to conducting field visits, an in-depth analysis can also be done by completing a root-cause analysis (RCA) of ‘at risk’ districts to further assess and identify causes for low performance. To facilitate the RCA, certain indicators relating to EPI and MNCH programme components e.g. TTCV2+ vaccination, focused antenatal care, and SBA need to be examined for programme and related management issues (see Table 2).

Table 2
Examples of indicators to be examined in the root cause analysis (RCA) per programme component

<table>
<thead>
<tr>
<th>Programme component</th>
<th>Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccination coverage with TTCV and PAB coverage</strong></td>
<td><strong>Commodities:</strong> — Proportion of facilities reporting stock-outs of TTCV vaccine for more than 7 days in the previous 3 months</td>
</tr>
<tr>
<td></td>
<td><strong>Human resources:</strong> — Proportion of facilities without trained nurses and midwives</td>
</tr>
<tr>
<td></td>
<td><strong>Access:</strong> — Existence of RED/REC plan (fixed/outreach/mobile teams) — Proportion of outreach and mobile sessions conducted in last 3 months</td>
</tr>
<tr>
<td></td>
<td><strong>Quality:</strong> — Proportion of pregnant women who were protected for tetanus (TTCV2+) and/or PAB — If implementing child or adolescent TTCV booster doses, percentage of children who received 6 TTCV doses by adolescence</td>
</tr>
<tr>
<td><strong>Focused antenatal care (ANC coverage)</strong></td>
<td><strong>Access:</strong> — Proportion of pregnant women who had at least 1 ANC visit — Proportion of health facilities providing TTCV vaccination at ANC visits</td>
</tr>
<tr>
<td></td>
<td><strong>Utilization:</strong> — Proportion of pregnant women who had at least 4 ANC contacts</td>
</tr>
<tr>
<td></td>
<td><strong>Quality:</strong> — Proportion of pregnant women who attended ANC within the first trimester</td>
</tr>
<tr>
<td><strong>Skilled birth attendance (SBA coverage)</strong></td>
<td><strong>Human resources:</strong> — Proportion of facilities with skilled health care workers (doctors, nurses, midwives)</td>
</tr>
<tr>
<td></td>
<td><strong>Access and utilization:</strong> — Proportion of live births delivered in a health facility</td>
</tr>
<tr>
<td></td>
<td><strong>Quality:</strong> — Proportion of deliveries who received postnatal visit within 24 hours.</td>
</tr>
</tbody>
</table>

It is essential to document and summarize the findings on issues and barriers to allow for their prioritization and to determine the necessary corrective actions (Step 5).
Step 5 (1 day workshop):
Create a MNTE priority action plan for implementation of proposed activities for action

For each of the issues identified through the in-depth analysis (Step 4), proposed corrective interventions should be consolidated into a MNTE priority action plan (see example of an outline in Table 3) during a workshop attended by EPI, MNCH, surveillance managers and partner representatives.

The MNTE priority action plan should also include immediate next steps, timeline for completion, and should identify the responsible person/organization, budget requirements and source of funding (if needed).

Table 3
Outline of MNTE priority action plan with examples of identified issues and proposed interventions

<table>
<thead>
<tr>
<th>Main issues identified</th>
<th>Proposed interventions for action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underutilization of TTCV vaccination services due to:</td>
<td>Example</td>
</tr>
<tr>
<td>— Insufficient number of outreach teams</td>
<td>— Map unreached and revisit RED/REC microplanning to ensure all pregnant women are within 5km of a vaccination site</td>
</tr>
<tr>
<td>— Limited access to ANC services</td>
<td>— Ensure at least 6 vaccination sessions per year for outreach</td>
</tr>
<tr>
<td>— Poor mobilization and under-vaccination of pregnant women at outreach sites (with or without ANC)</td>
<td>— Consider 2-4 PIRI per year for very hard-to-reach populations</td>
</tr>
<tr>
<td>— Insufficient involvement of CHWs</td>
<td>— Include additional interventions in PIRI based on community needs</td>
</tr>
<tr>
<td>— TTCV vaccine stock out</td>
<td>— Community-level identification and tracking of eligible women and infants, with defaulter tracing</td>
</tr>
<tr>
<td>— Underestimation of TTCV2+ coverage due to monitoring deficiencies</td>
<td>— Organize periodic review meetings with health facility workers and community representatives and CHWs</td>
</tr>
<tr>
<td>— Weak and unreliable NT surveillance due to poor health worker understanding</td>
<td>— Allocate required additional resources to reach all target population</td>
</tr>
<tr>
<td>— Etc.</td>
<td>— Distribute case definition of NT cases to all health facilities and provide refresher training via supportive supervision</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immediate next steps</th>
<th>Timeline for completion</th>
<th>Budget/funding source (if needed)</th>
<th>Responsible person/organization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>


Report on the Validation of Maternal and Neonatal Tetanus Elimination

The Philippines

November 2017
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ACRONYMS

AFP  Acute flaccid paralysis
ANC  antenatal care
ARMM  Autonomous Region of Muslim Mindanao
BHW  barangay health worker
CBR  crude birth rate
CDC  U. S. Centers for Disease Control and Prevention
CFR  case fatality rate
DOH  department of health
DPT  diphtheria-pertussis-tetanus
EPI  expanded program on immunization
FHSIS  Field Health Service Information System
GIDA  geographically isolated and depressed areas
HDI  human development index
IP  indigenous populations
LQA-CS  lot quality assurance-cluster survey
MCH  maternal and child health
MCV  measles containing vaccine
MNT  Maternal and neonatal tetanus
MNTE  maternal and neonatal tetanus elimination
NDHS  National Demographic Health Survey
NMR  neonatal mortality rate
NT  neonatal tetanus
nNT  non-neonatal tetanus
OPV  oral polio vaccine
PAB  protected at birth
SBA  skilled birth attendant
SIAs  supplementary immunization activities
Td  tetanus and diphtheria vaccine
TT  tetanus toxoid
TTCV  tetanus toxoid containing vaccine
UNICEF  United Nations Children’s Fund
VVM  vaccine vial monitor
VPDS  Vaccine preventable diseases surveillance
WHO  World Health Organization
1. BACKGROUND

Tetanus is an acute, potentially fatal disease caused by a neurotoxin produced by *Clostridium tetani* bacterium. Maternal and neonatal tetanus (MNT) are forms of generalized tetanus affecting mothers during pregnancy, due to unclean abortion or delivery, and infants during the first month of life. Neonatal tetanus (NT) infection begins when spores of the organism *C. tetani*, introduced into the umbilical tissue during delivery or cord care practices, produce a neurotoxin at the site of the umbilical cord wound that passes into the bloodstream of the new-born and into the central nervous system. This results in motor neuron hyperactivity, hypertonia and muscle spasms. Death occurs as a result of paralysis of the respiratory muscles and/or inability to breastfeed.

Maternal and neonatal tetanus are important preventable causes of maternal and neonatal mortality, particularly in developing and underdeveloped countries. The disease is a marker of economic and social inequity since most cases occur in the disadvantaged communities with poor access to health services. MNT cases often occur in remote communities where unhygienic obstetric and postnatal care practices prevail, and where there is limited access to immunization with tetanus toxoid-containing vaccines. The case fatality rate from tetanus in resource-constrained settings can be close to 100%, but can be reduced to 50% if access to basic medical care with experienced staff is available. The true extent of the tetanus death toll is not known, since many new-borns and mothers die at home and neither birth nor death is reported as there is often no vital events reporting in the affected communities. Deaths due to MNT are often underreported.

According to World Health Organization (WHO) estimates, in 2015 NT was responsible for 34,019 deaths worldwide, which is about 96% reduction in NT deaths when compared to the late 1980s. Several thousand mothers are also estimated to die annually of maternal tetanus.

The spores of tetanus are very resistant and remain in the environment in extremes of temperatures for a long period. Hence, technically it is not possible to eradicate tetanus, including NT. However, maternal and neonatal tetanus can be eliminated by reducing the disease incidence to such low levels that it ceases to be a public health problem. The disease is easily preventable through:

- Immunizing women of reproductive age with tetanus toxoid-containing vaccines before or during pregnancy for protection against tetanus – a child born to a woman protected against tetanus is also protected from the disease in the first few weeks of its life when the risk of infection is greatest;
- Hygienic birth practices to ensure infection is not contracted by mother or new-born during the delivery process;
- Proper post-natal cord care to ensure that contamination of the umbilical cord does not put the newborn at risk.

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• Surveillance to document the impact of elimination activities, but also monitor the elimination phase.

2. GLOBAL MATERNAL AND NEONATAL TETANUS ELIMINATION STATUS

In 1988, global deaths from NT were estimated at 787,000 per year. In response to the high burden of the disease, the 42nd World Health Assembly set the goal of eliminating NT worldwide by 1995, through the increased availability of tetanus toxoid (TT) vaccine, improved clean deliveries and improved surveillance. Elimination of NT as a public health problem was defined as an annual rate of less than one NT case per 1000 live births in every district (3rd administrative level). In 1991, the NT elimination goal was again endorsed by the 44th World Health Assembly. As maternal tetanus has the same risk factors and strategies for prevention as neonatal tetanus (tetanus vaccination and clean delivery practices), maternal tetanus elimination was added to the worldwide goal in 1999; and the programme title was changed to the Maternal and Neonatal Tetanus Elimination (MNTE) initiative.

By February 2015 when the initial validation survey was implemented in the Philippines, 35 countries had eliminated MNT, but the disease continued to be a major public health problem in 24 developing countries, including the Philippines, and accounts for a considerable proportion of neonatal deaths. However, by October 2017 when the last validation assessment for the country was being planned, the number of countries that attained MNTE had risen to 43 with the latest being Ethiopia and Haiti in 2017.

3. MATERNAL AND NEONATAL TETANUS ELIMINATION IN THE PHILIPPINES

The Republic of the Philippines is an archipelago of over 7,100 islands. The country is divided into 3 island groups: Luzon, Visayas and Mindanao. Administrative divisions include 17 regions, 80 provinces, 138 cities, 1,496 municipalities and 42,025 barangays, which are the smallest administrative units (figure 1). In the Philippines, a district is equivalent to a province.

The Philippines has an estimated population of approximately 100 million. The population is predominantly young, with 35% under 15 years of age. Because 65% of the land mass is comprised of mountains covered with tropical vegetation, the population resides disproportionately on coastal and other lowland areas. Severe overcrowding is prevalent in many urban areas. Roughly 20% of the country’s population lives in rugged mountainous terrain with difficult access (Geographically Isolated and Disadvantaged Areas or GIDAs), either year-round or during rainy seasons, on small islands accessible only by boat, and/or in areas characterized by substantial insecurity with armed conflict or banditry.

The Philippines has one of the highest literacy rates in the developing world: about 93% of the population ≥ 10 years of age is literate. The country has a human development index (HDI) of 0.644, which places it in the group of countries with “medium” development (ranked 112 of 194 countries evaluated). The daily income for 45% of the population of the Philippines remains less than $2.
History of EPI and early MNTE efforts in the Philippines

The Philippines Department of Health (DOH) Expanded Program on Immunization (EPI) was established in 1976 starting with Bacillus Calmette–Guérin (BCG) vaccination and expanded to include all infant vaccines in all provinces by 1979. Provision of TT to pregnant women was started in 1979 and was implemented nationwide in 1980.

A neonatal tetanus (NT) mortality survey was conducted in 4 provinces in 1982. NT was estimated to cause a total of 9700 deaths per year in the Philippines as a whole (approximately 11,000 cases per year, assuming a Case Fatality Rate (CFR) of 88%). Since NT comprises roughly half of all tetanus cases, the total tetanus burden in the Philippines was then estimated to be about 20,000 cases per year. The reporting efficiency of the NT surveillance system was found to be approximately 10%.

EPI in the Philippines progressed rapidly in the 1980s; by 1988, DPT3 (third dose of Diphtheria, Pertussis and Tetanus vaccine) coverage reached 80% (Figure 2), as had coverage with OPV3 (third dose of oral
polio vaccine) and MCV (measles containing vaccine). While TT immunization in pregnancy lagged, it too increased steadily during the 1980s, peaking at 70% in 1992. Reported tetanus, both NT and non-neonatal tetanus (nNT) declined in parallel with the increasing coverage with TT-containing vaccines (Figure 2).

**Figure 2. Reported Tetanus, DTP3 & PAB Coverage Estimates, Philippines 1980-2016**

(NT=neonatal tetanus; nNT = non-neonatal tetanus)

During the mid-1990s, TT acceptance plummeted due to allegations by pro-life groups that TT vaccine would cause miscarriages and/or sterilize recipients. The fears were mainly directed at TT supplemental immunization activities (SIAs), but also extended to routine immunization in some places.

A joint systematic review of the Philippines’ progress toward MNT elimination was conducted by the DOH EPI staff, WHO and UNICEF representatives in 2003. The conclusion was that the Philippines had achieved MNT elimination in most provinces but that TT SIAs were needed in some provinces in a phased manner over the following 3 years. However, the 2003 plans could not be executed as conceived because of the on-going rumours and controversies about TT vaccine, particularly in Manila, which led to cessation of TT use entirely from 2003 until 2006.

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A second systematic review was performed in 2009, again looking at provincial- and major city-level indicator data. Of the country’s 121 provinces and major cities, 89 were deemed low risk, 8 provinces and one city were judged to be clearly at high risk, requiring SIAs, and 23 provinces and cities were placed in an intermediate “risk” category. The extent of activities required to achieve MNTE in the “intermediate risk” group was unclear. An MNTE Lot Quality Assurance – Cluster Sampling (LQA-CS) survey was conducted in Negros Oriental (Region VII) in October 2009 to further assess the status of the “intermediate risk” provinces and cities. Negros Oriental was chosen as it was thought to be at highest risk among the 23 areas falling in the “intermediate risk” category. The survey results suggested that NT elimination had likely been achieved in Negros Oriental, and therefore also had been achieved in the other provinces and cities of that group. As a conclusion, it was decided that only the 8 provinces and one city identified as being at clearly high risk required TT SIAs.

Two rounds of TT SIAs were conducted in the 9 high-risk provinces and cities in 2011 and a third round was implemented in 2012. In this campaign, one city (Marawi City, which belonged to the intermediate risk category) located at the centre of one high-risk province (Lanao del Sur) was also included because many people from the province have temporary residence in the city. The TT coverage varied by province and by municipality.

According the National Demographic Health Survey (NDHS) of 2013, 82% of new-borns are protected at birth (PAB) through immunization of their mothers with tetanus toxoid containing vaccine (TTCV), 60% of new-borns are born in health facilities and 73% of the deliveries are assisted by skilled health workers.

4. VALIDATION PROCESS

Pre-validation

The broad objective of the pre-validation exercise was to evaluate the MNT elimination status of the provinces and to select the province at highest risk to perform the Lot Quality Assurance – Cluster Sampling (LQA-CS) validation survey.

The MNTE assessment process includes a desk-review of reported and coverage survey data. The decision for conducting the validation survey is also based on findings of a pre-validation field visit that was conducted in provinces considered to be at the highest potential risk for NT. The “highest risk province” is the province with the weakest clean delivery and TT and other immunization coverage indicators.

The desk review evaluated data on coverage of TT2+, institutional births, skilled birth attendance and DPT3 as well as NT incidence rates. The data source for the identification of the “at highest risk” province was the NDHS of 2013, the Field Health Service Information System (FHSIS) and the Multiple Indicator Cluster Survey (MICS).
If MNTE elimination can be confirmed in the province at the highest risk, it can be assumed that NT has been eliminated in provinces at lower risk, and therefore in the country as a whole.

Certain provinces in the Autonomous Region of Muslim Mindanao (ARMM) were considered at highest risk but the implementation of the validation survey was not possible for safety and security reasons. The province of Occidental Mindoro (Region IV-B) was selected as the province at highest risk of the remaining provinces.

**Maternal and Neonatal Tetanus Elimination Survey Design**

The Lot Quality Assurance – Cluster Sampling (LQA–CS) survey combines the principles of lot quality assurance and cluster sampling. This method was developed specifically to evaluate NT elimination and had been used in the MNTE validation surveys in 37 countries. The LQA–CS method is used to judge whether the rate of NT is below the elimination threshold of less than 1 NT case per 1000 live births during a 12-month period ending at least 1 month before the start of the survey. All neonatal deaths identified in the household survey need to be investigated by a physician using a verbal autopsy technique to determine if the death was due to NT. The standard WHO NT case definition is used to diagnose NT deaths: a new-born who feeds and cries normally during the first 2 days of life, and stops sucking and becomes stiff or develops spasms between 3 and 28 days of life.

The LQA-CS design does not allow determination of a point estimate of the neonatal mortality rate (NMR) incidence but rather tests whether the rate was likely to be below the elimination threshold for the selected eligibility period. A “pass” decision is made on the basis of the probability of finding less than a specified number of NT deaths in a sample of a specified size. A limitation of this methodology is that NT deaths rather than NT cases are assessed but the validity of the approach derives from the high case fatality rate for NT in areas where advanced medical care is unavailable. The number of neonatal deaths detected by the survey is compared to a reference number from the most recent DHS or other reliable surveys. The survey is deemed of low quality and the results are not accepted if less than 50% of the expected neonatal deaths are detected.

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7 Validation of Maternal and Neonatal Tetanus Elimination including a guide to the use of Lot Quality Assurance – Cluster Sample Surveys to assess neonatal tetanus mortality; August 2009. Available on request from WHO.
Survey Sample

A single sample design was chosen because of the high proportion of hard-to-reach clusters, and because the poor telecommunication coverage was inadequate to comfortably support a double-sample approach. The required sample size of 1,750 eligible live births, born between 1 January and 31 December 2014, was determined from the table of sample sizes recommended by WHO based on the estimate of 10,845 live births per year in Occidental Mindoro. The outcome is interpreted as follows: NT is considered eliminated in the Philippines if no more than one death attributable to NT (NT death ≤ 1) is found in the selected province. If two or more NT deaths were found, a “fail” status would be the decision.8

The survey also assessed coverage for TTCV, clean delivery and the use of traditional substances for new-born umbilical stump care based on information obtained from a sub-sample of mothers of eligible live births in each cluster.

Cluster size and number of clusters

The cluster size for the NT mortality survey was determined based on the assumption that an interviewer could visit an average of 100 households per day. Using the estimated national crude birth rate (CBR) of 24 per 1,000 inhabitants and an average household size of 5 persons, the cluster size was calculated as follows: 0.024 x 100 x 5 = 12 live births per cluster.

To identify the required sample size of 1,750 live births, a total of 146 clusters (1,750/12) were sampled in the districts.

Cluster selection

The location of the clusters to be surveyed was determined using the WHO-recommended procedure of systematic selection proportionate to population size, using an exhaustive list of population units and their corresponding population estimates, with a randomly selected starting point on the list.9 The Statistical Bureau of Occidental Mindoro provided the list of all barangays.

Data Collection and Entry Tools

Data collection tools and instructions were adapted from those recommended by WHO.

Form 1 (household-level data) is designed to collect information on the number of households visited, number of residents in each household, the number of women of reproductive age (aged 13 - 49 years) in the household and the number of women in the household who had been pregnant since 2013 as well as the outcome of those pregnancies (miscarriages/abortions, continued pregnancy, stillbirths or live births), and the number of eligible live births that were born in 2014 among them (See Annex 2).

8 Validation of Maternal and Neonatal Tetanus Elimination including a guide to the use of Lot Quality Assurance – Cluster Sample Surveys to assess neonatal tetanus mortality; August 2009. Available on request from WHO.

9 Immunization Coverage Cluster Survey - Reference Manual (WHO/IVB/04.23)
Form 2 (record of eligible live births) is designed to record details about eligible live births (date of birth, sex and survival status). The form is also designed to record information for a sub-sample of three mothers per cluster on the place of birth (health facility or home), whether the birth was attended by a trained birth attendant (medical doctor, licensed midwife or registered nurse - traditional birth attendants are excluded), whether a traditional remedy was used on the umbilical cord, and the mothers’ TT immunization status (see Annex 3).

Form 3 (neonatal death investigation) was used by the medical doctors (the supervisors), to record detailed information about each identified neonatal death using validated verbal autopsy questions to determine if the death was due to NT. Supplementary NT risk factor information was also collected. (See Annex 4)

A fourth form, the “supervision/ monitoring check list” was used by supervisors and monitors during the survey to evaluate the quality of work and to monitor progress.

**Survey Staff**

Surveyors were midwives and nurses from EPI, vaccine preventable diseases surveillance (VPDS) and maternal and child health (MCH) and were assigned to cluster locations where they did not normally work or live. Twenty of the 32 surveyors were females. The majority of the supervisors were doctors. There were six international monitors from WHO UNICEF and the U.S. Centres for Disease Control and Prevention (CDC), and five national monitors from the Department of Health (MOH). In each cluster location, a local guide, usually the barangay health worker (BHW) accompanied the surveyors.

**Training**

Two stages of training were conducted in San Jose in Occidental Mindoro:

- Monitors and supervisors were trained on 17 and 18 February 2015. The training was conducted in English. Participants were introduced to basic principles of NT disease and elimination, the survey design and implementation. Data collection and the use of the forms were discussed in detail, including a role-play exercise. Practical tools for supervision were discussed as well as the clinical signs and diagnosis of NT and the use of form 3. A mock survey exercise took place on the second day in San Jose.

- A second two-day training was conducted for the 32 surveyors by the monitors in English. On the first day, the discussion was on the survey implementation with special focus on the methodology (how to find the first and subsequent houses) and the use of the forms. This was complimented by the role-play. The second day, the complete team was divided in 5 groups for the mock survey exercise in San Jose. The experience was discussed afterwards.
Survey Implementation (2015)

With the exception of the teams covering the clusters in Lubang and Looc, all teams surveyed in the municipality of San Jose during the first survey day to allow monitors, supervisors and surveyors an opportunity to identify and correct mistakes in the survey or recording techniques.

Selection of the first household in each cluster site followed a standard protocol to ensure a random starting point. When a list of households was available, the interviewer chose the first household randomly from the list, using the serial number of a banknote. When the list of households was not available, the interviewers went to the centre of the cluster area and threw up a pen to determine the direction. Maps with cluster descriptions were made available by the statistical bureau of Occidental Mindoro. The surveyor counted all houses, from the centre to the edge of the barangay following the direction of the pen. The number of the first house was randomly selected using the serial number on a banknote. They then proceeded through the barangay by choosing the nearest household to the one just visited until a total of 12 eligible live births (born between 1 January and 31 December 2014) had been sampled in the cluster. If 12 eligible live births were not obtained in the selected barangay, the immediately adjacent barangay was surveyed until the required live births were identified.

Supervisors were responsible for ensuring that interviewers followed the survey protocol and for performing the neonatal death investigations. Monitors provided second level supervision and technical backstopping.

Some clusters were difficult to access and teams had to cross rivers with rafts or boats. Reaching isolated barangays sometimes took many hours.

The teams completed 146 clusters in 6 days. There were daily team meetings to discuss findings and to review progress and to prepare for the following day's work. There was good collaboration with health staff, the barangay health workers and the local population. The barangay and tribal leaders were mostly informed about the assessment in advance and were cooperative. There was excellent logistic support.

Data were entered into an MS Excel spreadsheet and analysed by computing point estimates and their respective 95% confidence intervals corrected for the effects of the cluster sampling design.

5. LQA-CS VALIDATION SURVEY RESULTS

In total 13,444 households were visited during the survey (an average of 92 households per cluster) comprising 59,820 household members. The average household size was 4.5. One thousand seven hundred and fifty five (1,755) eligible live births (born in 2014 were surveyed, yielding a crude birth rate (CBR) of 29 per 1000. A sub-sample of 438 mothers of eligible live births was interviewed regarding details of their last delivery and cord care practices. Results are shown in Tables 1 and 2.
Table 1: Characteristics and key findings

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of clusters</td>
<td>146</td>
</tr>
<tr>
<td>Number of households</td>
<td>13,444</td>
</tr>
<tr>
<td>Number of household residents</td>
<td>59,820</td>
</tr>
<tr>
<td>Average size of households</td>
<td>4.5</td>
</tr>
<tr>
<td>Number of live births</td>
<td>1,755</td>
</tr>
<tr>
<td>Number of mothers interviewed on TT vaccination status</td>
<td>438</td>
</tr>
<tr>
<td>Number of neonatal deaths</td>
<td>20</td>
</tr>
<tr>
<td>Number of neonatal tetanus deaths</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2: survey analysis results

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Estimated value</th>
<th>95% CI</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude birth rate (per 1000 population)</td>
<td>29</td>
<td>27-31</td>
<td>24</td>
</tr>
<tr>
<td>Neonatal death rate per 1000 live births</td>
<td>11</td>
<td>6-16</td>
<td>17</td>
</tr>
<tr>
<td>Neonatal Tetanus (≤ threshold of acceptance)</td>
<td>0</td>
<td></td>
<td>Maximum</td>
</tr>
<tr>
<td>Sex distribution of live births (% of boys)</td>
<td>50</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>Percentage of deliveries at health facilities</td>
<td>64%</td>
<td>57-70</td>
<td>56% (NDHS)</td>
</tr>
<tr>
<td>Percentage of live births assisted by a qualified health professional</td>
<td>66%</td>
<td>60-72</td>
<td>62% (NDHS)</td>
</tr>
<tr>
<td>Percentage use of traditional remedies on cord</td>
<td>13%</td>
<td>9-13</td>
<td></td>
</tr>
</tbody>
</table>

The CBR is higher than the reference value. This can possibly be from the fact that the survey was implemented in rural barangays where generally the families are larger than in urban areas.

Twenty neonatal deaths were detected, which is 67% of the expected number. The neonatal mortality rate of 17 neonatal deaths per 1000 live births found in the NDHS of 2013 for the province was used as the reference value.

The results of the in-depth interviews that the supervisors conducted with the caregivers of the 20 infants who had died during their first 28 days of life showed that 14 of these children (70%) died during the first two days of life. The probable cause of death of the neonates included: prematurity (11), asphyxia (4), infections (2), congenital heart disease (2) and bleeding (1). None of the neonatal deaths was due to NT.

One of the mothers had no antenatal care (ANC) visits at all and 5 mothers had one visit. Only five mothers (25%) had 4 or more ANC visits.
Among the subset of 438 mothers of the eligible live births surveyed, 64% delivered in a health facility and 66% delivered with a qualified health professional. Thirteen per cent (13%) of the mothers had used traditional remedies on the umbilical cord of their baby, including baby oil 17%, baby powder 35%, plants and ashes 35% and coconut oil 13%.

Table 3: Immunization findings

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Estimated value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of mother with card</td>
<td>49</td>
<td>43-56</td>
</tr>
<tr>
<td>% of mothers who received TT1 according to only cards with dates</td>
<td>38</td>
<td>32-44</td>
</tr>
<tr>
<td>% of mothers who received TT2 according to only cards with dates</td>
<td>38</td>
<td>32-44</td>
</tr>
<tr>
<td>% of mothers who received TT3 according to only cards with dates</td>
<td>21</td>
<td>17-25</td>
</tr>
<tr>
<td>% of mothers who received TT4 according to only cards with dates</td>
<td>9</td>
<td>6-12</td>
</tr>
<tr>
<td>% of mothers who received TT5 according to only card with dates</td>
<td>9</td>
<td>6-12</td>
</tr>
<tr>
<td>% of mother who received TT1 according to card and history</td>
<td>92</td>
<td>87-92</td>
</tr>
<tr>
<td>% of mothers who received TT2 according to card and history</td>
<td>87</td>
<td>82-92</td>
</tr>
<tr>
<td>% of mothers who received TT3 according to card and history</td>
<td>48</td>
<td>43-53</td>
</tr>
<tr>
<td>% of mothers who received TT4 according to card and history</td>
<td>23</td>
<td>19-28</td>
</tr>
<tr>
<td>% of mothers who received TT5 according to card and history</td>
<td>17</td>
<td>13-21</td>
</tr>
</tbody>
</table>

Forty-nine per cent of the 438 mothers had an immunization card, or information was provided in the register book, which was made available to the interviewers. Based on card and history, 87 per cent of mothers had received at least 2 doses of TT, 17 per cent of the women were protected throughout their reproductive lives with 5 TT doses (Table 3).

The quality indicators of the survey, besides CBR and NMR, were in accordance with reference quality standards; the percentage of locked houses was below 10% and the number of live births was 1.5 times higher than the number of eligible live births.

### 6. CONCLUSIONS FROM THE 2015 VALIDATION SURVEY

No case of NT was found among the eligible live births identified in the surveyed areas in Occidental Mindoro, indicating that NT has been eliminated in this province during the period covered by the survey. Because Occidental Mindoro was selected as the “highest-risk” province for NT in the Philippines, with the exception of ARMM, it is likely that NT has also been eliminated in the other provinces at lower risk. Elimination of MNT is therefore validated in all regions of the Philippines, with the exception of ARMM.

This conclusion is supported by the high percentage of TT2+ coverage (87%) and the skilled birth attendance rate of 66%.
7. RECOMMENDATIONS FROM THE 2015 MNTE VALIDATION SURVEY

A. Recommendations for validation in ARMM

- Conduct data desk review of all provinces and municipalities in ARMM to determine the risk of MNT
- Implement 3 rounds of TT SIAs, in high risk provinces targeting 80% for TT3
- Once the activity is completed, a data review can be done to validate the entire Philippines for attainment of MNT elimination

B. Recommendations to maintain the elimination of MNT

As tetanus spores cannot be removed from the environment, the risk of MNT is always present. Having achieved this milestone, the following efforts need to continue and even be expanded in order to maintain the elimination status.

1. Conduct annual desk reviews at national level to assess province performances and the risk factors for maternal and neonatal tetanus. This activity can be integrated into other EPI, VPDS and/or MCH related reviews.
   - Involve key stakeholders (EPI, VPDS and MCH) in the data review
   - Review the following indicators to identify poor performing provinces:
     - Quality of surveillance for maternal and neonatal deaths
     - Coverage of TT-containing vaccines or PAB including integration with ANC
     - Number of deliveries attended by skilled birth attendants (SBA)
   - Determine corrective strategies to address identified weaknesses

2. Sustain high TT protection and increase it further in pockets of weak coverage
   - Reinforce community awareness, especially among indigenous populations (IP) about the importance of tetanus and diphtheria vaccine (Td) vaccination. Train indigenous barangay health workers and volunteers
   - Plan to reach indigenous populations (IPs,) at least 6 x/year with an integrated package, including infant and child immunization, deworming, vitamin A, etc. and include provision of Td for women of reproductive age
   - Strengthen knowledge of health workers on the recommended Td immunization schedule, respect of cold chain and use of vaccine vial monitors (VVM)
   - Enhance regularity of routine and outreach services with assured availability of Td
   - Reduce missed opportunities for mother and child immunization, immunize mothers during the PAB check of the child
   - Involve private health practitioners in vaccinating pregnant women with TTCV
   - Improve documentation of the doses provided; provide cards and keep registers updated, improve the quality of reporting and standardize and monitor the registration of PAB
   - With high enrolment rates, schools offer a good opportunity to reach the school age population; Provide Td booster doses to boys and girls in the first grade of primary school and to 12 year
olds to close the Td immunity gap, to provide early protection of future pregnant women, and to increase protection against diphtheria. Also determine strategies to reach out-of-school children

3. **Promote health facility/assisted/clean delivery**
   - Explore means to address issues with financial accessibility: access to Philippine Health Insurance benefits and point of care, issues with cost for transport. Consider the feasibility of giving free delivery services to encourage women, especially from the IPs, to deliver in health facilities.
   - Improve/increase access to birthing homes with skilled birth attendants in geographically isolated areas
   - Re-evaluate the actual implemented strategies of providing incentives to mothers who deliver in health facilities and the system of fines for home deliveries
   - Improve community awareness, especially among IPs on safe and clean delivery (clean cord, clean surface and no use of traditional substances for cord care)
   - Address issues related to early communication and transportation for women in labour; Evaluate the impact of waiting (half way) houses

4. **Surveillance**
   - NT surveillance via case detection and case investigation should be continued to identify women at risk, reasons for the risk, potential clustering and corrective measures
   - All health facilities should report NT cases; the NT case definition should be available and displayed in all health facilities
   - There should be an active annual register review in hospitals to detect NT cases; this review needs to be integrated with the register review of acute flaccid paralysis (AFP) and measles, and during monitoring and technical support missions.
   - Encourage maternal and neonatal death registration and audits. Although the system is in place there is still underreporting of deaths; the reported NMR for Occidental Mindoro is 3 per 1000, versus 17 per 1000 in the NDHS and 11 per 1000 detected during this survey. What might have contributed to this might have been the community health workers’ perceived assumption that they would be judged as being responsible for the neonatal deaths if they report them.
   - Encourage community based surveillance: Barangay health workers and volunteers could track and report pregnant women, deliveries, maternal and neonatal deaths and midwives are well placed to report maternal and neonatal deaths during post-natal follow up

8. **FINAL MNTE VALIDATION ASSESSMENT IN ARMM**
   **27-29 NOVEMBER 2017**

**Objectives of this MNTE validation assessment**

- To assess the MNTE status in every province/Local Government Unit (LGU) of the Autonomous Region of Muslim Mindanao (ARMM)
• To assess the implementation and performance of the 2015 recommendations on specific strategic activities of MNTE in ARMM with focus on the Td SIAs in its high-risk areas using core and surrogate risk indicators as presented in the WHO risk algorithm.
• To conclude on the status of MNTE in ARMM and, by extension, the whole of the Philippines.
• To review the plan from the Department of Health (DOH) on its readiness in sustaining MNTE as per 2015 recommendation.

Assessment Methodology

The assessment team conducted in-depth review of reported data for routine immunization and reproductive health indicators and achievements of the recommended corrective Td SIAs including the results of the Rapid Coverage Assessment (RCA) conducted to validate reported administrative coverage data.

DOH filled the WHO recommended spreadsheet on MNTE core and surrogate risk indicators by province and cities for ARMM including RCA results.

Every high-risk area of ARMM presented their individual performance specifying critical activities planned and implemented to achieve highest possible TT protection in Women of Reproductive Age (WRA) and responded to questions and request for clarifications from the WHO/UNICEF validation team. Additional in-depth review of reported NT cases and investigation forms was done to reconfirm diagnosed NT cases.

Data review findings

The data compiled in the district data spreadsheet was used for the desk review and the WHO algorithm and its risk criteria was used to conclude on the MNTE risk status of each geographic area.

Is NT rate <1/100 live births in every province/LGU of ARMM?
Figure 3: Trend in neonatal tetanus (NT) rates

<table>
<thead>
<tr>
<th>Province / City</th>
<th>Confirmed?</th>
<th>NT rate per 1000 LBs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Basilan</td>
<td>2014</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Isabela City</td>
<td>2014</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Lanao del Sur</td>
<td>2014</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Marawi City</td>
<td>2014</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Maguindanao</td>
<td>2014</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>0.65</td>
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</tr>
<tr>
<td></td>
<td>2016</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Sulu</td>
<td>2014</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>0.75</td>
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</tr>
<tr>
<td></td>
<td>2016</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Tawi-tawi</td>
<td>2014</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

NT rate is below 1/1000 live births since 2014 to 2016 in the 7 LGUs and declining since 2014 including “0” cases in 3 LGUs (figure 3). However, Isabela city, Maguindanao and Sulu have reporting rates (after verification of case investigation forms) of 0.61, 0.22 and 0.23 respectively revealed few misdiagnoses by the current investigation processes that need to be corrected in the future. However, the quality of NT surveillance did not meet the WHO criteria for NT surveillance reliability in spite of progress made especially due to the absence of community involvement in reporting suspected NT cases and remoteness of many communities in ARMM with limited access to health facilities.

Issues with NT case definition and quality of NT case investigation were noted, reviewed and the reported NT rate was corrected and corrective measures were identified.

It was concluded that NT surveillance alone could not be used to determine the MNTE status in ARMM.

Is Skilled Birth Attendant (SBA) coverage above 70% in every province /LGU of ARMM?

Figure 4: Trend in skilled birth attendant coverage

<table>
<thead>
<tr>
<th>Province / City</th>
<th>% Health facility delivery (green&gt;70%, red&lt;70%)</th>
<th>% Skilled Birth Attendant rate (green&gt;70%)</th>
<th>RCA - SBA Delivery Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baslan</td>
<td>2016: 37</td>
<td>2016: 75</td>
<td>2017: 75</td>
</tr>
<tr>
<td></td>
<td>2014: 25</td>
<td>2015: 118</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2016: 99</td>
<td>2016: 81</td>
<td></td>
</tr>
<tr>
<td>Isabela City</td>
<td>2016: 66</td>
<td>2016: 73</td>
<td>2017: 73</td>
</tr>
<tr>
<td></td>
<td>2014: 70</td>
<td>2015: 77</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2016: 81</td>
<td>2016: 89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2014: 59</td>
<td>2015: 77</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2016: 85</td>
<td>2016: 89</td>
<td></td>
</tr>
<tr>
<td>Marawi City</td>
<td>2016: 79</td>
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<td>2017: 89</td>
</tr>
<tr>
<td></td>
<td>2014: 79</td>
<td>2015: 97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2016: 89</td>
<td>2016: 89</td>
<td></td>
</tr>
<tr>
<td>Maguindanao</td>
<td>2016: 54</td>
<td>2016: 73</td>
<td>2017: NA</td>
</tr>
<tr>
<td></td>
<td>2014: 50</td>
<td>2015: 69</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2016: 73</td>
<td>2016: 73</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2014: 31</td>
<td>2015: 43</td>
<td></td>
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<tr>
<td></td>
<td>2016: 25</td>
<td>2016: 25</td>
<td></td>
</tr>
<tr>
<td>Tawi-Tawi</td>
<td>2016: 75</td>
<td>2016: 84</td>
<td>2017: NA</td>
</tr>
<tr>
<td></td>
<td>2014: 68</td>
<td>2015: 84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2016: 84</td>
<td>2016: 84</td>
<td></td>
</tr>
</tbody>
</table>
Reported SBA coverage is over 70% in 5 out of the 7 LGUs except in Basilan and Sulu (59% and 29% respectively). The RCA conducted showed a higher coverage in Basilan (above 70%) confirmed coverage levels of Isabela city Marawi city and Sulu but showed a lower coverage for Lanao del Sur (figure 4). The SBA coverage often higher than health facility coverage reflects the role of the private sector and the number of deliveries done at home by skilled birth attendants, but not formally reporting their activities. Overall, we noted an improvement in SBA coverage in all LGUs except Sulu. It was reported that migratory trend to deliver in cheaper areas may mislead reported data in some LGUs and underestimate reported coverage. Exact contribution of the private sector remains unknown.

It was concluded that SBA coverage is >70% in all LGUs except Sulu and there was a questionable coverage in Lanao del Sur by the RCA.

**Is TT2+ coverage at least 80% in every province/LGU through routine immunization or Td SIAs?**

**Figure 5: TT2+ coverage from various sources**

<table>
<thead>
<tr>
<th>Province / City</th>
<th>% TT2+ Coverage of pregnant women (green: 80%)</th>
<th>% CRNE Coverage</th>
<th>% Td SA - % Coverage per Td Dose 2016-2017 (including mop-up)</th>
<th>RCA - 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basilan</td>
<td>31</td>
<td>50</td>
<td>95</td>
<td>91</td>
</tr>
<tr>
<td>Cagayan City</td>
<td>37</td>
<td>72</td>
<td>58</td>
<td>92</td>
</tr>
<tr>
<td>Lanao del Sur</td>
<td>55</td>
<td>92</td>
<td>98</td>
<td>93</td>
</tr>
<tr>
<td>Marawi City</td>
<td>51</td>
<td>89</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>Maguindanao</td>
<td>60</td>
<td>89</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Sulu</td>
<td>41</td>
<td>87</td>
<td>81</td>
<td>88</td>
</tr>
<tr>
<td>Tawi tawi</td>
<td>80</td>
<td>72</td>
<td>81</td>
<td>88</td>
</tr>
</tbody>
</table>

**Figure 6: TT2+ coverage, ANC, CPAB & ANC RCA**

<table>
<thead>
<tr>
<th>Province / City</th>
<th>% of ANC 2 visits</th>
<th>RCA - At least 2 ANC</th>
<th>% TT2+ Coverage of pregnant women</th>
<th>% CRNE Coverage (green: 80%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basilan</td>
<td>49</td>
<td>89</td>
<td>91</td>
<td>78</td>
</tr>
<tr>
<td>Isabela city</td>
<td>51</td>
<td>97</td>
<td>97</td>
<td>72</td>
</tr>
<tr>
<td>Lanao del Sur</td>
<td>81</td>
<td>97</td>
<td>97</td>
<td>72</td>
</tr>
<tr>
<td>Marawi City</td>
<td>72</td>
<td>89</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Maguindanao</td>
<td>78</td>
<td>NA</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Sulu</td>
<td>42</td>
<td>77</td>
<td>41</td>
<td>88</td>
</tr>
<tr>
<td>Tawi tawi</td>
<td>82</td>
<td>NA</td>
<td>80</td>
<td>72</td>
</tr>
</tbody>
</table>

Reported TT2+ coverage in 2016 through routine immunization of pregnant women is below 80% in all LGUs except Tawi tawi with the lowest performance (below 50%) reported in Basilan, Isabela city and Sulu (figure 5). The high level of reported coverage for protection at birth against tetanus assessed at
DPT1 contact cannot be considered due to the unknown ability of vaccinators to assess this especially in absence of documentation.

Exceptionally high levels of TT protection through each of the 3 rounds of Td SIAs was noted, with over 85% in the 5 LGUs that conducted Td SIAs even in the most challenging province of ARMM - Sulu. The high Td coverage achievement by at least 2 doses was confirmed by the RCA survey conducted.

While ANC 4 visits’ coverage remains low in most LGUs, the ANC coverage for 2 visits estimated via the RCA reveals major discrepancies between a high level of ANC2 coverage achieved and the reported TT2+ achieved in pregnant women through routine services (figure 6). The unclear reasons of discrepancies need to be further explored to optimize the ANC platform for the delivery of TTCV.

In conclusion, all provinces and LGUs enjoy a TT2+ protection level above 80% by either routine vaccination or Td SIAs. The remarkable Td coverage achievement thanks to the 3rd round of Td SIAs will provide at least 5 years protection to the women at risk that were reached.

Overall conclusions on the MNTE status of each province and LGU of ARMM

**Figure 7: Consolidated data for the MNTE validation assessment**

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Basilan</td>
<td>0.00</td>
<td>Inadequate</td>
<td>59</td>
<td>31</td>
<td>50</td>
<td>91</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Isabela City</td>
<td>0.61</td>
<td>Inadequate</td>
<td>81</td>
<td>37</td>
<td>72</td>
<td>92</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Lanao del Sur</td>
<td>0.10</td>
<td>Inadequate</td>
<td>85</td>
<td>56</td>
<td>92</td>
<td>93</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Marawi City</td>
<td>0.00</td>
<td>Adequate</td>
<td>89</td>
<td>51</td>
<td>89</td>
<td>95</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Maguindanao</td>
<td>0.72</td>
<td>Inadequate</td>
<td>73</td>
<td>69</td>
<td>88</td>
<td>89</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Sulu</td>
<td>0.23</td>
<td>Inadequate</td>
<td>29</td>
<td>41</td>
<td>57</td>
<td>89</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Tawi-Tawi</td>
<td>0.00</td>
<td>Inadequate</td>
<td>90</td>
<td>80</td>
<td>72</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. The NT rate is below 1 NT case per 1000 live births in each province but NT surveillance remains unreliable because a substantial number of confirmed NT cases through investigation are misdiagnosed or questionable.

b. Skilled birth attendant coverage is above 70% in 5 out 7 LGUs, with Basilan and Sulu provinces unable to reach such level.

c. Td2 and Td3 coverage is above 85% in the 5 LGUs that conducted SIAs including in the most challenging one, Sulu that is facing major geographical and security challenges.

The validation team concluded that, after consolidating all the risk-indicator data, the performance of each province and LGU of ARMM is compatible with MNTE status and, by extension, the whole of Philippines has achieved maternal and neonatal tetanus elimination.
To sustain MNTE the DOH has committed to the following:

- Periodic analysis of data using the high-risk approach
- Achieve over 95% coverage for all antigens in each province and municipality and over 80% coverage for protection a birth against NT.
- Revise and implement the new TTCV schedule in all health facilities based on the updated TTCV national policy
- Consult with professional societies and disseminate the policy to use Td for pregnant women
- Strengthen routine immunization through implementation of Reaching Every Purok (REP) strategy for all children, adolescent and pregnant women particularly in vulnerable populations through the updating of current health facility action plan taking into account the REP strategy.
- Develop area specific strategies to provide vulnerable populations in hard to reach areas more opportunities to get vaccinated including periodic review of performance and catch up immunization activities in high risk areas.
- Strengthen measles-rubella (MR), Td and HPV School-Based Immunization service delivery and open opportunities for adolescent health interventions i.e. Td boosters, HPV vaccination etc.
- Make Td vaccination available in fixed facilities and in outreach ANC clinics to minimize missed opportunities.
- Implement immunization response activity for women and children as necessary in areas with increased number of NT cases and where risk factors are high.
- Integrate TTCV with other interventions or opportunities (e.g. polio or measles immunization in areas with low TTCV coverage.
- Strengthen collaboration with the Safe Motherhood programme towards improving clean delivery and cord care practices.
- Strengthen surveillance for NT as part of integrated VPD disease surveillance, through training and capacity building.
9. ACKNOWLEDGEMENTS

Our special thanks go to the Department of Health, WHO and UNICEF country offices, the regional and provincial health authorities, to all the surveyors, supervisors, monitors and guides, and last but not least, to the interviewees for their participation in the survey.
10. ANNEXES: Survey forms

Form 1: MNTE house-to-house tally sheet

Form 1: Household Tally
(Use one line per household)

<table>
<thead>
<tr>
<th>Municipality:</th>
<th>Barangay:</th>
<th>Eligibility Period for Live Births:</th>
<th>Jan 1, 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>to Dec 31, 2014</td>
<td></td>
</tr>
</tbody>
</table>

Sitio/Purok: ____________________________
Cluster No: ______________
Location 1st HH: ______________

<table>
<thead>
<tr>
<th>HH #</th>
<th># Residents</th>
<th># Women (age 13 - 49 years)</th>
<th># Women pregnant since 2013 up to present</th>
<th>Outcomes of pregnancies between 2013 and now</th>
<th># Eligible Live Births (born from January 1, 2014 to December 31, 2014)</th>
<th>Has the household ever lost a child? Y/N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Still Pregnant</th>
<th>Live Birth</th>
<th>Miscarriage, Abortion</th>
<th>Stillbirth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>

Interviewer’s name(s): _____________________________
Date: ________________

If Yes, was the child born from January 1, 2014 to December 31, 2014? Y/N
## Form 2. Live births, conditions at birth and mothers’ TT status

### Part A. Baby’s information

<table>
<thead>
<tr>
<th>Serial No</th>
<th># HH</th>
<th>Mother’s or Father’s Name</th>
<th>Date of Birth</th>
<th>Sex</th>
<th>Died?</th>
<th>Died at ≤28 days?</th>
<th>TT1 rec’d (card or recall)?</th>
<th>TT2 rec’d? (card or recall)?</th>
<th>TT3 rec’d? (card or recall)?</th>
<th>TT4 rec’d? (card or recall)?</th>
<th>TT5 rec’d? (card or recall)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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</tr>
</tbody>
</table>

### Part C. Mother’s information related to this Live Birth

<table>
<thead>
<tr>
<th></th>
<th>TT1</th>
<th>TT2</th>
<th>TT3</th>
<th>TT4</th>
<th>TT5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### Field Supervisor:

- Male: Gender: (Y) (Male)  (N) (Female)
- (Skilled)  (Card)  (Subst.)
- TT1  TT2  TT3  TT4  TT5

### Notes:

* Any traditional substance placed on umbilical stump at birth or during the first 3 days of life?
  
  eg., ash, animal dung, leaves/herbs, etc

* What substance:
  1
  2
  3
### Form 3. Neonatal death investigation form

**Municipality:** ____________________  
**Barangay:** ____________________  
**Sitio:** ____________________  

Cluster no: _____  Household No (Forms 1 & 2): _____  Medical Officer’s name: ____________________

<table>
<thead>
<tr>
<th>Case identification &amp; household location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Respondent: ____________________</td>
</tr>
<tr>
<td>Complete Address of the Respondent: ____________________</td>
</tr>
<tr>
<td>Baby’s date of birth: ____ / ____ / ____</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>mm / dd / yy</td>
</tr>
<tr>
<td>mm / dd / yy</td>
</tr>
<tr>
<td>Age at death in days: _____</td>
</tr>
</tbody>
</table>

Did the mother have an immunization card (Tick)? Yes □  No □

Immunization history by: card □  memory □  both □  unknown □

How many TT doses did the mother receive in the last pregnancy: _____

How many TT doses has the mother received before the last pregnancy: _____ (on any occasion)

Dates (all TT doses): ___ / ___ / ___  ___ / ___ / ___  ___ / ___ / ___  ___ / ___ / ___  ___ / ___ / ___  ___ / ___ / ___

<table>
<thead>
<tr>
<th>Mother’s antenatal care history</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many antenatal care visits were made during this pregnancy? _____</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Delivery practices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Where was the baby delivered? Health facility □  Home □  Unknown □  Other □______________</td>
</tr>
<tr>
<td>Who assisted with the delivery? Doctor □  Nurse □  Midwife □  TBA □  Relative □</td>
</tr>
<tr>
<td>Nobody □  Unknown □  Other: □______________</td>
</tr>
<tr>
<td>On what surface was the baby delivered? ____________________  Clean? Yes □  No □</td>
</tr>
<tr>
<td>What was used to cut the cord? ____________________  Clean? Yes □  No □</td>
</tr>
<tr>
<td>Was any substance put on the cord stump? Yes □  No □</td>
</tr>
<tr>
<td>If yes, specify ____________________</td>
</tr>
</tbody>
</table>
**Baby's signs/symptoms:** ask respondent to describe the symptoms and the history (use open-ended questions)

Then complete the questions below. **Do not ask the questions literally**

## Treatment & outcome

Was the sick baby treated to a health facility?  Yes □  No □  Unknown □

If yes, record name of health facility:  ___________________________

*(Visit the health facility if there is doubt whether the case died of neonatal tetanus)*

## Health Facility Confirmation – if symptoms suggest Tetanus – CALL Monitor

Conducted? Yes □  No □  If NO, why not?  ____________________________________________

Facility Name:  ___________________________  Date visited: ____/____/____ (mm/dd/yy)

Location/Address:  ___________________________  Attending doctor's name:  ___________________________

Baby's medical record available?  Yes □  No □

Admitting date: ____/____/____ (mm/dd/yy)  Admitting diagnosis:  ___________________________

Discharge date: ____/____/____ (mm/dd/yy)  Discharge diagnosis:  ___________________________

## Conclusion

What does the respondent say was the cause of the baby's death?  ___________________________

Your impression of cause of death?  ________________________________________________

Based on the information you received, was this a case of neonatal tetanus?  Yes □  No □  Unknown □

Comments:  ________________________________________________

Signature & Date:  ___________________________

*(Medical Officer and/or other medical personnel investigating the case)*
### Form 4. MNTE supervision/monitoring checklist

**MNTE Supervision / Monitoring Checklist**

<table>
<thead>
<tr>
<th>Supervisor/Monitor:</th>
<th>Municipality:</th>
<th>Base station:</th>
<th>Date:</th>
<th>Sitio:</th>
</tr>
</thead>
</table>

#### Period of Eligibility of Live Births: January 1, 2014 to December 31, 2014

<table>
<thead>
<tr>
<th>Cluster No:</th>
<th>Cluster No:</th>
<th>Cluster No:</th>
<th>Cluster No:</th>
<th>Cluster No:</th>
<th>Cluster No:</th>
</tr>
</thead>
</table>

**Visit 5 houses with surveyor and observe**

1. Surveyor found?            Y / N  Y / N  Y / N  Y / N  Y / N
2. Local Guide present with the surveyor?  Y / N  Y / N  Y / N  Y / N  Y / N
3. Is the local guide from the same area/village?  Y / N  Y / N  Y / N  Y / N  Y / N
4. First house selected correctly?  Y / N  Y / N  Y / N  Y / N  Y / N
5. Surveyor going to next houses correctly?  Y / N  Y / N  Y / N  Y / N  Y / N
6. Does surveyor know the correct eligible period of live birth?  Y / N  Y / N  Y / N  Y / N  Y / N
7. Does surveyor ask questions systematically and well?  Y / N  Y / N  Y / N  Y / N  Y / N
8. Identifying eligible live births (Lbs) correctly?  Y / N  Y / N  Y / N  Y / N  Y / N
9. Filling out Form 1 correctly?  Y / N  Y / N  Y / N  Y / N  Y / N
10. Identifying eligible neonatal deaths (NDS) correctly?  Y / N  Y / N  Y / N  Y / N  Y / N
11. Collecting clean delivery & cord care history correctly?  Y / N  Y / N  Y / N  Y / N  Y / N
12. Filling out Form 2 correctly?  Y / N  Y / N  Y / N  Y / N  Y / N

**Validate information filled by surveyor (form 1 & form 2)**

13. Stillbirth(s) information found correct?  Y / N  Y / N  Y / N  Y / N  Y / N
14. If eligible live birth found correct?  Y / N  Y / N  Y / N  Y / N  Y / N
15. If NDS information found to be correct?  Y / N  Y / N  Y / N  Y / N  Y / N

**Visit 3 houses with eligible children and validate**

16. History of TT doses recorded correctly (starting from most recent in dd/mm/yyyy) based on card or history (Check for 3 children)  Y / N  Y / N  Y / N  Y / N  Y / N

**During compilation at end of activity each day**

17. Are all dates of birth on form 2 in eligible period?  Y / N  Y / N  Y / N  Y / N  Y / N
18. If eligible neonatal death found, was supervisor notified?  Y / N  Y / N  Y / N  Y / N  Y / N
19. Number of pregnancies exceeds number of eligible live births?  Y / N  Y / N  Y / N  Y / N  Y / N
20. Any problems? If yes, note on back including solution  Y / N  Y / N  Y / N  Y / N  Y / N
21. If Monitor: did the Supervisor visit the surveyor today?  Y / N  Y / N  Y / N  Y / N  Y / N

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Supervisor's Signature

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Form 5. Supervisor daily compilation format

**MNTE: Supervisor Daily Compilation Format**  Form 5

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<th>Cluster No:</th>
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<tr>
<td>Total Houses found locked</td>
<td></td>
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</tbody>
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\[
\% \text{ locked houses} = \frac{\% \text{ total number of locked houses}}{\text{total number of houses visited}} \times 100
\]

<p>| |</p>
<table>
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<tbody>
<tr>
<td>Total Residents</td>
</tr>
<tr>
<td>Total eligible Live Birth</td>
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<tr>
<td>Total Neonatal Deaths</td>
</tr>
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**Compiled Report**

<table>
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</thead>
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<td>Total eligible Live Birth</td>
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<tr>
<td>Total Neonatal Deaths</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Were all Neonatal Deaths (NDs) visited by M.O.  Yes/No.
If no, write the no. of cluster in which ND was not visited.

Why was it not visited (reasons)  Supervisor Signature
Maternal and neonatal tetanus validation assessment in Region 4, Indonesia, May 2016

Introduction
Tetanus is an acute, potentially fatal disease caused by a neurotoxin produced by the bacterium Clostridium tetani. Maternal and neonatal tetanus (MNT) are forms of generalized tetanus affecting mothers during pregnancy, due to unclean abortion or delivery, and infants during the first month of life. Neonatal tetanus (NT) infection begins when C. tetani spores are introduced into the umbilical tissue during delivery. The organisms produce a neurotoxin at the site of the umbilical cord wound which passes into the blood stream of the newborn infant and into the central nervous system. This results in motor neuron hyperactivity, hypertonia and muscle spasms. Death occurs as a result of paralysis of the respiratory muscles and/or inability to feed.

MNT is an important preventable cause of neonatal and maternal mortality, particularly in developing countries. Although easily prevented by maternal immunization with tetanus toxoid containing vaccines (TTCV) and aseptic obstetric and postnatal umbilical cord care practices, both maternal and neonatal tetanus persist as public health problems. Most cases occur in poor, remote and isolated communities where unhygienic obstetric and postnatal practices prevail, along with poor access to health services. The case-fatality rate due to NT is close to 80% in the absence of high quality health-care services.

The spores of tetanus are very resistant and remain in the environment in extremes of temperature for long periods.
Hence, technically it is not possible to eradicate tetanus, including NT. However, MNT can be eliminated by reducing the disease incidence to such low levels that it ceases to be a public health problem. The disease is easily preventable through:

- clean delivery and umbilical cord care practices to ensure infection is not contracted by mother or newborn during the delivery process;
- delivery of appropriate doses of TTCV to pregnant women through antenatal care services and other routine contacts;
- vaccination campaigns with TTCV targeting all women of reproductive age in high-risk areas; and
- strengthening surveillance to identify women at risk, reasons for the risk, and potential clustering.

Global maternal and neonatal tetanus elimination status

In the 1980s, over 1 million deaths every year were attributable to tetanus, with an estimated 787,000 deaths in 1988 from NT alone. Recognizing the substantial burden of NT in developing countries, the 42nd World Health Assembly adopted a resolution to eliminate NT by 1995, through the increased availability of TTCV, clean deliveries and improved surveillance. The elimination of NT was defined as <1 case per 1000 live births (LB) in every district per year. In the early 1990s, it was estimated that maternal tetanus accounted for about 5% of maternal mortality, or 15,000–30,000 deaths every year. As a result, in 1999, the elimination of maternal tetanus (MT) was added to the goals of the elimination programme for neonatal tetanus, and the programme title was changed to Maternal and Neonatal Tetanus Elimination (MNTE). Since NT is linked to the immunization status of mothers, elimination of NT has been adopted as a proxy for the elimination of MT.

The implementation of various initiatives under the MNTE programme led to a significant reduction in cases. The initiatives included promotion of maternal tetanus immunization along with safe delivery, the avoidance of unsafe abortion and umbilical cord care practices. According to WHO estimates, substantial progress has been made in the past decade in reducing neonatal incidence and deaths from an estimated 200,000 deaths in 2000 to 49,000 in 2013 – a 94% reduction from the situation in the late 1980s.

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Élimination du tétanos maternel et néonatal à l’échelle mondiale

Dans les années 1980, plus d’un million de décès par an étaient attribuables au tétanos, avec une mortalité estimée à 787 000 décès en 1988 pour le seul TN. Reconnaissant la charge substantielle du TN dans les pays en développement, la 42e Assemblée mondiale de la Santé a alors adopté une résolution visant à éliminer le TN à l’horizon 1995, grâce à une disponibilité accrue des vaccins contenant l’anatoxine tétanique, au respect des règles d’hygiène lors des accouchements et au renforcement de la surveillance. L’élimination du TN a été définie comme la présence de <1 cas de tétanos par an pour 1000 naissances vivantes dans chaque district. Au début des années 1990, il a été estimé que le tétanos maternel (TM) était responsable d’environ 5% de la mortalité maternelle, soit 15 000-30 000 décès chaque année. En conséquence, en 1999, l’élimination du TM a été ajoutée aux objectifs du programme d’élimination du tétanos néonatal, et celui-ci a pris le nom d’initiative pour l’élimination du tétanos maternel et néonatal (TMN). Le TN étant lié au statut vaccinal des mères, son élimination a été adoptée comme indicateur indirect de l’élimination du TM.

La mise en œuvre de diverses initiatives sous les auspices du programme d’élimination du TMN a entraîné une réduction importante du nombre de cas. Ces initiatives consistaient notamment à promouvoir la vaccination antitétanique maternelle, à assurer des conditions sûres d’accouchement et à éviter les pratiques à risque en matière d’avortement et de soins du cordon ombilical. Selon les estimations de l’OMS, des progrès substantiels ont été accomplis au cours de la dernière décennie dans la réduction de l’incidence du TN et de la mortalité associée, qui est passée de quelque 200 000 décès en 2000 à 49 000 décès en 2013, avec une baisse de 94% par rapport à la situation à la fin des années 1980.
MNT was eliminated between 2000 and 2015 in 38 of 59 priority countries,1 30 of 34 provinces in Indonesia,2 and all of Ethiopia (except in the security-compromised Somali Region). As of January 2016, MNT continues to be a major public health problem in 21 developing countries including Indonesia and accounts for a considerable proportion of neonatal deaths. Activities to achieve the goal of elimination are ongoing in these countries, with many likely to realize this in the near future. Indonesia was the only country in the WHO South-East Asia Region that has not yet eliminated MNT by the beginning of 2016.

Maternal and neonatal tetanus elimination status in Indonesia

Indonesia has a long-standing history and commitment to MNTE though vaccination and safe motherhood strategies. The country made efforts to eliminate NT through routine TCCV immunization of pregnant women and “brides-to-be”, school-based immunization (Bulan Imunisasi Anak Sekolah or BIAS) with diphtheria toxoid or low-dose diphtheria toxoid vaccines, targeted supplemental TCCV immunization activities (SIAs) of all women of reproductive age in areas considered high risk for NT, as well as through clean and safe infant deliveries.

In 2009, a joint review of the status of MNT elimination in Indonesia by the Government of Indonesia EPI3 staff, WHO and UNICEF concluded that MNT was most likely eliminated, and recommended MNTE validation using a lot quality assurance cluster sampling (LQA-CS) survey in all 34 provinces. However, the government, in consultation with partners, later decided that this process would be costly and time-consuming and that validation using a regional approach, such as the State-wise method adopted in India, would be more efficient in terms of personnel and funds.

In May 2010, for MNTE validation, the government and partners categorized Indonesia into 4 regions based on the following characteristics: provinces; island groups; terrain; access to health services; quality of health services; infrastructure; management; and progress of the regions with MNT elimination.

MNTE was validated in Region 1 (Bali and Java) in August 2010; in Region 2 (Sumatera) in November 2010; and in Region 3 (Kalimantan, Nusa Tenggara Barat (NTB), Nusa Tenggara Timur (NTT) and Sulawesi) in August 2010; in Region 2 (Sumatera) in November 2010; and in Region 3 (Kalimantan, Nusa Tenggara Barat (NTB), Nusa Tenggara Timur (NTT) and Sulawesi) in August 2010; in Region 2 (Sumatera) in November 2010; and in Region 3 (Kalimantan, Nusa Tenggara Barat (NTB), Nusa Tenggara Timur (NTT) and Sulawesi) in July 2011. Ensemble,

1 MNT was a public health problem in 19 countries: Afghanistan, Angola, Central African Republic, Chad, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Guinea, Haiti, Kenya, Mali, Nigeria, Pakistan, Papua New Guinea, Philipines, Somalia, Sudan, South Sudan and Yemen. And 40 other countries had eliminated MNT as of January 2016: Bangladesh, Benin, Burkina Faso, Burundi, Cambodia, Cameroon, China, Comoros, Côte d’Ivoire, Egypt, Eritrea, Gabon, Ghana, Guinea-Bissau, India, Indonesia, Iraq, Laos People’s Democratic Republic, Liberia, Madagascar, Malawi, Mauritania, Mozambique, Myanmar, Namibia, Nepal, Niger, Republic of Congo, Rwanda, Senegal, Sierra Leone, South Africa, Timor-Leste, Turkey, Uganda, United Republic of Tanzania, Vietnam, Zambia and Zimbabwe.

2 Of 34 provinces in Indonesia, 30 have been validated for achieving MNTE using the WHO recommended methodology as of December 2015.

3 The WHO Expanded Programme on Immunization.


2 L’élimination du TMN a été validée dans 30 des 34 provinces d’Indonésie, selon la méthodologie préconisée par l’OMS en décembre 2015.

3 Programme élargi de vaccination de l’OMS.

**Élimination du tétanos maternal et néonatal en Indonésie**

L’Indonésie s’est engagée de longue date à éliminer le TMN, au moyen de stratégies de vaccination et de promotion de la maternité sans risque. Le pays a déployé de nombreux efforts pour éliminer le TN: vaccination systématique des femmes enceintes et des «futurs mariés» par le vaccin contenant l’anatoxine tétanique; vaccination dans les écoles (Bulan Imunisasi Anak Sekolah ou BIAS) en association avec des vaccins contenant l’anatoxine diphtérique ou l’anatoxine diphtérique faiblement dosée; activités ciblées de vaccination supplémentaire (AVS) par l’anatoxine tétanique auprès de toutes les femmes en âge de procréer dans les zones jugées à haut risque de TN; et enfin promotion de pratiques d’accouchement sûres et respectueuses des règles d’hygiène.

En 2009, un examen conjoint de l’avancement des efforts d’élimination du TMN en Indonésie, mené par les membres du personnel du PEVI appartenant au Gouvernement indonésien, l’OMS et l’UNICEF, a conclu que le TMN avait très probablement été éliminé et a recommandé de procéder à une validation de cette élimination à l’aide d’un sondage en grappes pour le contrôle de la qualité des lots (LQA-CS) dans toutes les provinces du pays, au nombre de 34. Toutefois, le Gouvernement, en concertation avec les partenaires, a par la suite décidé que cette procédure serait trop longue et coûteuse qu’il serait plus efficace, en termes de ressources humaines et financières, de procéder à la validation selon une approche régionale, à l’instar de la méthode adoptée en Inde à l’échelle des États.

En mai 2010, aux fins de la validation de l’élimination du TMN, le Gouvernement et les partenaires ont divisé l’Indonésie en 4 régions sur la base des caractéristiques suivantes: provinces; groupes d’îles; type de terrain; accès aux services de santé; qualité des services de santé; infrastructures; gestion; et avancement de l’élimination du TMN au niveau régional.

L’élimination a été validée dans la région 1 (Bali et Java) en août 2010; dans la région 2 (Sumatra) en novembre 2010; et dans la région 3 (Kalimantan, Nusa Tenggara Barat (NTB), Nusa Tenggara Timur (NTT) et Sulawesi) en juillet 2011. Ensemble,
July 2011. The 3 regions combined, account for 88.7% of the cities or districts of Indonesia and 97.4% of the Indonesian population (Map 1).

**Maternal and neonatal tetanus elimination in Region 4**

Region 4 consists of 4 provinces (Maluku, North Maluku, Papua, West Papua) with a total of 63 districts and, in 2012, reported an estimated 132 300 LB. Of these districts, 33 reported <2000 LB per year. SIAs with TTCV were implemented in 18 high-risk districts in 2 phases, the first in 2006–2007 and the second in 2010–2011. Reported TT2+ coverage varied widely at 8–75%. All districts reported <1 NT case per 1000 LB in 2010 and 2011. The country therefore requested that the validation process be conducted for Region 4.

In March 2012, the MNTE Ad Hoc Committee reviewed the LQA-CS survey methodology and recommended quality indicators for the validation process. However, the scattered population and geographic and security situations of the Papua and Maluku provinces resulted in a limitation in the number of potential substitution clusters should the selected clusters become inaccessible and implementation of a quality LQA-CS survey thus proved challenging. The already existing alternative method, conducted through in-depth desk review complemented with field visits, was therefore selected for validation.

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4. *Imunisasi programme*
5. *The proportion of pregnant women receiving at least 2 doses of tetanus-toxoid vaccine.*
In December 2012, the first national and international evaluation of MNTE for Region 4 was conducted and the performance of every district assessed. The review concluded that 18 districts remained at high risk (14 districts in Papua Province, 2 districts in Maluku Province and 2 districts in West Papua Province). Implementation of 2 rounds of TCCV SIAs in the 18 districts was recommended and technical assistance was provided for implementation and the preparation of micro-plans.

The first round of TCCV SIAs of women of reproductive age (WRA) aged 15–39 years was conducted in 2013, with an overall total of 189,494 of 294,431 women targeted (64%) receiving a TCCV dose. In the second round, in 2014, 155,262 women (53%), received a dose; however, due to poor recording and reporting of numbers, and discrepancies in the denominator used, the achieved coverage of vaccinated WRA was estimated to be higher. For various reasons, a number of reports from health centres did not reach district and provincial health offices, and some WRA were screened for eligibility during the TCCV SIA.

In August 2015, a second joint national and international evaluation was carried out with the active engagement of the Ministry of Health of Indonesia, WHO and UNICEF teams who reviewed the data on core and surrogate indicators for MNTE during 2012–2014. The MNT risk indicators included coverage of TT2+ and DTP3 and clean delivery or skilled birth attendance (SBA). Three districts in Papua Province (Jayawijaya, Paniai and Tolikara) were selected for field visits based on population density, considerations from the 2012 desk review, district performance, and security concerns. Following the field visits, the teams concluded that these 3 districts were at low risk. The provinces of Maluku and West Papua were not selected for field visits due to the reported high coverage of TCCV SIAs, resulting from the 2012 review and supported by rapid coverage assessments (RCA) conducted by UNICEF.

Based on the desk review, it was recommended that 2 corrective rounds of TCCV SIAs be implemented in the highly populated pocket areas of the 5 lowest performing districts in Papua Province (Membarano Raya, Nduga, Puncak Jaya, Pegunungan Bintang and Yahukimo). Additionally, to validate the reported coverages of SIAs and ANC, a further review was recommended of the locally available data and RCA implementation in the 4 districts of Maluku Province and West Papua Province that had been previously classified as high risk.

En décembre 2012, la première évaluation nationale et internationale de l’élimination du TMN dans la région 4 a eu lieu et les résultats de chaque district ont été analysés. Il est ressorti de cet examen que 18 districts continuaient d’être exposés à un risque élevé (14 districts dans la province de Papouasie, 2 dans la province des Moluques et 2 dans la province de Papouasie occidentale). La réalisation de 2 tournées d’AVS par l’anatoxine tétanique a été recommandée dans ces 18 districts et une assistance technique a été fournie pour la mise en œuvre et la préparation de microplans.

La première tournée d’AVS par l’anatoxine tétanique a été menée en 2013 chez les femmes en âge de procréer (15-39 ans), aboutissant à l’administration d’une dose de vaccin contenant l’anatoxine tétanique à 189,494 femmes parmi les 294,431 qui étaient ciblées (64%). Lors de la seconde tournée, en 2014, 155,262 femmes (53%) ont reçu une dose; toutefois, en raison d’un enregistrement et d’une communication inadéquats des chiffres et de divergences entre les dénominateurs utilisés, on estime que la couverture vaccinale obtenue chez les femmes en âge de procréer était en réalité supérieure. Pour diverses raisons, un certain nombre de rapports provenant des centres de soins ne sont pas parvenus aux bureaux sanitaires au niveau des districts et des provinces, et certaines femmes en âge de procréer ont été soumises à une évaluation de leur admissibilité durant les AVS par l’anatoxine tétanique.

En août 2015, une deuxième évaluation conjointe nationale et internationale a été réalisée avec la participation active d’équipes du Ministère de la santé de l’Indonésie, de l’OMS et de l’UNICEF, qui ont examiné les données relatives aux indicateurs de base et de substitution sur l’élimination du TMN dans la période 2012-2014. Parmi les indicateurs de risque du TMN figuraient la couverture par l’AT2+ et le DTC3, ainsi que la pratique d’accouchements dans de bonnes conditions d’hygiène et en présence de personnel qualifié. Trois districts de la province de Papouasie (Jayawijaya, Paniai et Tolikara) ont été choisis pour faire l’objet de visites sur le terrain, la sélection ayant été réalisée en tenant compte de la densité de population, de considérations issues de l’examen sur dossier de 2012, des résultats obtenus par les districts et des conditions de sécurité. Suite aux visites sur le terrain, les équipes ont conclu que ces 3 districts étaient à faible risque. Il a été décidé de ne pas effectuer de visites sur le terrain dans les provinces des Moluques et de Papouasie occidentale en raison du taux élevé de couverture des AVS par l’anatoxine tétanique, mis en évidence dans l’examen de 2012 et étayé par des évaluations rapides de la couverture effectuées par l’UNICEF.

Suite à cet examen sur dossier, il a été recommandé de réaliser 2 tournées correctives d’AVS par l’anatoxine tétanique dans les poches fortement peuplées des 5 districts les moins performants de la province de Papouasie (Membarano Raya, Nduga, Puncak Jaya, Pegunungan Bintang et Yahukimo). En outre, pour valider les taux signalés de couverture des AVS et des services de soins prénataux, il a été recommandé de procéder à un nouvel examen des données locales disponibles, ainsi qu’à des évaluations rapides de la couverture dans les 4 districts des provinces des Moluques et de Papouasie occidentale qui avaient préalablement été classés comme étant à risque élevé.

6 Three doses of combined diphtheria, tetanus and pertussis vaccines.

6 Trois doses de vaccin antitétanique-antipertuis-anticoquelucheux combiné.
En décembre 2015, 5 consultants nationaux et un coordonnateur provincial ont été déployés par l’OMS en vue de renforcer les capacités techniques des administrateurs locaux du PEV dans les 5 districts de la province de Papouasie pour suivre et soutenir la mise en œuvre des AVS par l’anatoxine tétanique dans les 35 sous-districts les plus fortement peuplés. Lors de la journée nationale de vaccination contre la poliomyélite en mars 2016, le vaccin contenant l’anatoxine tétanique a été administré à 13 440 femmes en âge de procréer, 6 682 autres femmes ayant par ailleurs été vaccinées lors d’une nouvelle tournée d’AVS par l’anatoxine tétanique en avril 2016. En outre, une flambée de coqueluche survenue dans un des 5 districts à haut risque de la province de Papouasie a nécessité une vaccination de riposte par tous les antigènes, ciblant les enfants de <5 ans et incluant 2 281 femmes en âge de procréer, qui ont reçu des doses d’anatoxine tétanique en 2 tournées. Ces chiffres sont importants dans la mesure où ils reflètent la possibilité de cibler les femmes en âge de procréer risquant d’échapper à la vaccination.

### Enquête de validation de l’élimination du TMN dans la région 4

Par définition, le TMN est considéré comme éliminé en tant que problème de santé publique lorsque l’on observe <1 cas de TN par an pour 1 000 naissances vivantes dans chaque district où une surveillance active est en place; pour la validation, il est recommandé d’enquêter sur une population où le nombre de naissances vivantes par an est de 10 000 au minimum. Pour la région 4, l’OMS a recommandé que la validation de l’élimination du TMN soit effectuée par province, compte tenu de la très petite taille de la population au niveau des districts, plus de la moitié d’entre eux signalant <2 000 naissances vivantes par an.

Conformément à la méthode préconisée par l’OMS, on peut considérer que le TMN est éliminé dans toute la région 4 dès lors que l’élimination est avérée dans la province la moins performante.

En l’absence de données fiables de surveillance du TN, l’expérience a démontré que l’élimination du TMN est compatible avec une couverture par l’AT2+ ≥80% ou une proportion ≥70% d’accouchements pratiqués en présence de personnel qualifié.

En mai 2016, une équipe d’experts internationaux et nationaux a de nouveau réalisé un examen sur dossier approfondi des données provenant des 18 districts à haut risque identifiés en 2012. Cette analyse s’appuyait sur une compilation des indicateurs de risque de base et de substitution du TMN pour la période de 3 ans précédente (2013, 2014 et 2015) pour chacun des 18 districts à risque élevé. Au cours de cet examen, la proportion d’accouchements pratiqués en présence de personnel qualifié, la couverture des soins prénatals, le taux signalé de couverture de la vaccination systématique par l’AT2+ et de vaccination par le DTC3, les résultats des AVS par l’anatoxine tétanique et les conclusions des évaluations rapides de la couverture ont de nouveau été analysés. Cet examen sur dossier a abouti à la conclusion que parmi les provinces de la région 4, la Papouasie était celle qui continuait de présenter le plus grand risque (Tableau 1).
1. Examiner l’exhaustivité et la qualité des données communiquées sur la couverture; 
2. Clarifier les dénominateurs/chiffres de population; 
3. Évaluer le système de surveillance du TN; et 
4. Évaluer la qualité de la mise en œuvre de la stratégie d’élimination du TMN (vaccination systématique, soins prénataux, conditions d’accouchement, quantité et qualité des activités de proximité, efficacité de la planification et de la mise en œuvre des AVS, vaccination en milieu scolaire (BIAS) et programme destiné aux “futures mariées”).

The 6 potentially high-risk districts of Papua Province (SBA <40% and TT2+ (including SIAs) <50%) represent 18% of the total population; 4 further districts of Papua Province were considered as medium-risk (SBA<50%; TT2+ 50–70%);

Maybrat is the sole district in West Papua Province that remains at low risk, as well as Waropen in Papua Province and Sorong Selatan in West Papua Province (based on TT2+ or coverage of SIAs of >80%).

As shown in Map 2, 3 potentially high-risk districts (Deiyai, Memberano Raya and Yahukimo in Papua Province), and 3 medium-risk districts (Dogiyai and Lanny Jaya in Papua, and Maybrat in West Papua Province) were visited, with the objective of assessing the level of MNT risk.
The teams visited 2 health centres in each district and a minimum of 2 villages with the largest population size for each health centre. RCA was conducted in the selected villages through interviewing WRA (aged 15–39 years) who had delivered a child in the previous 24 months (i.e. May 2014–May 2016).

**Results**

The teams visited a total of 6 district health offices, 12 health centres and 24 villages in the districts, and interviewed a total of 503 women who had delivered a child during the 24-month timeframe.

The percentage of women who delivered in the presence of SBA was <50% in 5 of the 6 districts visited; the exception was Maybrat district in West Papua Province with 81% (Figure 1).

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**Map 2** Map of Papua and West Papua provinces indicating the different levels of risk by district and the districts visited for validation

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**Figure 1** Deliveries attended by skilled birth attendants, rapid coverage assessment, May 2016

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**Figure 1** Accouchements pratiqués en présence de personnel qualifié, évaluation rapide de la couverture, mai 2016
The TT2+ coverage among WRAs with eligible LB was >60% in 5 of the districts, and >80% in 3 districts (Figure 2) including Maybrat in West Papua Province.

Less than 22% of the deliveries investigated reported harmful cord care practices except Lanny Jaya district that reported a higher incidence of women applying substances (particularly hemostatic leaves and talcum powder) on the umbilical stump as shown in Figure 3.

La couverture par l’AT2+ chez les femmes en âge de procréer et répondant aux critères relatifs aux naissances vivantes était >60% dans 5 districts et >80% dans 3 districts, y compris Maybrat en Papouasie occidentale (Figure 2).

Moins de 22% des accouchements étudiés étaient associés à des pratiques préjudiciables de soins du cordon ombilical, sauf dans le district de Lanny Jaya, où une proportion plus importante de femmes appliquaient des substances (principalement des feuilles hémostatiques et de la poudre de talc) sur le moignon ombilical, comme indiqué dans la Figure 3.

Discussions

Overall, for the 6 lowest performing districts visited for MNT, including one medium-risk district in West Papua Province, the findings from the field show TT2+ coverage far higher than reported. The main reason for this could be the actual targeted population being substantially lower than the official population figures. True coverage could be double the official reported estimate. Furthermore, the completeness of immunization coverage reports was found to be very low in several districts despite data being available at the health facility level; this, similarly, would result in an underestimation of the true coverage.

These findings are consistent with the results of the basic health survey (BHS) or Riskesdas conducted in 2013, in which a total of 1 105 593 WRAs were surveyed. This survey showed that ANC coverage was 70% for Papua Province, 82% for West Papua Province, 81% for Maluku Province and 90% for North Maluku Province. This indicates a high chance of achieving 80% tetanus toxoid protection of pregnant women as TTV vaccine is systematically offered during ANC following national policy. Screening is not systematically carried out, and every woman receives 2 doses of TTV during each pregnancy. Women who received a single dose of TTV and who are registered as TT1 may have protection from TTV doses received during previous pregnancies.

Discussion

Globalement, les visites d’évaluation du TMN effectuées sur le terrain dans les 6 districts les moins performants, dont un district à risque modéré dans la province de Papouasie occidentale, ont montré que la couverture par l’AT2+ était bien supérieure à ce qui avait été signalé. La principale raison pourrait en être que dans la réalité, la population cible peut être beaucoup moins nombreuse que les chiffres officiels ne l’indiquent. La couverture réelle pourrait ainsi être 2 fois supérieure aux estimations officielles. En outre, dans plusieurs districts, les rapports transmis sur la couverture vaccinale se sont avérés très incomplets, bien que les données aient été disponibles au niveau des établissements de santé; ce facteur peut également mener à une sous estimation de la couverture réelle.

Ces résultats rejoignent ceux de l’enquête sanitaire de base, ou Riskesdas, menée en 2013, qui incluait 1 105 593 femmes en âge de procréer. Cette enquête indiquait que la couverture des soins prénataux était de 70% dans la province de Papouasie, de 82% en Papouasie occidentale, de 81% aux Molukas et de 90% aux Molukas du Nord. Cela montre qu’il est fort possible de parvenir à une protection de 80% des femmes enceintes par l’anatoxine tétanique lorsque le vaccin est offert de manière systématique en consultation prénatals, conformément à la politique nationale. Le dépistage n’est pas systématique, et chaque femme reçoit 2 doses de vaccin contenant l’anatoxine tétanique durant chaque grossesse. Il est possible que les femmes ayant reçu une dose unique de vaccin contenant l’anatoxine tétanique et classées comme AT1 soient protégées par des doses d’anatoxine tétanique reçues lors de grossesses précédentes.

Notes:

1. Registered as having received a single dose of tetanus toxoid vaccine at first contact, or as early as possible in pregnancy.

2. Inscrites dans les registres comme ayant reçu une dose unique de vaccin contenant l’anatoxine tétanique lors du premier contact avec le système de santé ou le plus tôt possible au cours de la grossesse.
The RCA finding on health facility delivery was also consistent with the findings of the BHS, which showed a rate of <50% for the 4 provinces.

The RCA finding on harmful cord care practices (<22% in all districts except for Lanny Jaya) was consistent with the evaluation of cord care practices during the same survey for Papua Province. This survey showed 37% dry cord care and 48% use of betadine and alcohol (i.e. a total of 85% of safe cord care practices and 15% only of potential harmful practices).

Based on the findings of the visits to the district health offices, the health facilities and the interviews, the teams believe that in the districts of Maybrat, Lanny Jaya and Dogiyai, >80% of pregnant women received at least 2 doses of TTCV during ANC, and/or TTCV SIAs, and that the districts classified at medium risk can now be considered at low risk.

In the districts of Membarano Raya, Yahukimo and Deiyai, some important pockets of women and infants remain unreached with routine immunization or through SIAs. These districts, classified during the desk review as being potentially at high risk, can, based on the field visits, be reclassified as being at medium risk, with TT2+ coverage likely to be between 50–70%.

While small groups of women remain unreached, the total proportion of protected women by TTCV immunization in Papua Province, the lowest performing province of Region 4, is estimated to be >80%, a TTCV coverage achievement compatible with elimination of MNT.

**Conclusion**

Based on data review and field visits, the review team concludes that the elimination of MNT as a public health problem has been achieved in Papua Province and as a consequence in Region 4, and by extension in Indonesia as a whole.

En ce qui concerne la proportion d'accouchements pratiqués dans un établissement de santé, les conclusions des évaluations rapides de la couverture vont également dans le même sens que ceux de l’enquête sanitaire de base, qui révélait un taux <50% dans les 4 provinces.

Pour ce qui est des soins du cordon ombrical, les résultats des évaluations rapides de la couverture (<22% de pratiques préjudiciables dans tous les districts sauf Lanny Jaya) correspondaient à l’évaluation faite des pratiques de soins du cordon ombrical dans le cadre de la même enquête dans la province de Papouasie. Selon cette enquête, les soins du cordon reposaient dans 37% des cas sur le séchage naturel et dans 48% des cas sur l’utilisation de la bétadine et de l’alcool (soit au total 85% de pratiques sûres en matière de soins du cordon et seulement 15% de pratiques potentiellement préjudiciables).

Sur la base des visites effectuées dans les bureaux sanitaires de district et les centres de soins et compte tenu des entretiens menés, les équipes estiment que dans les districts de Maybrat, Lanny Jaya et Dogiyai, >80% des femmes enceintes ont reçu au moins 2 doses d’anatoxine tétanique, dans le cadre des soins prénatals et/ou des AVS contre le tétanos, et que ces districts, qui étaient classés comme présentant un risque modéré, peuvent désormais être considérés comme des districts à faible risque.

Dans les districts de Membarano Raya, Yahukimo et Deiyai, il subsiste d’importantes poches où les femmes et les nourrissons n’ont pas été couverts par la vaccination systématique ou les AVS. Ces districts, classés comme présentant un risque potentiellement élevé lors de l’examen sur dossier, peuvent désormais, sur la base des visites sur le terrain, passer dans la catégorie des districts à risque modéré, avec une couverture par l’AT2+ qui s’élève probablement à 50%–70%.

Bien qu’il reste des petits groupes de femmes échappant à la vaccination, la proportion totale de femmes protégées par le vaccin contenant l’anatoxine tétanique en Papouasie, la province la moins performante de la région 4, est estimée à >80%, un niveau de couverture compatible avec l’élimination du TMN.

**Conclusion**

Sur la base de l’analyse des données et des visites sur le terrain, l’équipe d’évaluation a conclu que le TMN a été éliminé en tant que problème de santé publique dans la province de Papouasie et donc, par extension, dans la région 4 et sur l’ensemble du territoire indonésien.
**Recommendations to maintain MNT elimination**

The Government of Indonesia has made substantial efforts to eliminate MNT and to maintain the elimination status with an integrated approach. The BIAS in particular, is well established in most provinces of the country as well as in some districts of Region 4.

Since tetanus spores remain present in the environment, a high level of prevention through TTCV immunization and/or deliveries by trained attendants needs to be maintained and increased. This can be achieved through the following:

1. All provinces in Indonesia conducting an annual review of district-level data to identify districts requiring corrective actions to maintain their MNTE status. This may include:
   a. periodic tetanus toxoid SIAs for WRA underserved by routine ANC or immunization services.
   b. provision of TTCV to women of reproductive age through outreach sessions, or posyandus,
   c. conducting NT case–response through investigation following confirmed NT cases.
   d. promotion of health facility delivery and the use of skilled birth attendants.
   e. promotion of hygienic cord care practices at home and in integrated post-partum care.
   f. focusing on increasing the implementation of BIAS in all schools over time and developing strategies to reach out-of-school children;

2. Ensuring the availability and quality of TTCV in all health facilities, or puskesmas, by allocating solar refrigerators, and ensuring functioning cold chain, and good vaccine management.

3. Strengthening sensitive NT surveillance systems by retraining hospital and puskesmas staff in NT diagnosis, and reporting and case investigation.

4. Instituting a monitoring and reporting accountability mechanism to monitor the implementation of all planned posyandus and coverage performance.

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**Recommandations pour le maintien de l’élimination du TMN**

Le Gouvernement indonésien a déployé des efforts considérables pour éliminer le TMN et préserver cette élimination au moyen d’une approche intégrée. Le programme BIAS, en particulier, est bien établi dans la plupart des provinces du pays, ainsi que dans certains districts de la région 4.

Étant donné que les spores du tétanos demeurent présentes dans l’environnement, une prévention de haut niveau, reposant sur la vaccination par l’anatoxine tétanique et/ou la présence de personnel qualifié lors des accouchements, doit être maintenue et renforcée. Ces efforts s’appuieront sur les actions suivantes:

1. Procéder, dans toutes les provinces de l’Indonésie, à un examen annuel des données provenant des districts afin d’identifier ceux dans lesquels des mesures correctives s’imposent pour préserver l’élimination du TMN. Ces mesures peuvent comprendre:
   a. des AVS périodiques par l’anatoxine tétanique chez les femmes en âge de procréer qui sont mal desservies par les services de soins prénatals ou de vaccination systématique;
   b. l’administration du vaccin contenant l’anatoxine tétanique aux femmes en âge de procréer dans le cadre de services de proximité, les posyandus,
   c. des activités de riposte fondées sur l’investigation des cas confirmés de TN;
   d. la promotion des accouchements pratiqués dans les établissements de santé et en présence de personnel qualifié;
   e. la promotion de pratiques hygiéniques en matière de soins du cordon ombilical, à domicile et dans le cadre des soins post-partum intégrés;
   f. une attention particulière portée à l’extension du programme BIAS pour atteindre progressivement toutes les écoles, ainsi qu’à l’élaboration de stratégies pour couvrir les enfants non scolarisés.

2. Veiller à la disponibilité et à la qualité du vaccin contenant l’anatoxine tétanique dans tous les établissements de santé, ou puskesmas, en distribuant des réfrigérateurs solaires et en assurant une chaîne du froid efficace et une bonne gestion des vaccins.


4. Mettre en place un mécanisme de responsabilisation en matière de suivi et de notification pour surveiller la mise en œuvre de tous les posyandus prévus, ainsi que l’efficacité de la couverture.

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*Pos Pelayanan Repadu (integrated service post in Indonesian), known by its acronym Posyandu, is a monthly clinic for children and pregnant women, providing vaccinations and nutritional supplements.*

*Les Pos Pelayanan Repadu, terme qui signifie « poste de services intégrés » en indonésien et qui est connu sous l’acronyme Posyandu, sont des dispensaires assurant des services mensuels de vaccination et de supplémentation nutritionnelle destinés aux enfants et aux femmes enceintes.*
Recommendations specific for Papua Province

- Provide all puskesmas with a functional solar cold chain and train cold chain managers on, among other things, preventive maintenance.
- Provide assurance of a minimum of 4 contacts per year through posyandus to reach areas to provide immunization services including TTCV to WRA, integrated with other health interventions such as deworming, distribution of bednets, etc.
- All posyandus should include TTCV vaccination and ANC. TTCV should be given even in the absence of ANC services.
- Organize on-the-job training for vaccination staff and health managers.
- Organize periodic risk reviews and corrective rounds of TT SIAs as may be required (warranted by SIAs having been used to achieve MNT elimination in some of the regions).
- Deploy staff from the province and/or lower-risk districts for at least 1 month in the higher-risk districts for on-the-job training and monitoring.

With the establishment of a collaboration between the Ministry of Education, the Ministry of Religious Affairs, Ministry of Internal affairs and the Ministry of Health on the implementation of BIAS, the programme should be reviewed to evaluate its coverage and establish mechanisms for making it more functional in Papua.

Recommandations propres à la province de Papouasie

- Fournir à tous les puskesmas des équipements solaires fonctionnels pour la chaîne du froid et assurer la formation des responsables de la chaîne du froid, notamment en matière d’entretien préventif.
- Garantir au minimum 4 contacts par an au travers des posyandus pour atteindre les zones nécessitant des services de vaccination, notamment l’administration du vaccin contenant l’anatoxine tétanique aux femmes en âge de procréer, intégrés à d’autres interventions sanitaires comme le déparasitage, la distribution de moustiquaires, etc.
- Veiller à ce que tous les posyandus assurent une vaccination par l’anatoxine tétanique et des soins prénatals. Le vaccin contenant l’anatoxine tétanique devrait être administré même en l'absence de services prénatals.
- Organiser une formation sur le terrain pour le personnel de vaccination et les administrateurs de la santé.
- Mener régulièrement une analyse des risques et organiser des tournées correctives d’AVS par l’anatoxine tétanique selon les besoins (approche justifiée par l’obtention de l’élimination du TMN dans certaines régions grâce aux AVS).
- Mobiliser des membres du personnel travaillant au niveau de la province et/ou des districts à faible risque pour les déployer pendant au moins 1 mois dans des districts à risque plus élevé aux fins d’une formation et d’un suivi sur le terrain.

Dans le cadre de la collaboration établie entre le Ministère de l’éducation, le Ministère des affaires religieuses, le Ministère de l’intérieur et le Ministère de la santé pour mettre en œuvre le programme BIAS, ce dernier devrait être réexaminé afin d’en évaluer la couverture et d’instaurer des mécanismes susceptibles de le rendre plus efficace en Papouasie.

How to obtain the WER through the Internet

1. WHO WWW server: Use WWW navigation software to connect to the WER pages at the following address: http://www.who.int/wer/

2. An e-mail subscription service exists, which provides by electronic mail the table of contents of the WER, together with other short epidemiological bulletins. To subscribe, send a message to listserv@who.int. The subject field should be left blank and the body of the message should contain only the line subscribe wer-reh. A request for confirmation will be sent in reply.

Comment accéder au REH sur Internet?


2. Il existe également un service d’abonnement permettant de recevoir chaque semaine par courrier électronique la table des matières du REH ainsi que d’autres bulletins épidémiologiques. Pour vous abonner, merci d’envoyer un message à listserv@who.int en laissant vide le champ du sujet. Le texte lui-même ne devra contenir que la phrase suivante: subscribe wer-reh.
Session 5

*Estimating the value of vaccines in preventing antimicrobial resistance*
Estimating the value of vaccines in preventing AMR

Mateusz Hasso-Agopsowicz, MSc, PhD
Technical Officer, Vaccine Product & Delivery Research
Department of Immunization, Vaccines & Biologicals
World Health Organization
The burden of AMR

- AMR is a global health threat with **1.27 million deaths attributable** to bacterial AMR and **4.95 million deaths associated** with bacterial AMR worldwide in 2019;

- **Attributable**: deaths are the result of a progression from a drug sensitive to a drug resistant infection;

- **Associated**: deaths are the result of a progression from no infection to a drug resistant infection;

- The **six leading pathogens** for deaths associated with resistance were responsible for **929,000 (660,000–1,270,000) deaths attributable to AMR** and **3.57 million (2.62–4.78) deaths associated with AMR** in 2019.

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02724-0/fulltext
How do vaccines reduce AMR?

- Vaccines prevent infections with drug-susceptible and resistant pathogens
- Reduce secondary infections
- Vaccines prevent individuals and communities from getting sick
- Decrease antibiotic use
- Suppress resistance evolution and decrease transmission of resistant pathogens
The Action Framework to leverage vaccines against AMR and AMU

Expanding use of licensed vaccines to maximize impact on AMR

Develop new vaccines that contribute to prevention and control of AMR

Expanding and sharing knowledge of vaccine impact on AMR

https://www.who.int/publications/m/item/leveraging-vaccines-to-reduce-antibiotic-use-and-prevent-antimicrobial-resistance

Annex to Immunization Agenda 2030

Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance:
An Action Framework
Bacterial vaccines in clinical and preclinical development 2021: clinical results

- **61 vaccines** in active clinical development identified (activity in the last 3 years, still list on company portfolio)
- **The highest number** of vaccine candidates for *S. pneumoniae*, TB, and *Shigella flexneri*
- **No candidates in clinical development**: *E. faecium*, *H. pylori*, *P. aeruginosa*, *A. baumannii*, *Enterobacter* spp, or *Campylobacter* spp.

![Number of candidates in clinical development by pathogen](chart_url)
AMR is a key component of the full value of vaccines

- Vaccines have value in low and middle income countries but limited commercial incentive
- To prioritise vaccine development, introduction and use, we need to articulate the value of vaccines in its full capacity;
- The value of vaccines can be measured across numerous criteria, beyond mortality;
- AMR is an important aspect of the value of vaccines;

Vaccine Value

- Mortality
- Morbidity
- Many other...
- Microbiome
- Equity & Social Justice
- Economic burden
- AMR

Estimating the value of vaccines in preventing AMR
Methodology and results
Value of vaccines in reducing AMR: goals

- Communicate the role of vaccines in preventing AMR
- Highlight knowledge gaps
- Articulate the value of vaccines for their impact on AMR
- Prioritisation of vaccine development and use
- Synthesise evidence for the impact of vaccines against AMR

Complexities in assessing the value of vaccines in reducing AMR:

- Limited understanding of AMR burden/in some cases susceptible disease burden
- Paucity of data, especially in LMICs
- Predicting future resistance patterns
- Vaccines need to be considered in context of other approaches to contain AMR
- Technical feasibility of vaccine development
- Identifying target population

However, decisions about vaccine development and use are being made now.
### Value of vaccines in reducing AMR: list of pathogens

#### Bacteria
- Acinetobacter baumannii
- Campylobacter jejuni
- Chlamydia trachomatis
- Cholera
- Clostridioides difficile
- *E. coli* (ETEC)
- *E. coli* (ExPEC)
- Enterococcus faecium
- GAS
- *Haemophilus influenzae* b (Hib)
- Helicobacter pylori
- Klebsiella pneumoniae
- Mycobacterium tuberculosis
- Neisseria gonorrhoeae
- Neisseria meningitidis
- Pseudomonas aeruginosa
- Salmonella paratyphi
- Salmonella typhi
- Salmonella non-typhoid

#### Bacteria (cont.)
- Shigella spp
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*

#### Parasites & Fungi
- Candida spp.
- Malaria

#### Viruses
- HIV
- Influenza
- Measles
- Norovirus
- Rotavirus
- RSV

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- 29 pathogens in scope (WHO PPL, CDC AMR threats, expert consultation)

- Pathogens included because of antibacterial, antiviral, antimalarial burden, or high volume of antibiotic used (appropriate or inappropriate)

- Vaccine value estimated where relevant and data available
## Value of vaccines in reducing AMR: list of criteria

### Quantitative Criteria (Focus for Today)

1. Vaccine averted AMR health burden
   - Number of resistant infections, deaths and DALYs averted by a vaccine
   - Incremental cost of treating a resistant infection
   - Loss of productivity due to a resistant infection
   - Vaccine averted cost of treating a resistant infection
   - Vaccine averted loss of productivity due to a resistant infection

2. Vaccine averted AMR economic burden
   - Syndrome and pathogen associated antibiotic use
   - Vaccine averted syndrome and pathogen associated antibiotic use

### Narrative Criteria

3. Vaccine averted antibiotic use
   - Measure of urgency to develop approaches to contain AMR

4. Urgency of the AMR threat
   - Pathogen related impacts on agency, association and respect

5. Pathogen impact on equity and social justice
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<tr>
<th>Time</th>
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<th>Speaker(s)</th>
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<tbody>
<tr>
<td>13:00 - 13:10 10’</td>
<td>Background</td>
<td>M Hasso-Agopsowicz</td>
</tr>
<tr>
<td>13:10 - 13:30 20’</td>
<td>Technical presentation 1</td>
<td>K Abbas, C Kim</td>
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<td>13:30 - 13:50 20’</td>
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<td>13:50 - 14:20 20’</td>
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<td>14:20 - 14:50 30’</td>
<td>Q&amp;A and discussion to inform IVIR-AC recommendations</td>
<td>V Pitzer, HH Farooqui, P Luz, X Wang</td>
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**Estimating the value of vaccines in preventing antimicrobial resistance**

- **Methodology and results**
  - **Background reading materials**: see Sharepoint

**Agenda**

- **Introduction to the WHO programme on the role of vaccines in reducing AMR**
- **The value of vaccines in reducing health burden associated with drug-resistant infections**
- **The value of vaccines in reducing antibiotic use**
- **The value of vaccines in reducing economic burden associated with drug-resistant infections**
- **IVIR-AC discusses presentation, clarifies on content and acknowledges main issues**
  - Does IVIR-AC agree that the presented analyses are technically appropriate to inform prioritisation of development and use of vaccines in reducing AMR?
  - Does IVIR-AC agree with the draft recommendations to be included in the report on the value of vaccines in reducing AMR?
  - What are IVIR-AC's suggestions for ensuring that the value of vaccines in reducing AMR is systematically incorporated into policy decisions?
Questions to IVIR-AC

• Does IVIR-AC agree that the presented analyses are technically appropriate to inform prioritisation of development and use of vaccines in reducing AMR?

• Does IVIR-AC agree with the draft recommendations and key messages to be included in the report on the value of vaccines in reducing AMR?

• What are IVIR-AC’s suggestions for ensuring that the value of vaccines in reducing AMR is systematically incorporated into policy decisions?
Global and Regional Burden of Attributable and Associated Bacterial Antimicrobial Resistance Avertable by Vaccination: Modelling Study

Chaelin Kim,1 Marianne Holm,1 Isabel Frost,2 Mateusz Hasso-Agopsowicz,2 Kaja Abbas3

1 International Vaccine Institute, Seoul, Republic of Korea
2 World Health Organization, Geneva, Switzerland
3 London School of Hygiene & Tropical Medicine, London, United Kingdom
Background & Aim

● **Background:**
  ○ AMR is a global health threat with **1.27 million deaths attributable to** bacterial AMR and **4.95 million deaths associated with** bacterial AMR worldwide in 2019*
  ○ Vaccines can reduce AMR by preventing infections, but there is a research gap in measuring their contribution to reducing AMR

● **Objective:** Our aim is to estimate **the vaccine avertable bacterial AMR burden** based on profiles of existing and future vaccines at the global and regional levels

AMR Burden Data

- AMR burden estimates from the Global Research on Antimicrobial Resistance (GRAM) project
  - Based on statistical predictive modelling of data from systematic reviews, surveillance systems, hospital systems, and other sources to generate estimates in 2019
  - Provided data for age-specific deaths and DALYs associated with and attributable to AMR by pathogen, infectious syndrome, and region for 2019

- Two sets of estimates; based on an alternative scenario
  - *Burden attributable to AMR*; all drug-resistant infections were replaced by drug-susceptible infections
  - *Burden associated with AMR*; all drug-resistant infections were replaced by no infection
A static proportional impact model was used to estimate the vaccination impact

\[
\text{AMR burden averted at age } i = \text{AMR burden at age } i \text{ pre-vaccination} \times \text{vaccine efficacy} \times \text{vaccine coverage}
\]

We estimated vaccine-avertable deaths and disability-adjusted life-years (DALYs) attributable to and associated with antimicrobial resistance by WHO region, infectious syndrome, and pathogen for **fifteen bacterial pathogens**

* Vaccine target pathogen, infectious syndrome, and age-specific pre-vaccination AMR associated and attributable deaths and DALYs (protection from vaccine-derived immunity was also taken into account)

** Acinetobacter baumannii, Enterococcus faecium, Escherichia coli, Group A Streptococcus, Haemophilus influenzae, Klebsiella pneumoniae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, non-typhoidal Salmonella, Pseudomonas aeruginosa, Salmonella Paratyphi, Salmonella Typhi, Shigella spp., Staphylococcus aureus, and Streptococcus pneumoniae.
Two Scenarios

- **Baseline scenario** for primary vaccination of specific age-groups
- **High-potential scenario** that includes additional age groups at risk
  - A subset of 6 pathogens (nosocomial): all age groups
    - Pathogens with great uncertainty in vaccine delivery
      - *Acinetobacter baumannii*, *Enterococcus faecium*, *Extraintestinal Pathogenic Escherichia coli* (ExPEC), *Klebsiella pneumoniae* (all syndromes), *Pseudomonas aeruginosa*, and *Staphylococcus aureus*
    - Vaccination of at risk individuals across all age groups
  - *Streptococcus pneumoniae*: an elderly population with the highest disease burden
    - Exploring the potential impact by administering a vaccine to an elderly population
Impact of existing vaccines

Existing *Haemophilus influenzae* type B (Hib) and pneumococcal conjugate vaccines (PCVs)

(1) No vaccination AMR burden estimation for 2019
- We estimated AMR burden for the counterfactual scenario of no vaccination in direct proportion to efficacy, real coverage estimates (WUENIC), target population for protection, and duration of protection

(1) Estimating impact of existing vaccines
- Vaccination at 2019 coverage levels (WUENIC)
- WHO recommended coverage level (90%)
  (the strategic priority on coverage and equity of Immunisation Agenda 2030)
Uncertainty analysis

- **Monte Carlo simulation** to propagate the uncertainty in the AMR burden, vaccine efficacy, and coverage to estimate the uncertainty in the projected vaccination impact
  - 95% uncertainty intervals (UIs)

- Uncertainties around *AMR burden, efficacy, and coverage*.
  - **AMR burden**: the mean, the 2.5th and 97.5th percentiles of the AMR burden
  - **Efficacy** and **coverage**
    - Hypothetical vaccines: ± 20% to the vaccine efficacy and coverage on the vaccine profile
    - Existing vaccines: confidence intervals of the vaccine efficacy from studies, ± 5% to vaccine coverage
Existing vaccines

Vaccines against *H. influenzae* type *b*, *Streptococcus pneumoniae*, and *Salmonella* Typhi

The vaccine profiles expand coverage of the current vaccines in order to meet the strategic priority on coverage and equity of Immunisation Agenda 2030.

Not yet available vaccines

Vaccines against other bacterial pathogens*

Hypothetical profiles were developed based on preferred product characteristics (PPCs), target product profiles (TPPs), attributes of advanced vaccine candidates, and expert consultations with WHO working groups, PATH, and pathogen experts.

*Acinetobacter baumannii, Enterococcus faecium, Escherichia coli, Group A Streptococcus, Klebsiella pneumoniae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, non-typhoidal Salmonella, Pseudomonas aeruginosa, Salmonella Paratyphi, Shigella spp., Staphylococcus aureus*
## Vaccine profiles (2) - Examples

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease presentation</th>
<th>Vaccine</th>
<th>Vaccination scenarios (age of vaccination)</th>
<th>Justification</th>
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<tbody>
<tr>
<td><strong>Haemophilus influenzae type B (Hib)</strong></td>
<td>All (CNS infections, LRI and thorax infections)</td>
<td>59; 92; 93(^\dagger) (69 for LRI)</td>
<td>90</td>
<td>5 years</td>
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<td><strong>Shigella</strong></td>
<td>All (Diarrhoea)</td>
<td>60</td>
<td>70</td>
<td>5 years</td>
</tr>
<tr>
<td><strong>Group A streptococcus (GAS)</strong></td>
<td>All (Bacterial skin infections, Bone and joint infections, BSI, Cardiac infections)</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
</tr>
</tbody>
</table>

\(^\dagger\) Efficacy corresponding to first, second, and third doses respectively.
Vaccine Impact on AMR Burden by Pathogen (1)

*Mycobacterium tuberculosis*: 118,316 (107,061-130,567) deaths associated with resistance could have been averted by a vaccine which meets WHO’s PPC criteria of 80% efficacy, when given to infants with life-long immunity or boosting.

*Streptococcus pneumoniae*: 98,987 (86,231-115,406) deaths associated with resistance could have been averted by a vaccine with 50% efficacy against LRI, 70% efficacy against other presentations and strains.

*Results are in a table format in background slides*
Vaccine Impact on AMR Burden by Pathogen (2)

<table>
<thead>
<tr>
<th>Pathogen (Justification)</th>
<th>Disease presentation</th>
<th>Vaccine</th>
<th>Vaccination scenarios (age of vaccination)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mycobacterium tuberculosis - M72</strong> (WHO Preferred Product Characteristics &amp; Expert opinion &amp; Advanced candidate)</td>
<td>Tuberculosis</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae - all</strong> (Hypothetical vaccine based on expert opinion)</td>
<td>All (Bacterial skin infections, Bone and joint infections, BSI, Cardiac infections, CNS infections, Intra-abdominal infections, LRI and thorax infections, UTI)</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td><strong>E. Coli - non diarrheagenic</strong> (Hypothetical vaccine based on expert opinion)</td>
<td>Bacterial skin infections, bone and joint infections, BSI, cardiac infections, CNS infections, intra-abdominal infections, LRI and thorax infections, and UTI</td>
<td>70</td>
<td>70</td>
</tr>
</tbody>
</table>
### Vaccine Impact on AMR Burden by Pathogen (3)

<table>
<thead>
<tr>
<th>Pathogen (Justification)</th>
<th>Disease presentation</th>
<th>Vaccine</th>
<th>Vaccination scenarios (age of vaccination)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mycobacterium tuberculosis</strong> - M72† (WHO Preferred Product Characteristics &amp; Expert opinion &amp; Advanced candidate)</td>
<td>Tuberculosis</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td><strong>Mycobacterium tuberculosis</strong> - Improved (WHO Preferred Product Characteristics &amp; Expert opinion)</td>
<td>Tuberculosis</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong> (Existing vaccine)</td>
<td>BSI, CNS infections, Cardiac infections, LRI</td>
<td>29; 58; 58§ (27 for LRI)</td>
<td>90</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong> - Improved† (Hypothetical vaccine based on expert opinion)</td>
<td>BSI, CNS infections, Cardiac infections, LRI</td>
<td>70 (50 for LRI)</td>
<td>90</td>
</tr>
</tbody>
</table>
Vaccine Impact on AMR Burden by Pathogen (4) - licensed vaccines

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Vaccine avertable deaths associated with AMR</th>
<th>Real coverage in 2019</th>
<th>Increased coverage</th>
<th>Expanding the coverage to elderly populations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemophilus influenzae B</strong></td>
<td></td>
<td>11,318 (9,690 - 13,114)</td>
<td>13,027 (11,058 - 15,180)†</td>
<td>Not estimated</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td></td>
<td>44,251 (37,185 - 51,580)</td>
<td>58,922 (50,170 - 69,048)†</td>
<td>71,343 (62,610 - 81,314)</td>
</tr>
<tr>
<td><strong>Salmonella Typhi</strong></td>
<td></td>
<td>0 (0 - 0)*</td>
<td>34,478 (26,029 - 44,037)**</td>
<td>Not estimated</td>
</tr>
</tbody>
</table>

* We assumed minimal coverage (0%) of typhoid conjugate vaccine in 2019
† 90% coverage
‡‡ 70% coverage
## Vaccine Impact on AMR Burden by Pathogen (5) - combinations

<table>
<thead>
<tr>
<th>Target</th>
<th>Pathogen (Vaccine)</th>
<th>Vaccine avertable deaths associated with AMR</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salmonella</em> spp.</td>
<td><em>Salmonella</em> Typhi, non-typhoidal <em>Salmonella</em>, <em>Salmonella</em> Paratyphi</td>
<td>37,761</td>
</tr>
<tr>
<td><em>Diarrhoeal pathogens</em></td>
<td>ETEC, <em>Shigella</em></td>
<td>6,912</td>
</tr>
<tr>
<td><em>Bloodstream Infections</em></td>
<td><em>Acinetobacter baumannii</em> - BSI, <em>ExPEC</em> - BSI, <em>Klebsiella pneumoniae</em> - BSI</td>
<td>60,709</td>
</tr>
</tbody>
</table>
Vaccine Avertable AMR Burden by Infectious Syndrome and Pathogen

*Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Klebsiella pneumoniae* account for most of the vaccine avertable AMR burden associated with lower respiratory infections.

*Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Escherichia coli* account for most of the vaccine avertable AMR burden associated with bloodstream infections.

*Others include bacterial skin infections, bone and joint infections, cardiac infections, CNS infections, diarrhoea, gonorrhoea and chlamydia, intra-abdominal infections, typhoid, paratyphoid, and iNTS, urinary tract infections.*
### Vaccine impact on AMR burden for pathogens in high potential scenario

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Vaccine avertable deaths associated with AMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline scenario</td>
</tr>
<tr>
<td><strong>E. coli - non-diarrhetic</strong></td>
<td>62,424 (56,454 - 68,555)</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae - all</strong></td>
<td>64,484 (58,747 - 72,028)</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>56,141 (50,768 - 62,454)</td>
</tr>
</tbody>
</table>

*High-potential scenario* shows the maximum potential impact vaccines could have if challenges around vaccine development and delivery were to be resolved.

Therefore, the estimates are *optimistic* given the unanswered questions about the feasibility of producing vaccines with long-term immunity and timely delivery to populations at risk.
Limitations (1)

- We excluded indirect effect and transmission dynamics of AMR pathogens → To allow pan-pathogen analyses (using a static proportional impact model)

- Our analysis only focused on 15 bacterial pathogens → Inclusion of other pathogens appears unlikely to significantly affect our overall inferences considering that the included 15 pathogens are responsible for the majority of the AMR burden
Limitations (2)

- **Limited input data to the GRAM project** especially from low- and middle-income countries
  → The estimates generated by the GRAM project are the most comprehensive estimates of bacterial AMR burden to date

- **Geographic and socioeconomic clustering** of vaccination coverage was not considered
  → Future studies can further investigate heterogeneity in vaccination impact on lowering AMR burden (among subpopulations with higher risk of disease or with lower health care access including access to vaccination services)
Discussion

- **Pan-pathogen analyses** with standardised methodologies are critical to inform vaccine funding and development and should be followed up with detailed vaccine-specific analyses.

- There are multiple challenges that need overcoming such as immunisation of adults and the elderly, timely immunisation to prevent nosocomial infections, vaccine demand, and financing.

- The comprehensive assessment of the value of vaccines against AMR should include indicators beyond mortality such as the impact on antibiotic use, economic burden, and social equity.

- The vaccine-avertable burden of AMR should be included in the Full Value of Vaccine Assessments.
Policy Implications

**Existing vaccines**
(e.g. *Haemophilus influenzae* type b (Hib) vaccine, *Pneumococcal* conjugate vaccine (PCV), and *typhoid* conjugate vaccines (TCV))

- To scale up existing vaccines to high and equitable immunisation coverage, and the acceleration of TCV introductions in high burden countries

**Vaccines in late-stage clinical development**
(e.g. vaccines against *Escherichia coli* and *Mycobacterium tuberculosis*)

- To accelerate the anticipated licensure of these products
- To collect data on vaccine impact on AMR during trials to inform policy decision and country uptake

**Remaining pathogens**
(e.g. vaccines against *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Acinetobacter baumannii*)

- To enhance biological understanding and improve the feasibility of developing vaccines for these pathogens
Thank you

https://doi.org/10.1101/2022.05.08.22274821
Chaelin Kim (chaelin.kim@ivi.int / ckim0509@gmail.com)
Extra slides
# Vaccine profiles

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease presentation</th>
<th>Vaccine</th>
<th>Vaccination scenarios (age of vaccination)</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Efficacy (%)</td>
<td>Coverage (%)</td>
<td>Duration of protection</td>
</tr>
<tr>
<td>Acinetobacter baumannii - BSI*</td>
<td>BSI</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
</tr>
<tr>
<td>Acinetobacter baumannii - all</td>
<td>All (Bacterial skin infections, BSI, Cardiac infections, LRI and thorax infections, UTI)</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>All (Bone and joint infections, BSI, Cardiac infections, Intra-abdominal infections, UTI)</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
</tr>
<tr>
<td>Enterotoxigenic Escherichia coli (ETEC)</td>
<td>Diarrhoea</td>
<td>60</td>
<td>70</td>
<td>5 years</td>
</tr>
</tbody>
</table>

† BSI: Bloodstream infection
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease</th>
<th>Age</th>
<th>Duration</th>
<th>Description</th>
<th>Groups</th>
<th>Vaccine Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extraintestinal Pathogenic Escherichia coli (ExPEC)</strong> - <strong>BSI</strong>†</td>
<td>BSI</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>All age groups</td>
<td>Hypothetical vaccine based on expert opinion</td>
</tr>
<tr>
<td><strong>Extraintestinal Pathogenic Escherichia coli (ExPEC)</strong> - <strong>UTI</strong>†</td>
<td>UTI</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>All age groups</td>
<td>Hypothetical vaccine based on expert opinion</td>
</tr>
<tr>
<td><strong>E. Coli - non diarrheagenic</strong></td>
<td></td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>All age groups</td>
<td>Hypothetical vaccine based on expert opinion</td>
</tr>
<tr>
<td><strong>Group A streptococcus (GAS)</strong></td>
<td></td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>All age groups</td>
<td>WHO Preferred Product Characteristics &amp; Expert opinion</td>
</tr>
<tr>
<td><strong>Haemophilus influenzae type B (Hib)</strong></td>
<td></td>
<td>59; 92; 93⁵</td>
<td>90</td>
<td>5 years</td>
<td>6, 10, 14 weeks</td>
<td>-</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae - BSI</strong></td>
<td>BSI</td>
<td>70</td>
<td>70</td>
<td>6 months</td>
<td>All age groups</td>
<td>Hypothetical vaccine based on expert opinion</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae - all</strong></td>
<td></td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>All age groups</td>
<td>Hypothetical vaccine based on expert opinion</td>
</tr>
<tr>
<td>Pathogen</td>
<td>Disease</td>
<td>Efficacy</td>
<td>Age</td>
<td>Duration</td>
<td>booster duration</td>
<td>Status</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>----------------------------------</td>
<td>----------</td>
<td>-----</td>
<td>----------</td>
<td>-----------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td><strong>Mycobacterium tuberculosis - M72</strong></td>
<td>Tuberculosis</td>
<td>50</td>
<td>70</td>
<td>10 years</td>
<td>10 years + boost every 10 years</td>
<td>WHO Preferred Product Characteristics &amp; Expert opinion &amp; Advanced candidate</td>
</tr>
<tr>
<td><strong>Mycobacterium tuberculosis - Improved</strong></td>
<td>Tuberculosis</td>
<td>80</td>
<td>70</td>
<td>10 years</td>
<td>0 weeks + boost every 10 years</td>
<td>WHO Preferred Product Characteristics &amp; Expert opinion</td>
</tr>
<tr>
<td><strong>Neisseria gonorrhoeae</strong></td>
<td>Gonorrhoea</td>
<td>70</td>
<td>70</td>
<td>10 years</td>
<td>15 years</td>
<td>WHO Preferred Product Characteristics &amp; Expert opinion</td>
</tr>
<tr>
<td><strong>non-typhoidal Salmonella</strong></td>
<td>All (BSI, Cardiac infections, Diarrhoea, Typhoid, paratyphoid, and iNTS)</td>
<td>80</td>
<td>70</td>
<td>5 years</td>
<td>6 weeks, 9 months</td>
<td>Hypothetical vaccine based on expert opinion</td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa</strong></td>
<td>BSI, LRI and thorax infections</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>6 weeks, elderly age group with highest burden</td>
<td>Hypothetical vaccine based on expert opinion</td>
</tr>
<tr>
<td><strong>Salmonella Paratyphi</strong></td>
<td>Typhoid, paratyphoid, and iNTS</td>
<td>70</td>
<td>70</td>
<td>5 years</td>
<td>9 months</td>
<td>Hypothetical vaccine based on expert opinion</td>
</tr>
<tr>
<td><strong>Salmonella Typhi</strong></td>
<td>All (BSI, Cardiac infections, Typhoid, paratyphoid, and iNTS)</td>
<td>85</td>
<td>70</td>
<td>15 years</td>
<td>9 months</td>
<td>Existing vaccine &amp; Expert opinion</td>
</tr>
<tr>
<td><strong>Shigella</strong></td>
<td>All (Diarrhoea)</td>
<td>60</td>
<td>70</td>
<td>5 years</td>
<td>6 months</td>
<td>WHO Preferred Product Characteristics &amp; Expert opinion &amp; Advanced candidate</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>All (Bacterial skin infections, Bone and joint infections, BSI, Cardiac infections, CNS infections, Intra-abdominal infections, LRI and thorax infections, UTI)</td>
<td>60</td>
<td>70</td>
<td>5 years</td>
<td>6 weeks, elderly age group with highest burden</td>
<td>All age groups</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----</td>
<td>-----</td>
<td>---------</td>
<td>-----------------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>BSI, CNS infections, Cardiac infections, LRI</td>
<td>29; 58; 58§ (27 for LRI)</td>
<td>90</td>
<td>5 years</td>
<td>6, 10, 14 weeks</td>
<td>6, 10, 14 weeks, elderly age group with highest burden</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae - Improved†</strong></td>
<td>BSI, CNS infections, Cardiac infections, LRI</td>
<td>70 (50 for LRI)</td>
<td>90</td>
<td>5 years</td>
<td>6 weeks</td>
<td>6 weeks, elderly age group with highest burden</td>
</tr>
</tbody>
</table>

† The effects of these vaccines were not added to the aggregated impact of vaccination on AMR burden by region and by infectious syndrome.
§ Efficacy corresponding to first, second, and third doses respectively.
Vaccine avertable AMR health burden globally and by WHO region, 2019

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Vaccine avertable deaths</th>
<th>Vaccine avertable DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Associated with resistance</td>
<td>Attributable to resistance</td>
</tr>
<tr>
<td>Africa</td>
<td>166,105 (154,785 - 180,343)</td>
<td>44,745 (40,658 - 49,196)</td>
</tr>
<tr>
<td>Americas</td>
<td>32,901 (30,020 - 35,892)</td>
<td>8,824 (7,949 - 9,939)</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>61,060 (56,445 - 66,784)</td>
<td>18,105 (16,426 - 20,194)</td>
</tr>
<tr>
<td>Europe</td>
<td>32,218 (29,145 - 37,168)</td>
<td>9,721 (8,646 - 11,126)</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>162,699 (147,461 - 179,566)</td>
<td>54,989 (47,336 - 64,667)</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>58,701 (52,392 - 67,736)</td>
<td>16,569 (14,593 - 19,491)</td>
</tr>
<tr>
<td>Global</td>
<td>514,631 (491,550 - 540,336)</td>
<td>153,009 (144,253 - 165,008)</td>
</tr>
</tbody>
</table>
### Vaccine impact on AMR burden by vaccine profile, 2019

#### Baseline scenario

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease presentation</th>
<th>Vaccine avertable deaths</th>
<th>Vaccine avertable DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Associated with resistance</td>
<td>Attributable to resistance</td>
</tr>
<tr>
<td><strong>Acinetobacter baumannii</strong></td>
<td>BSI</td>
<td>18,060 (13,305 - 25,668)</td>
<td>5,723 (4,142 - 8,442)</td>
</tr>
<tr>
<td><strong>Acinetobacter baumannii</strong></td>
<td>All (Bacterial skin infections, BSI, Cardiac infections, LRI and thorax infections, UTI)</td>
<td>34,327 (28,241 - 43,094)</td>
<td>10,799 (8,651 - 14,129)</td>
</tr>
<tr>
<td><strong>Enterococcus faecium</strong></td>
<td>All (Bone and joint infections, BSI, Cardiac infections, Intra-abdominal infections, UTI)</td>
<td>13,933 (12,268 - 16,025)</td>
<td>3,641 (3,094 - 4,469)</td>
</tr>
<tr>
<td><strong>Enterotoxigenic Escherichia coli (ETEC)</strong></td>
<td>Diarrhoea</td>
<td>2,779 (2,043 - 4,136)</td>
<td>784 (545 - 1,094)</td>
</tr>
<tr>
<td><strong>Extraintestinal Pathogenic Escherichia coli (ExPEC)</strong></td>
<td>BSI</td>
<td>15,316 (11,794 - 19,992)</td>
<td>3,938 (3,060 - 5,348)</td>
</tr>
<tr>
<td>Pathogen</td>
<td>Source</td>
<td>Infections</td>
<td>UTI (Cases)</td>
</tr>
<tr>
<td>----------</td>
<td>--------</td>
<td>----------------------------------------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Extraintestinal Pathogenic Escherichia coli (ExPEC) - UTI</td>
<td>UTI</td>
<td>6,727 (5,659 - 7,934)</td>
<td>1,787 (1,469 - 2,172)</td>
</tr>
<tr>
<td>E. Coli - non diarrheagenic</td>
<td>All (Bacterial skin infections, bone and joint infections, BSI, cardiac infections, CNS infections, intra-abdominal infections, LRI and thorax infections, and UTI)</td>
<td>62,424 (56,454 - 68,555)</td>
<td>16,405 (15,090 - 18,344)</td>
</tr>
<tr>
<td>Group A streptococcus (GAS)</td>
<td>All (Bacterial skin infections, Bone and joint infections, BSI, Cardiac infections)</td>
<td>792 (643 - 998)</td>
<td>82 (55 - 130)</td>
</tr>
<tr>
<td>Haemophilus influenzae type B (Hib)</td>
<td>All (CNS infections, LRI and thorax infections)</td>
<td>13,027 (11,058 - 15,180)</td>
<td>2,946 (2,412 - 3,622)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae - BSI</td>
<td>BSI</td>
<td>27,333 (22,045 - 34,905)</td>
<td>8,116 (6,508 - 10,273)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae - all</td>
<td>All (Bacterial skin infections, Bone and joint infections, BSI, Cardiac infections, CNS infections, Intra-abdominal infections, LRI and thorax infections, UTI)</td>
<td>64,484 (58,747 - 72,028)</td>
<td>19,397 (16,971 - 21,761)</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis - M72</td>
<td>Tuberculosis</td>
<td>70,704 (64,053 - 77,951)</td>
<td>31,040 (26,956 - 37,850)</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis - Improved</td>
<td>Tuberculosis</td>
<td>118,316 (107,061 - 130,567)</td>
<td>51,675 (45,223 - 61,401)</td>
</tr>
<tr>
<td>Organism</td>
<td>Source of infection</td>
<td>Incidence (95% CI)</td>
<td>Mortality (95% CI)</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>gonorrhoea</td>
<td>NA (NA - NA)</td>
<td>NA (NA - NA)</td>
</tr>
<tr>
<td>non-typhoidal Salmonella</td>
<td>All (BSI, Cardiac infections, Diarrhoea, Typhoid, paratyphoid, and iNTS)</td>
<td>1,820 (1,412 - 2,624)</td>
<td>396 (290 - 618)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>BSI, LRI and thorax infections</td>
<td>20,700 (18,148 - 23,443)</td>
<td>5,314 (4,633 - 6,081)</td>
</tr>
<tr>
<td>Salmonella Paratyphi</td>
<td>Typhoid, paratyphoid, and iNTS</td>
<td>1,463 (853 - 2,793)</td>
<td>301 (149 - 637)</td>
</tr>
<tr>
<td>Salmonella Typhi</td>
<td>All (BSI, Cardiac infections, Typhoid, paratyphoid, and iNTS)</td>
<td>34,478 (26,029 - 44,037)</td>
<td>6,630 (5,022 - 8,959)</td>
</tr>
<tr>
<td>Shigella</td>
<td>All (Diarrhoea)</td>
<td>4,133 (2,765 - 6,132)</td>
<td>860 (545 - 1,557)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>All (Bacterial skin infections, Bone and joint infections, BSI, Cardiac infections, CNS infections, Intra-abdominal infections, LRI and thorax infections, UTI)</td>
<td>56,141 (50,768 - 62,454)</td>
<td>13,322 (11,924 - 15,169)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>BSI, CNS infections, Cardiac infections, LRI</td>
<td>58,922 (50,170 - 69,048)</td>
<td>12,179 (10,178 - 14,772)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae - Improved</td>
<td>BSI, CNS infections, Cardiac infections, LRI</td>
<td>98,987 (86,231 - 115,406)</td>
<td>20,415 (17,330 - 24,803)</td>
</tr>
</tbody>
</table>
## Vaccine impact on AMR burden by vaccine profile, 2019

### High-potential scenario

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease presentation</th>
<th>Vaccine avertable deaths</th>
<th>Vaccine avertable DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Associated with resistance</td>
<td>Attributable to resistance</td>
</tr>
<tr>
<td><strong>Acinetobacter baumannii - BSI</strong></td>
<td>BSI</td>
<td>116,141 (105,342 - 128,342)</td>
<td>36,641 (33,081 - 41,272)</td>
</tr>
<tr>
<td><strong>Acinetobacter baumannii - all</strong></td>
<td>All (Bacterial skin infections, BSI, Cardiac infections, LRI and thorax infections, UTI)</td>
<td>216,584 (201,748 - 231,987)</td>
<td>67,905 (63,384 - 73,535)</td>
</tr>
<tr>
<td><strong>Enterococcus faecium</strong></td>
<td>All (Bone and joint infections, BSI, Cardiac infections, Intra-abdominal infections, UTI)</td>
<td>100,814 (95,339 - 105,798)</td>
<td>26,342 (24,611 - 28,209)</td>
</tr>
<tr>
<td><strong>Extraintestinal Pathogenic Escherichia coli (ExPEC) - BSI</strong></td>
<td>BSI</td>
<td>103,016 (93,650 - 114,889)</td>
<td>26,551 (24,078 - 29,292)</td>
</tr>
<tr>
<td><strong>Extraintestinal Pathogenic Escherichia coli (ExPEC) - UTI</strong></td>
<td>UTI</td>
<td>49,669 (46,732 - 52,824)</td>
<td>13,003 (12,189 - 13,885)</td>
</tr>
<tr>
<td>Bacterial Strain</td>
<td>Clinical Manifestations</td>
<td>Number of Infections (99th, 50th, 99th)</td>
<td></td>
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<tr>
<td>------------------</td>
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<td>----------------------------------------</td>
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</tr>
<tr>
<td><strong>E. coli - non-diarrhogenic</strong></td>
<td>Bacterial skin infections, bone and joint infections, BSI, cardiac infections, CNS infections, intra-abdominal infections, LRI and thorax infections, and UTI</td>
<td>389,043 (373,393 - 404,859) 102,352 (97,917 - 106,919) 12,648,212 (12,044,182 - 13,489,274) 3,375,286 (3,163,077 - 3,641,542)</td>
<td></td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae - all</strong></td>
<td>All (Bacterial skin infections, Bone and joint infections, BSI, Cardiac infections, CNS infections, Intra-abdominal infections, LRI and thorax infections, UTI)</td>
<td>321,242 (308,878 - 335,698) 97,026 (92,013 - 102,088) 13,709,546 (12,834,241 - 14,723,484) 4,068,201 (3,801,569 - 4,425,285)</td>
<td></td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa</strong></td>
<td>BSI, LRI and thorax infections</td>
<td>118,966 (113,054 - 125,950) 30,495 (28,728 - 32,634) 4,821,442 (4,495,854 - 5,257,746) 1,237,497 (1,149,086 - 1,347,794)</td>
<td></td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>All (Bacterial skin infections, Bone and joint infections, BSI, Cardiac infections, CNS infections, Intra-abdominal infections, LRI and thorax infections, UTI)</td>
<td>319,112 (307,397 - 331,431) 76,796 (73,583 - 80,782) 10,579,419 (10,085,244 - 11,164,417) 2,499,704 (2,357,371 - 2,664,681)</td>
<td></td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>BSI, CNS infections, Cardiac infections, LRI</td>
<td>71,343 (62,610 - 81,314) 14,728 (12,661 - 17,487) 5,324,115 (4,648,050 - 6,118,739) 1,107,245 (930,760 - 1,296,970)</td>
<td></td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae - Improved</strong></td>
<td>BSI, CNS infections, Cardiac infections, LRI</td>
<td>118,645 (103,983 - 135,056) 24,471 (20,943 - 28,957) 8,980,361 (7,882,947 - 10,255,670) 1,848,190 (1,559,623 - 2,190,715)</td>
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Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance: An Action Framework
Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance: An Action Framework
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Box 2. Wellcome’s assessment of vaccine priorities for targeting WHO AMR priority bacteria

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Table 1. Action Framework at a glance

Table 2. Recommended use of selected licensed vaccines and potential impact on AMR

Table 3. Selected WHO priority disease areas for which vaccines are critically needed and available evidence supports a favourable technical feasibility assessment and potential impact on AMR

Fig. 1. Strategic objectives of the Global Action Plan on Antimicrobial Resistance

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Abbreviations

AMR | antimicrobial resistance
CARB-X | Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
EDCTP | European & Developing Countries Clinical Trials Partnership
ETEC | Enterotoxigenic Escherichia coli
FAO | Food and Agriculture Organization of the United Nations
FDA | Food and Drug Administration
Gates MRI | Bill & Melinda Gates Medical Research Institute
Gavi | Gavi, the Vaccine Alliance
GBS | group B Streptococcus
Hib | Haemophilus Influenzae type b
IA2030 | Immunisation Agenda 2030
LMICs | low- and middle-income countries
OIE | World Organisation for Animal Health
PCV | pneumococcal conjugate vaccine
PDVAC | Product Development for Vaccines Advisory Committee
R&D | research and development
RSV | respiratory syncytial virus
SAGE | Strategic Advisory Group of Experts on Immunization
SP | strategic priority
TB | tuberculosis
TCV | typhoid conjugate vaccine
UN | United Nations
UNICEF | United Nations Children's Fund
WHO | World Health Organization
Target audience

This report is aimed at any individual or organization interested and/or active in the fields of vaccines and prevention of infectious diseases, antimicrobial resistance (AMR), vaccine research and development (R&D), funding of vaccines and AMR control, vaccine policy and regulatory decision-making, and immunization programmes. This covers sectors such as academia, philanthropy, the private sector, government, supranational organizations, the United Nations (UN), and the general public. The following sectors that play a role in global health should consider the priorities presented here as they take actions related to vaccines and AMR:

- **Governments, national immunization technical advisory groups, and agencies** implementing national AMR action plans and immunization strategies, which can use the considerations presented here to prioritize and harmonize their plans, optimizing the role of vaccines;

- **Health-care workers, professional medical associations, patient groups, civil society and subnational organizations**, whose decisions influence vaccine uptake, access and public perceptions;

- **Regulators and policy-makers** who assess evidence and health technologies, and through benefit-risk analyses recommend or implement public health interventions to protect individuals and populations;

- **The pharmaceutical industry**, which can identify new investment avenues and initiate new product development partnerships, and help generate data relevant to vaccine impact on AMR;

- **Academic researchers**, who can focus on topics of scientific interest and potential public health impact in areas such as antigen discovery, epidemiologic research, health economic impact assessment, and determinants of vaccine confidence and health-seeking behaviours;

- **Funders of research** on product development and use of interventions from the private, philanthropic and public sectors, which can direct resources to priority actions to achieve greater impact, address bottlenecks, accelerate discovery and remove barriers to implementation;

- **Media and educators**, who can use these priority actions to frame communications and improve understanding of the role of vaccines in controlling AMR;

- **The agricultural and animal industry sectors**, which need to consider the potential of vaccines to reduce antibiotic use in animals;

- **Public health advocates**, including many of the stakeholders named above, who can use the recommendations presented here to shape their message and strengthen their public outreach and education.
Methodology and acknowledgments

This Action Framework, intended to guide vaccine stakeholders in efforts to maximize the impact of vaccines in preventing and containing AMR, was generated through a consensus-building consultative process. While the role of vaccines in tackling AMR has been considered in the scientific literature and deliberations of international organizations, a comprehensive global Action Framework has not been proposed. In response, the World Health Organization (WHO), in collaboration with the Bill & Melinda Gates Foundation (BMGF), Wellcome and the Center for Disease Dynamics, Economics & Policy (CDDEP), undertook an effort to build on expert discussions and develop specific actions to strengthen the use of vaccines for prevention and control of the devastating consequences of AMR, with a long term view. To gather information and opinions, WHO consulted experts from academic research institutions, country representatives, nongovernmental organizations, and the pharmaceutical industry. A formally constituted WHO expert working group: Anthony Fiore (Centers for Disease Control and Prevention, Atlanta, GA, USA), William P. Hausdorff (PATH, Washington, DC, USA), Mark Jit, (London School of Hygiene and Tropical Medicine (LSHTM), London, UK); Gagandeep Kang (Translational Health Science and Technology Institute, Faridabad, India), Marc Lipsitch (Harvard T.H. Chan School of Public Health, Boston, MA, USA), Angela Brueggemann (University of Oxford, Oxford, UK), Buddha Basnyat (Oxford University Clinical Research Unit, Kathmandu, Nepal), Gordon Dougan (University of Cambridge, Cambridge, UK), Francis Ndowa (Skin and GU Medicine Clinic, Harare, Zimbabwe), Iruka Okeke (University of Ibadan, Ibadan, Nigeria), David Salisbury (Chatham House, London, UK), Anthony Scott (LSHTM, London, UK), JP Sevilla (Harvard T.H. Chan School of Public Health, Boston, MA, USA), Lone Simonsen (Roskilde University, Roskilde, Denmark)) provided input throughout the process. The Action Framework was first drafted following a stakeholder consultation held in London on 26–27 February 2019. The document has been circulated widely for comment, including an opportunity for public review through the WHO website.

The Department of Immunization, Vaccines and Biologicals at WHO (WHO IVB) would like to thank the many individuals who contributed to the development of this document. We extend additional thanks to the following key contributors: Laetitia Bigger (International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland), Isabel Frost (CDDEP, New Delhi, India), Elizabeth J. Klemm (Wellcome Trust, London, UK), Ramanan Laxminarayan (CDDEP, New Delhi, India), Stefano Messori (World Organisation for Animal Health (OIE), Paris, France), Wilson Mok (Gavi, Geneva, Switzerland), Holly Prudden (International AIDS Society, Geneva, Switzerland), Padmini Srikantiah (BMGF, Seattle, WA, USA), Robert Taylor (Scientific Writer, Boston, MA, USA), the WHO IVB Secretariat, Geneva, Switzerland, the WHO AMR Secretariat, Geneva, Switzerland.

Coordinating authors: Mateusz Hasso-Agopsowicz and Johan Vekemans, WHO IVB, Geneva, Switzerland.
Overview

There is increasing awareness of the significant threats to individuals and public health from the growing burden of antimicrobial-resistant microbes. Multiple approaches are needed to prevent infections and reduce the use of antimicrobial drugs. Among these, vaccines are effective tools to prevent infections, and they have the potential to make a major contribution to the control and prevention of AMR.

Vaccines protect people and communities by preventing infections and their onward transmission, whether antimicrobial resistant or not. Prevention of infections results in reduced use of antimicrobials for treatment, thereby reducing the selective pressures on microbial populations that drive the emergence of resistance.

This document presents a strategic vision for vaccines to contribute fully, sustainably and equitably to the prevention and control of AMR by preventing infections and reducing antimicrobial use. It identifies a series of priority actions to be taken by stakeholders in the fields of immunization and AMR, in three areas:

- Expanding the use of licensed vaccines to maximize impact on AMR
- Developing new vaccines that contribute to the prevention and control of AMR
- Expanding and sharing knowledge on the impact of vaccines on AMR.

Table 1 summarizes the objectives and priority actions under each of these areas to achieve the AMR-related sections of the Immunization Agenda 2030. A full description of each of these elements is provided under the section Strategic vision of the Action Framework.

**BOX 1** AMR-related objectives of the Immunization Agenda 2030

This document complements the high-level global immunization strategy, the Immunization Agenda 2030: A Global Strategy to Leave No One Behind (IA2030). It summarizes how, in addition to its public health benefit in directly preventing infection, immunization can also contribute to the control of AMR. The current document is of particular relevance to the following IA2030 strategic priorities (SP):

- **SP1** Immunization programmes for primary health care and universal health coverage
- **SP3** Coverage and equity
- **SP4** Life course and integration
- **SP6** Supply and sustainability
- **SP7** Research and innovation.
## Table 1. Action Framework at a glance

### GOAL
**Expand use of licensed vaccines to maximize impact on AMR**

### OBJECTIVES

1. **Increase coverage of vaccines with impact on AMR.**

2. **Update recommendations and normative guidance in both the vaccine and AMR sectors to include the role of vaccines to control AMR.**

3. **Improve awareness and understanding of the role of vaccines in limiting AMR through effective communication, education and training.**

### ACTIONS

1. **Countries should implement existing vaccine-related recommendations of the Global Action Plan on AMR.**

2. **Where justified, normative guidance, regulatory indications, policy recommendations and health regulations for vaccine use should be adapted to account specifically for the use of vaccines to impact AMR.**

3. **Countries, funders and other stakeholders should include the role of vaccines in limiting AMR in communication materials used to present their related activities.**

### AUDIENCE

- **Key:**
  - governments, national immunization technical advisory groups, and agencies
  - regulators and policy-makers
  - health-care workers, professional medical associations, patient groups, civil society and subnational organizations
  - media and educators
  - the pharmaceutical industry
  - academic researchers
  - funders of research
  - the agricultural and animal industry sectors
  - public health advocates

<table>
<thead>
<tr>
<th>GOAL</th>
<th>OBJECTIVES</th>
<th>ACTIONS</th>
<th>AUDIENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Expand use of licensed vaccines to maximise impact on AMR</strong></td>
<td>1. Increase coverage of vaccines with impact on AMR.</td>
<td>1a. Countries should implement existing vaccine-related recommendations of the Global Action Plan on AMR.</td>
<td>governments, national immunization technical advisory groups, and agencies</td>
</tr>
<tr>
<td></td>
<td>1. Increase coverage of vaccines with impact on AMR.</td>
<td>1b. Donors, countries and other health payers should maintain and expand immunization financing and strengthen capacities, ensuring affordable supply, functional delivery systems and programmatic sustainability.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Update recommendations and normative guidance in both the vaccine and AMR sectors to include the role of vaccines to control AMR.</td>
<td>2a. Where justified, normative guidance, regulatory indications, policy recommendations and health regulations for vaccine use should be adapted to account specifically for the use of vaccines to impact AMR.</td>
<td>health-care workers, professional medical associations, patient groups, civil society and subnational organizations</td>
</tr>
<tr>
<td></td>
<td>2. Update recommendations and normative guidance in both the vaccine and AMR sectors to include the role of vaccines to control AMR.</td>
<td>2b. AMR national action plans and international organizations dedicated to AMR control should consistently include vaccines in the armamentarium of interventions planned for use against AMR, and build capacity for the full realization of vaccine impact as individual or combined interventions.</td>
<td></td>
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<tr>
<td></td>
<td>3. Improve awareness and understanding of the role of vaccines in limiting AMR through effective communication, education and training.</td>
<td>3a. Countries, funders and other stakeholders should include the role of vaccines in limiting AMR in communication materials used to present their related activities.</td>
<td>regulators and policy-makers</td>
</tr>
<tr>
<td></td>
<td>3. Improve awareness and understanding of the role of vaccines in limiting AMR through effective communication, education and training.</td>
<td>3b. Institutions involved in the vaccine and AMR sectors should develop communication, education and training materials about the role of vaccines in controlling AMR, targeting audiences ranging from the general public to infectious disease experts.</td>
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</tbody>
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In a “One Health” perspective, bodies such as the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE) and the World Health Organization (WHO), in collaboration with the agricultural industry and animal health stakeholders, should update recommendations and regulations and develop an action plan to maximize the use of animal vaccines to reduce antibiotic use in animals.
## GOAL

**Develop new vaccines that contribute to prevention and control of AMR**

### OBJECTIVES

<table>
<thead>
<tr>
<th>ACTION</th>
<th>AUDIENCE</th>
</tr>
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<tbody>
<tr>
<td>4a.</td>
<td>Funders, industry, governments, nongovernmental and supranational organizations, academic institutions and researchers should increase investments in vaccine candidates with anticipated benefits for AMR.</td>
</tr>
<tr>
<td>4b.</td>
<td>Funders, including governments and nongovernmental organizations, product development sponsors and industry, should create novel financing mechanisms for late-stage vaccine evaluation, introduction, evaluation of new vaccine effectiveness and impact, and to ensure sufficient manufacturing capacity to meet global needs for vaccines expected to reduce AMR.</td>
</tr>
<tr>
<td>5a.</td>
<td>Vaccine development sponsors and regulatory authorities should systematically assess the potential to prevent and control AMR and related data packages generated in clinical development to expand knowledge of investigational product risk-benefit balance.</td>
</tr>
<tr>
<td>5b.</td>
<td>Regulators and policy-makers should develop means to accelerate access to vaccines of urgent medical need, including impacts on AMR, without jeopardizing the required confidence in safety and efficacy.</td>
</tr>
<tr>
<td>5c.</td>
<td>WHO, through its Product Development for Vaccines Advisory Committee (PDVAC) and Strategic Advisory Group of Experts (SAGE) on Immunization, and other stakeholders who shape progress in vaccine R&amp;D should include evaluation of AMR impacts in their product landscape analyses and guidance.</td>
</tr>
<tr>
<td>5d.</td>
<td>Vaccine development sponsors and regulators should discuss clinical research requirements for regulatory labeling to include specifications about impact on AMR and antimicrobial use.</td>
</tr>
<tr>
<td>5e.</td>
<td>Sponsors of post-licensure vaccine evaluations, such as health-economic impact studies, should discuss with regulators and policy-makers, during the approval process, when and how to include evaluation of a vaccine’s potential to reduce antimicrobial use and AMR in these studies.</td>
</tr>
</tbody>
</table>

### Key:

- **governments, national immunization technical advisory groups, and agencies**
- **regulators and policy-makers**
- **health-care workers, professional medical associations, patient groups, civil society and subnational organizations**
- **the pharmaceutical industry**
- **academic researchers**
- **funders of research**
- **media and educators**
- **the agricultural and animal industry sectors**
- **public health advocates**
GOAL
Expand and share knowledge of vaccine impact on AMR

OBJECTIVES

6. Improve methodologies and increase collection and analysis of relevant data to assess vaccine impact on AMR, including antimicrobial use.

- **6a.** Normative bodies should provide guidance for health technology assessment and evaluation of vaccine impact on AMR and antimicrobial use.
- **6b.** Funders and researchers should analyse existing datasets from epidemiologic studies, trials and routine surveillance in order to estimate vaccine impact on AMR.
- **6c.** When relevant, sponsors, funders and investigators conducting new trials and studies using existing and candidate vaccines should assess vaccine impact on AMR, including antimicrobial use.
- **6d.** Public health authorities at the global, national and subnational levels should enhance surveillance systems to link vaccination data with antimicrobial use and resistance data, with the greatest practical level of geographic and demographic granularity to enable interventions that focus on the most vulnerable. In resource-limited settings, building capacity for data collection and analysis should be included in immunization and AMR country action plans.
- **6e.** Researchers should continue to generate new evidence on:
  - how to use vaccines with the specific aim of controlling drug-resistant pathogens when highly prevalent or causing epidemics;
  - how vaccines can complement other infection control strategies and stewardship efforts to prolong or restore effective use of antibiotics against specific pathogens;
  - socioeconomic and ethical aspects of vaccine impact on AMR.
- **6f.** Researchers and their sponsors should ensure that new data and evidence are made rapidly and publicly available through prompt public posting and scientific publications, preprints, and data-sharing platforms.

7. Develop estimates of vaccine value to avert the full public health and socioeconomic burden of AMR.

- **7a.** Funders should support researchers to develop and improve methodologies for estimating impact of vaccines on AMR.
- **7b.** Health delivery payers and investors in R&D should develop and use standardized health technology assessments and value-attribution frameworks to inform the estimation of the full value of vaccines to prevent and control AMR.

Key:
- governments, national immunization technical advisory groups, and agencies
- health-care workers, professional medical associations, patient groups, civil society and subnational organizations
- regulators and policy-makers
- the pharmaceutical industry
- academic researchers
- funders of research
- media and educators
- the agricultural and animal industry sectors
- public health advocates
Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance
1. Background

The ability to prevent and effectively treat many infectious diseases is one of humanity’s greatest achievements

Between the 19th and 21st centuries, infectious disease mortality—especially among children—dramatically decreased, initially in industrialized countries and later in low- and middle-income countries (LMICs).1 The large reduction in deaths from infectious diseases was driven by several linked advances. Hygiene and improved infrastructure for wastewater management, clean water delivery, and economic and social development paved the way for better housing, education and nutrition. Basic science and the study of disease dynamics led to the discovery that microbes cause disease. The discovery of modern antimicrobials, which first appeared in the 1930s, provided the extraordinary ability to treat and cure many diseases that were previously untreatable and often life-threatening. Vaccines, delivered through routine immunization programmes that often constituted the backbone of primary health care, helped to eliminate or vastly reduce many once-common viral diseases such as smallpox, polio and measles, as well as bacterial infections such as diphtheria, tetanus and pertussis. More recently, countries that expanded immunization programmes to include childhood vaccination against Haemophilus influenzae type b (Hib) and Streptococcus pneumoniae have achieved substantial reductions in disease due to these bacterial pathogens.

Antimicrobial resistance: a major global health threat

Antimicrobial resistance now threatens to undermine the effectiveness of antimicrobials and partially undo progress made against infectious diseases. Antimicrobials selectively kill or slow the growth of microbes by blocking crucial biochemical processes such as protein synthesis and genome replication. However, when a person takes an antimicrobial drug, the whole pool of microbes that the individual carries in the gastrointestinal tract, on the skin and in mucosae is exposed to that drug, in a “bystander” effect. Microbes that are less susceptible to the drug are more likely to survive, and in so doing will pass that trait to their progeny, and to be spread to other persons. Furthermore, mobile genetic elements such as plasmids, which carry genes that make the microbe drug-resistant, can be transferred to other strains of the same species and even other bacterial species, thus propagating resistance.

AMR is now an alarming and growing global problem. Penicillin-resistant bacteria were noted shortly after penicillin was first introduced. Today, pathogens resistant to all classes of antimicrobials can be found throughout the world, and the incidence of resistant infections is growing sharply. In some countries, more than 40% of infections are resistant,2 and many strains of pathogens that cause common blood, skin, digestive and respiratory infections are resistant to two or more classes of antibiotics. Some pathogens, such as the bacterium that causes gonorrhoea, have evolved strains that can no longer be treated successfully with any licensed antibiotic.

The risk of AMR infection in increased in clinical care settings, where the use of antibiotics is frequent and infections sometimes transmitted from one patient to another. This threatens the continuity of safe access to routine care, including surgical procedures.

Unless current trends are reversed, many more pathogens will become resistant to first-line antibiotics. The second- or third-line drugs used as replacements typically have more side effects, are more expensive and sometimes can be administered only in hospital settings; these factors make them less accessible to people living in LMICs, raising questions of equity.

In a connected world, AMR is a global problem, and the human and societal impact of resistant pathogens is increasing. All countries have a stake in stemming this global problem, and need to contribute through national and globally coordinated actions. Unless there is a rapid and multifaceted response to prevent and control AMR, very significant economic costs from lost productivity and social disruption by 2050 are highly likely.3

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Addressing AMR will require concerted action in the human health, animal health, and agricultural, economic and environmental domains. WHO, in collaboration with FAO and OIE, published the Global Action Plan on Antimicrobial Resistance in 2015, and in 2016 the UN Secretary-General convened the Interagency Coordination Group on AMR to explore how best to structure the global response. The group’s final report, published in 2019, outlines an ambitious and comprehensive blueprint for global stakeholders to drive progress against AMR.

Controlling AMR will require improvements in infection prevention, antimicrobial stewardship, and antimicrobial discovery. Infection prevention reduces the need for antibiotic treatment. Antimicrobial stewardship encourages more responsible use of antimicrobials and minimizes the selection pressures that drive the development of resistance (Fig. 1).

The discovery and use of new antibiotics constitute an increasingly complex economic and scientific challenge. While numerous distinct classes of antibiotics were licensed for use before 1970, few have been developed in the last half-century. As for antibiotics developed in the past, resistant isolates in the bacterial population can emerge in the relatively short term, jeopardizing effective and sustainable use.

**Fig. 1. Strategic objectives of the Global Action Plan on Antimicrobial Resistance**
VACCINES

**DECREASE INFECTIONS**
Caused by both resistant and non-resistant pathogens

**PROTECT INDIVIDUALS**
Prevent vaccinees from getting sick

**PREVENT COMPLICATIONS**
Reduce the incidence of secondary infections

**SAFEGUARD COMMUNITIES**
Decrease transmission through herd immunity

**DECREASE ANTIBIOTIC USE**
Diseases prevented by vaccination do not require antibiotic treatment

**SUPPRESS RESISTANCE EVOLUTION**
Decrease exposure of pathogens residing in and on the body to antibiotics that select for resistance

**DECREASE INDIVIDUAL RISK**
and transmission of resistant pathogens

**MORE EFFECTIVE ANTIBIOTICS**
Current antibiotics can be used for a lot longer; less need to develop new antibiotics

Fig. 2. Impact of vaccines on AMR: a schematic pathway
Vaccines contribute to the battle against AMR by preventing infections and by reducing antimicrobial use

The most direct way in which vaccines contribute to prevention and control of AMR is by reducing the incidence of disease from resistant pathogens (Fig. 2). Vaccines against *S. pneumoniae*, *Hib*, *Salmonella Typhi*, *Bordetella pertussis*, tuberculosis (TB), and *Neisseria meningitidis* can prevent morbidity and mortality due to these pathogens, including drug-resistant forms. By preventing people from transmitting infection, use of vaccines extends population protection by reducing the risk of infection among those who are not vaccinated—“herd immunity”. For some of these vaccines the specific impact on resistant infection has been estimated, for example *S. pneumoniae* (Fig. 3)\(^7\) and *Hib*.\(^8\)

The importance of protecting against resistant strains of *S. Typhi* led WHO in 2018 to recommend use of such vaccines in children 6 months of age or older in countries where typhoid is endemic, with priority given to countries with a high typhoid burden or high levels of AMR.\(^9\) In late 2019, one country, Pakistan, embarked on a phased introduction campaign with a typhoid conjugate vaccine (TCV) in all children from 9 months to 15 years old to help control the spread of extensively drug-resistant typhoid disease (Fig. 4).\(^10\)

In the future, vaccines may play a major role in the realization of public health goals against TB, malaria, gonorrhoea, *Shigella* or other infections with an important AMR burden.

Another key benefit of vaccines is reduction of antibiotic use. Since the clinical presentations of many infections, such as fever, respiratory infection or diarrhoea, do not appreciably differ whether caused by bacteria or viruses, and antibiotic use is often empiric...
Background

(i.e., syndromes are treated without any etiological diagnosis), vaccines that reduce the incidence of syndromic diseases may also reduce antibiotic use.

For example, influenza vaccines can reduce the frequently inappropriate use of antibiotics among patients with respiratory symptoms. Moreover, several viral infections, such as influenza, measles and respiratory syncytial virus (RSV), predispose to secondary bacterial infections, which then require antibiotic treatment.

Vaccines that reduce the incidence of antibiotic use can contribute to reducing selection for AMR in the target pathogen (for bacterial vaccines) as well as in bystander bacterial species, often present in the normal flora, which can in turn be transmitted and cause disease in specific circumstances, such as *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter* and *S. aureus*.

Some vaccines have the potential to reduce antibiotic use to an extent that exceeds the causal fraction of the disease syndrome due to the vaccine target pathogen. This could occur when a single bacterial pathogen constitutes the primary reason for antibiotic treatment of a clinical syndrome that can also be caused by other pathogens that do not require antibiotics. For example, many viruses cause sore throat, but prevention of the adverse consequences of group A *Streptococcus* pharyngitis is about the only reason one would appropriately treat a sore throat with antibiotics. A vaccine effective against group A *Streptococcus* would greatly reduce the need for presumptive antibiotic treatment for pharyngitis.
These considerations show that single or combination vaccines effective against key pathogens causing a given clinical syndrome might ultimately result in synergistic effects on antimicrobial use and therefore resistance. In this way, vaccines become a tool to reinforce policies of antibiotic stewardship.

Another benefit from reducing antibiotic use will be to decrease dysbiosis, perturbation of the healthy microbiome that can result from antibiotic exposure. For example, genital or oral candidiasis and Clostridium difficile infections are frequently triggered by antibiotic treatment. A group B Streptococcus (GBS) vaccine for maternal immunization during pregnancy could not only reduce the frequent preventive use of antibiotics perinatally and the risk of invasive GBS disease, but also protect the normal development of the neonatal microbiome.

A “One Health” approach
Antimicrobials used in animals are identical or related to those used in humans. The role of veterinary vaccines in preventing AMR burden in humans needs to be further characterized. OIE vaccine development priorities for chicken, swine, sheep, goat, bovine and fish diseases have been expressed. They aim to address bottlenecks and market barriers across the product life cycle, from fundamental research to registration and equitable and affordable access and stewardship.\(^\text{11, 12}\) As expressed in the Global Action Plan on AMR\(^\text{13}\) and in a 2019 report to the UN Secretary-General,\(^\text{14}\) recommendations for industry practices need to be renewed, strengthened and implemented.

Prioritization of activities: based on best available evidence
Efforts are ongoing to expand the knowledge base on the epidemiology of AMR.\(^\text{15}\) In addition, understanding the full potential impact of vaccines is essential to inform the value proposition, justify the need for investment and define the use case, in all populations and all parts of the world. Evidence on the magnitude of this effect is compelling for some vaccines, suggestive for others, and uncertain for still others.

Health technology assessment and informed decision-making require evidence on the existing impact on AMR and the potential to expand that impact through better use of vaccines. Impact estimates are also needed for not-yet-licensed vaccines. Where available, evidence on the role of other interventions should be used to assess the comparative value of investments in alternative approaches, for example, innovative drug discovery versus development of novel vaccines. Economic, social and equity effects of vaccines and alternatives on AMR must be assessed to understand their value, and be promptly and transparently disseminated in order to inform rational investment, and regulatory and policy decision-making.

While better evidence will enhance confidence in decisions, the urgency of the AMR threat, combined with the long time lag for some types of investments to pay off, demands that we make decisions and investment based on currently available data.

Reaching public health goals require investments, capacity, collaboration, political will, and public confidence.
Maximizing the potential of vaccines to reduce AMR will require innovative research, informed planning, and substantial investment of resources over a long period. Increasing the use of existing vaccines and meeting uptake targets are essential short-term goals. In the long term, new vaccines are needed to protect against disease due to resistant pathogens and to reduce antimicrobial use. Bringing new vaccines from basic discovery to regulatory approval, policy decision for use, and financing availability and global use is a long process. It requires a collaborative endeavour involving both the public and private sectors. Equitable access will depend on sustained investments, capacity strengthening, collaboration, political will and public confidence.

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The required were identified. Prioritization was based on potential for health impact, globally at ~70% and 45%, respectively. A new, conjugated mucoccal conjugate vaccine (PCV) population uptake are with effective licensed vaccines. Hib vaccines and pneumococcal conjugate vaccines targeting these pathogens was undertaken. Following an extensive consultation and review process, using a systematic methodology taking into account factors such as overall mortality, availability of effective therapy, health-care burden, and increasing drug resistance, pathogens were classified into three categories. It is important to note that this exercise focused on antibiotic-resistant bacteria, and did not consider the value of vaccines against viral pathogens.

**Priority 1: CRITICAL**

*A. baumannii, Pseudomonas aeruginosa, Enterobacteriaceae (K. pneumoniae, E. coli, Enterobacter spp., Serratia spp., Proteus spp., Providencia spp., Morganella spp.).* Mycobacterium tuberculosis was not included in this prioritization exercise, but is also a recognized priority pathogen.

**Priority 2: HIGH**

*Enterococcus faecium, Staphylococcus aureus, Helicobacter pylori, Campylobacter, Salmonella spp., N. gonorrhoeae.*

**Priority 3: MEDIUM**

*S. pneumoniae, Hib, Shigella spp.*

Subsequently, a prioritization exercise on the role of vaccines targeting these pathogens was undertaken. Prioritization was based on potential for health impact, probability of R&D success and probability of uptake. Pathogen clusters for which different interventions are required were identified.

The “increase uptake” cluster is composed of pathogens with effective licensed vaccines. Hib vaccines and pneumococcal conjugate vaccine (PCV) population uptake are globally at ~70% and 45%, respectively. A new, conjugated S. Typhi vaccine has recently been prequalified by WHO and is supported by Gavi for introduction. Continued efforts are needed to maintain and expand uptake.

The “bring to market” cluster is composed of pathogens with significant health impact and sufficiently advanced R&D to recommend concentrating on accelerating vaccines through clinical development to market. The high antigenic diversity of *E. coli* (enteric) is a challenge for vaccine development, but inclusion of heat-labile toxoid and fimbral antigens may help increase vaccine strain cover. Vaccines against non-typhoidal Salmonella and against *Shigella* appear technically feasible and potentially impactful against high disease burdens in Africa and other LMICs. *M. tuberculosis* was included in the “advance early R&D” cluster. Since this report was published, phase 2 trial data of protection against progression to pulmonary TB disease justify its inclusion in the ‘bring to market’ cluster.

The “advance early R&D” cluster is composed of pathogens with significant health impact but unclear R&D feasibility, where more investment in early-stage R&D is needed to advance a robust pipeline of vaccine candidates. The case for development of a vaccine targeting *N. gonorrhoeae* is strong due to high incidence, high morbidity, and current circulation of resistant strains. Evidence of *N. meningitidis* B vaccine to cross-protect against *N. gonorrhoeae* has fostered optimism. The incidence of extraintestinal *E. coli* infections is high and constitutes an important target for vaccination, but antigen selection remains a challenge. Vaccine development for *P. aeruginosa* is particularly needed for high-risk groups such as cystic fibrosis patients and other immunocompromised patients, but clinical testing in such patients is complex. Morbidity and mortality from *S. aureus* in high-income countries means the market for a vaccine is attractive, but significant gaps remain in understanding disease burden and identifying vaccine targets, and animal models have limited predictive capability.

The “collect data, explore alternatives” cluster is composed of pathogens for which significant gaps remain, or alternative control strategies may be preferable. *S. Paratyphi* has low incidence and low associated mortality and morbidity. Uptake of a standalone vaccine is unlikely and combination vaccines with S. Typhi should be contemplated. More data are needed on *Campylobacter* in LMICs, particularly to understand transmission pathways and whether animal vaccination would be a preferred approach. A better understanding of the link between *H. pylori* and gastric cancer, and of how AMR is likely to evolve due to relative current treatability of the pathogen, is necessary. *K. pneumoniae* has a higher burden than most other hospital-acquired infections, but more data are needed to help determine whether there are predictable sub-populations to target for clinical development and vaccine delivery. *Enterobacteriaceae, A. baumannii and E. faecium* have comparatively low incidence. These pathogens cause hospital-acquired infections in small, immunocompromised target populations. These characteristics present particularly challenging hurdles for vaccine strategies. Alternatives, such as passive immunization, should be explored.

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**BOX 2**

**Wellcome’s assessment of vaccine priorities for targeting WHO AMR priority bacteria**

In 2016, the World Health Assembly directed WHO to create a list of antibiotic-resistant bacteria for which new antibiotics were most urgently needed; to help set funding priorities; and to facilitate global coordination of antibiotic R&D strategies against AMR. Following an extensive consultation and review process, using a systematic methodology taking into account factors such as overall mortality, availability of effective therapy, health-care burden, and increasing drug resistance, pathogens were classified into three categories. It is important to note that this exercise focused on antibiotic-resistant bacteria, and did not consider the value of vaccines against viral pathogens.

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**Priority 2: HIGH**

*Enterococcus faecium, Staphylococcus aureus, Helicobacter pylori, Campylobacter, Salmonella spp., N. gonorrhoeae.*

**Priority 3: MEDIUM**

*S. pneumoniae, Hib, Shigella spp.*

Subsequently, a prioritization exercise on the role of vaccines targeting these pathogens was undertaken. Prioritization was based on potential for health impact, probability of R&D success and probability of uptake. Pathogen clusters for which different interventions are required were identified.

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*b* Vaccines to tackle drug resistant infections: An evaluation of R&D opportunities. 2018.
2. Strategic vision

For vaccines to contribute fully, sustainably and equitably to the prevention and control of antimicrobial resistance by preventing infections and reducing antimicrobial use.
3. Goals, objectives and priority actions

Specific objectives and priority actions in three goal areas will significantly enhance the contribution of vaccines to the control of AMR. These goals are:

1. Expanding use of licensed vaccines to maximize impact on AMR

2. Developing new vaccines that contribute to prevention and control of AMR

3. Expanding and sharing knowledge of vaccine impact on AMR
Expanding the use of licensed vaccines will require reaching current uptake targets, and setting and achieving ambitious coverage targets as new vaccines are approved. Reduction in the incidence of infection through effective sanitation, hygiene and infection prevention measures, including immunization, is an integral part of the Global Action Plan on AMR (Objective 3). The framework for action on AMR urges all Member States to have national action plans defining priorities and activities.

For currently licensed vaccines, there is significant room for improvement in coverage (Table 2). Recent data from WHO and the United Nations Children’s Fund (UNICEF) show that more than 1 in 10 children missed out on life-saving vaccines in 2018, with most unvaccinated children living in LMICs. Out of six world regions, four have not yet met vaccine uptake targets included in the Decade of Vaccine’s Global Vaccine Action Plan 2011-2020. The Immunization Agenda 2030 will play an essential role in ensuring that all people, at all ages, everywhere, enjoy the full benefits of vaccines, including through prevention and control of AMR.

**Objective 1.**

**Increase coverage of vaccines with impact on AMR**

Maximizing the impact of immunization on AMR will depend on the successful implementation of a global strategy with an integrated Action Framework linking immunization to primary health care and universal health coverage.

**Priority actions**

1a. Countries should implement existing vaccine-related recommendations of the Global Action Plan on AMR. Priority should be given to completion of the full basic series of PCV, Hib vaccine, rotavirus vaccine, measles-containing vaccines as well as increasing coverage for influenza and TCV.

1b. Donors, countries and other health payers should maintain and expand immunization financing and strengthen capacities, ensuring affordable supply, functional delivery systems and programmatic sustainability. Public and private sector partnerships are important to help ensure equitable access to quality-assured products and technologies, through fair pricing and donations for the poorest populations. Global financing mechanisms need to support procurement, access and delivery, and sustainable functioning of health systems, including mechanisms for surveillance and vaccine safety and effectiveness monitoring.

**Objective 2.**

**Update recommendations and normative guidance in both the vaccine and AMR sectors to include the role of vaccines to control AMR**

In addition to the objectives and indicators set out in the Global Action Plan on AMR and existing WHO recommendations, new activities are needed to expand the impact of vaccines on AMR. Expanding the benefits of immunization throughout the life course will play a major role. When research and

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epidemiologic data emerge that justify changes in optimal vaccine use, revised recommendations should be developed. This may include situations where vaccines are used to protect the effectiveness of antimicrobials.

For instance, increased TCV use may help contain the emergence of multidrug-resistant S. Typhi. In some geographical areas, azithromycin is the only oral typhoid treatment available. As azithromycin is also being used in mass campaigns for trachoma, TCV deployment might be useful in protecting azithromycin effectiveness. As another example, if evidence accumulates on the potential for influenza and PCV vaccines to reduce antibiotic use in specific population groups, recommendations for vaccine use in such populations should be strengthened.

Specific vaccine use recommendations could also be developed for vulnerable groups who, for medical reasons, use antibiotics chronically or frequently, or who are at increased risk of exposure to drug-resistant microbes, such as health-care workers.

### Priority actions

2a. Where justified, normative guidance, regulatory indications, policy recommendations and health regulations for vaccine use should be adapted to account specifically for the use of vaccines to impact AMR.

### Table 2. Recommended use of selected licensed vaccines and potential impact on AMR

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>WHO recommendation</th>
<th>Global coverage in 2018&lt;sup&gt;a&lt;/sup&gt;</th>
<th>WHO coverage target&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Vaccine impact on AMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV</td>
<td>All children, through routine immunization.</td>
<td>47%</td>
<td>90% nationally, 80% at district level.</td>
<td>Reduces resistant and non-resistant pneumococcal disease; reduces antibiotic use in children.¹</td>
</tr>
<tr>
<td>TCV</td>
<td>In endemic countries, programmatic delivery to children 9 months old or in the second year of life and catch-up campaign in children up to 15 years of age.</td>
<td>NA</td>
<td>Access to be prioritized in settings with high endemicity and high levels of AMR.</td>
<td>Modelling suggests vaccine use will proportionally reduce incidence of resistant and non-resistant typhoid, including number of chronic typhoid carriers.⁵</td>
</tr>
<tr>
<td>Hib vaccine</td>
<td>All children, through routine immunization.</td>
<td>72%</td>
<td>90% nationally, 80% at district level.</td>
<td>Reduces resistant and non-resistant Hib disease; may have reduced overall proportion of resistant strains. Some evidence that Hib introduction modestly reduced antibiotic prescriptions among children &lt;5 years.⁶</td>
</tr>
<tr>
<td>Influenza vaccines</td>
<td>All pregnant women, children 6–59 months, adults &gt;65 years, people with chronic medical conditions and health-care workers.</td>
<td>NA</td>
<td>Varies according to risk group.</td>
<td>Good evidence that influenza vaccine reduces antibiotic use by reducing misuse of antibiotics and treatment of secondary bacterial infections.⁷</td>
</tr>
<tr>
<td>Rotavirus vaccine</td>
<td>All children, through routine immunization.</td>
<td>35%</td>
<td>90% nationally, 80% at district level.</td>
<td>Expected to reduce antibiotic use but no confirmatory data available.</td>
</tr>
<tr>
<td>Measles vaccine</td>
<td>All children, through routine immunization.</td>
<td>69%</td>
<td>90% nationally, 80% at district level.</td>
<td>Expected to reduce antibiotic use against secondary bacterial complications, but no confirmatory data available.</td>
</tr>
</tbody>
</table>

NA: not available; PCV: pneumococcal conjugate vaccine; TCV: typhoid conjugate vaccine; WHO: World Health Organization.

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<sup>a</sup> World Health Organization (WHO). Global and regional immunization profile. 2019.


<sup>c</sup> Klugman KP, Black S. Impact of existing vaccines in reducing antibiotic resistance: Primary and secondary effects. Proceedings of the National Academy of Sciences of the United States of America. 2018;115(51).


AMR national action plans and international organizations dedicated to AMR control should consistently include vaccines in the armamentarium of interventions planned for use against AMR, and build capacity for the full realization of vaccine impact as individual or combined interventions.

Immunization programmes should be strengthened to reach children beyond the first year of life and immunization services broadened to support vaccination with impact on AMR throughout the life course.

In a “One Health” perspective, bodies such as WHO, FAO and OIE, in collaboration with the agricultural industry and animal health stakeholders, should update recommendations and regulations and develop an action plan to maximize the use of animal vaccines to reduce antibiotic use in animals.

Objective 3.
Improve awareness and understanding of the role of vaccines in limiting AMR through effective communication, education and training

The value of vaccines in preventing disease at the individual and population levels is not completely understood in parts of public and professional communities. This has contributed to low and decreasing coverage and confidence in vaccines in some areas. Communicating the additional benefit of the use of vaccines to fight AMR requires the development of carefully constructed and evaluated communication strategies and tools. Vaccination should not be presented as a panacea for all AMR, but its potential to deliver public health benefits should be communicated when relevant. Such communication may contribute to the overarching goal of building confidence in immunization programs (Fig. 5).

Priority actions
3a. Countries, funders and other stakeholders should include the role of vaccines in limiting AMR in communication materials used to present their related activities.

3b. Institutions involved in the vaccine and AMR sectors should develop communication, education and training materials about the role of vaccines in controlling AMR, targeting audiences ranging from the general public to infectious disease experts.

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Fig. 5. Visuals from the International Vaccine Institute’s advocacy campaign about the contribution of vaccines in the fight against AMR

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New vaccine R&D is an integral part of the Global Action Plan on AMR. Addressing AMR will require new tools and technologies to complement currently available strategies and interventions. Few new antimicrobials have been developed recently or are anticipated to be available soon, and all are threatened by the emergence of resistance. In contrast, vaccines have traditionally had sustainable impact, and there has been little or no evidence of escape from immunity.

The pipeline of vaccines with potential impact on AMR includes many early-stage candidates, and some in clinical evaluation. Technologies supporting vaccine discovery and development are expanding. Progress in structural and systems biology, genomics and reverse vaccinology, adjuvants, monoclonal antibody development, and nucleic acid vaccines offer promise for next-generation vaccines targeting a variety of pathogens.

The development and use of new or improved vaccines is of particular importance to prevent diseases becoming difficult to treat or untreatable owing to antimicrobial resistance. For some resistant infections, technologies such as phage-based medicine or microbiome interventions offer promise. Pathogen areas to be prioritized for investments into vaccine R&D should be informed by public value and feasibility assessments, taking into account alternative options (Table 3).

Objective 4.

Bridge the funding gap for R&D of new vaccines with potential for global AMR impact

Investment in the development of new vaccines to impact global health is often impeded by market failures and decades-long development, licensure and implementation timelines, making them frequently unattractive business investments.

Funding of research to bring candidates to regulatory submission can be costly. The large-scale randomized trials and complex regulatory review that products must undergo are time-consuming, labour-intensive and expensive, and even after a vaccine is approved, further evaluation can be necessary to support decision-making on implementation. In addition, further investment is required to ensure manufacturing supply at scale, procurement and affordable access according to medical need, and delivery through functional health systems. Surveillance systems also need to be in place to monitor safety and effectiveness of newly introduced vaccines and demonstrate population-level impact.

New mechanisms are needed to overcome these obstacles and encourage renewed investment in R&D of new vaccines for use in LMICs. Innovative financing mechanisms channelling substantial public-sector funding and private-sector investment will be needed to support new vaccine development, and to bring candidates from discovery through preclinical and clinical testing to licensure, adoption and implementation.

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### Table 3. Selected WHO priority disease areas for which vaccines are critically needed and available evidence supports a favourable technical feasibility assessment and potential impact on AMR

<table>
<thead>
<tr>
<th>Target pathogen and disease</th>
<th>Burden</th>
<th>AMR-related impact</th>
<th>Vaccine outlook</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. tuberculosis</em>, tuberculosis (TB)</td>
<td>A quarter of global population latently infected;¹ in 2019, 10 million people fell ill with TB and 1.4 million died.²</td>
<td>Resistant TB rising sharply. There were 465,00 rifampicin-resistant diagnoses in 2019, 78% of which were resistant to more than one drug; 182 000 people died from drug-resistant TB infections.³</td>
<td>A highly effective vaccine is feasible: most infected people do not develop disease and the existing BCG vaccine protects children against severe disease. Recent phase 2B trial of candidate M72/AS01 in adults with latent infection reduced progression to active pulmonary TB by around 50% over 3 years follow-up.⁴</td>
</tr>
<tr>
<td><em>N. gonorrhoeae</em>, pelvic inflammatory disease, infertility</td>
<td>78 million new cases per year among people aged 15–49 years;⁵ can cause infertility and other severe sequelae.</td>
<td>Once universally susceptible to antibiotics, strains resistant to every current class of antibiotic have emerged; complete treatment failure has been reported.⁶</td>
<td><em>N</em> gonorrhoeae shares 80–90% of its genetic sequence with <em>N. meningitidis</em>, a common cause of meningitis. There is some evidence that type B <em>N. meningitidis</em> vaccine partially protects against some <em>N. gonorrhoeae</em>, suggesting a vaccine is feasible.⁷</td>
</tr>
<tr>
<td><em>Plasmodium falciparum</em>, malaria</td>
<td>228 million cases worldwide in 2018, 405 000 deaths.⁸ Important driver of antibiotic use for non-specific febrile illness in high endemicity areas.</td>
<td>Artemisinin resistance emerged in South-East Asia in early 2000s; several artemisinin combination therapies now failing.⁹ Potential to reduce malaria-driven antibiotic use.</td>
<td>RTS,S/AS01 vaccine provides partial protection in young children, showing that a vaccine is feasible.⁷ RTS,S/AS01 is in pilot implementation through routine immunization programmes in Ghana, Kenya and Malawi. Other candidates continue to be developed.</td>
</tr>
<tr>
<td>RSV, respiratory disease</td>
<td>A very common respiratory tract infection that affects all ages; most severe in early childhood. Important driver of antibiotic use for undocumented respiratory illness globally.</td>
<td>Potential to reduce RSV-driven antibiotic use.</td>
<td>Proof of concept is established for the potential of vaccines delivered to pregnant women to prevent severe RSV disease early in life. RSV vaccine candidates aiming to provide longer protection to children and adults are in the pipeline.</td>
</tr>
<tr>
<td><strong>Enterotoxigenic Escherichia coli (ETEC) and Shigella</strong></td>
<td>ETEC caused 51 186 deaths globally including 18 669 deaths in children under 5 years old in 2016. Shigellosis caused 212 438 deaths globally including 63 713 in children under 5 years old in 2016.</td>
<td>High and growing rates of multidrug resistance.</td>
<td>Several candidate vaccines are in development. Controlled human infection models may be able to accelerate clinical development.</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BCG: bacille Calmette-Guérin (vaccine); RSV: Respiratory Syncytial Virus.

Related activities should be monitored and evaluated, in line with the Global Action Plan monitoring and evaluation framework for new products and funding instruments.

**Priority actions**

4a. Funders, industry, governments, nongovernmental and supranational organizations, academic institutions and researchers should increase investments in vaccine candidates with anticipated benefits for AMR.

4b. Funders, including governments and nongovernmental organizations, product development sponsors and industry, should create novel financing mechanisms for late-stage vaccine evaluation, introduction, evaluation of new vaccine effectiveness and impact, and to ensure sufficient manufacturing capacity to meet global needs for vaccines expected to reduce AMR.

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**BOX 3 A sample of organizations investing in vaccine candidates to control AMR**

**CARB-X** is a public-private partnership to support R&D to tackle AMR in bacteria. Founded in 2016, it supports early development of antibiotics, diagnostics, vaccines and alternative therapies to combat the most serious drug-resistant bacteria. CARB-X has supported several vaccine projects, including work on candidate vaccines for *K. pneumoniae*, group A *Streptococcus*, and *S. aureus*. CARB-X does not require a monetary return on its investment. Recipients of funding must have intellectual property rights to a promising product that will help prevent or control AMR, and need to be able to cost-share the funding required to move that product through preclinical development or phase 1 clinical trials. The funding agreements with awardees contain specific stewardship and access provisions. For every dollar CARB-X has invested in its projects, private capital has subsequently invested eight more. For more information see [https://carb-x.org](https://carb-x.org).


**Bill & Melinda Gates Medical Research Institute (Gates MRI).** The development of effective vaccines against drug-sensitive and -resistant malaria, TB and diarrhoeal diseases constitute research priorities for product development activities.

**IAVI and Serum Institute of India** have recently announced a product development partnership to develop and manufacture globally affordable and accessible antibody products, including monoclonal antibodies targeting AMR pathogens.

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**BOX 4 Gavi adds AMR impact to its Vaccine investment strategy criteria**

Gavi, the Vaccine Alliance, brings together public and private sectors with the mission to increase equitable use of vaccines in lower-income countries. Gavi formally redevelops its guiding Vaccine Investment Strategy every five years, and is currently working on its strategy for 2021-2025. The strategy identifies and prioritizes opportunities for investment in vaccines and immunization products for Gavi-supported countries in terms of impact, cost, value and programme feasibility. In 2018, Gavi decided to include impact on AMR as one of the indicators of a vaccine’s value. In its assessments, most weight is given to a vaccine’s potential to reduce AMR-related mortality and morbidity and to reduce antibiotic use. PCV, TCV and malaria vaccines were given higher scores for AMR impact. Gavi plans to enhance its assessment methodology using quantitative data as they become available.

For further information see [https://www.gavi.org/about/strategy/vaccine-investment-strategy/](https://www.gavi.org/about/strategy/vaccine-investment-strategy/).
Objective 5.
Develop regulatory and policy mechanisms to accelerate approval and use of new vaccines that can reduce AMR

Most vaccines are developed for use in a large target population, although some are for more restricted use in specific groups at risk. Vaccines are usually given to large numbers of healthy people, and are subject to strict regulatory oversight, with licensure requiring a favourable benefit-risk assessment. In-country use is based on policy decisions that, in addition, consider health-economic questions and public value more broadly.

In the field of global health, WHO recommendations inform decision-making at multiple levels, including international financing bodies supporting vaccine procurement and distribution. Regulators and policy-makers engage in discussions with funders and vaccine developers to prioritize disease areas, product development, investments and activities, and create scientific consensus. Throughout, specific modalities should be adopted to consider and facilitate vaccine impact on AMR, all along regulatory and policy-making pathways.

Priority actions

5a. Vaccine development sponsors and regulatory authorities should systematically assess the potential to prevent and control AMR and related data packages generated in clinical development to expand knowledge of investigational product risk-benefit balance.

5b. Regulators and policy-makers should develop means to accelerate access to vaccines of urgent medical need, including impacts on AMR, without jeopardizing the required confidence in safety and efficacy.

5c. WHO, through its PDVAC and SAGE, and other stakeholders who shape progress in vaccine R&D should include evaluation of AMR impacts in their product landscape analyses and guidance.

5d. Vaccine development sponsors and regulators should discuss clinical research requirements for regulatory labelling to include specifications about impact on AMR and antimicrobial use.

5e. Sponsors of post-licensure vaccine evaluations, such as health-economic impact studies, should discuss with regulators and policy-makers, during the approval process, when and how to include evaluation of a vaccine’s potential to reduce antimicrobial use and AMR in these studies.

Accelerated approval pathways similar to those being developed for some epidemic vaccines may be appropriate for AMR-reducing vaccines. This includes vaccines involving controlled human infectious challenge models and using immune correlates of protection, and animal protection data, when pre-licensure clinical efficacy trials are not feasible or highly problematic. Indirect evidence can lead to conditional approvals pending confirmation of effectiveness through early introduction studies. Some related regulatory mechanisms are as follows.

FDA priority review vouchers. The US Congress created the priority review voucher programme in 2007 to encourage the development of products for neglected diseases. The developer benefits from an accelerated review by the Food and Drug Administration (FDA) for the product in question, and a voucher for a faster review of a different drug. The developer can sell the voucher, which has potentially large commercial value.

Conditional marketing authorization. Several regulatory authorities have provisions aiming to accelerate access to products that meet an urgent medical need, when early assessments of benefit-risk balances are positive, and plans are agreed for post-approval investigations.
Continuing research is needed to strengthen the knowledge base on the potential role of vaccines in prevention and control of AMR, and this knowledge disseminated to stakeholders. Better estimates of impact will improve policy-making and rational prioritization of investments. Data on immunization should inform formulation of policy for prevention and control of AMR, and data on AMR should inform decision-making in the immunization field.

Decision-making and evidence generation should be an iterative process whereby new evidence informs existing recommendations and investments, and vaccine prioritization is updated. National governments, intergovernmental organizations, agencies, professional organizations, nongovernmental organizations, industry and academia have important roles in generating such knowledge. Knowledge dissemination is essential to build public trust and increase vaccine confidence.

**Objective 6.**

**Improve methodologies and increase collection and analysis of data to assess vaccine impact on AMR, including antimicrobial use**

Many types of data and study results are required to understand the impact of vaccines on AMR. Since few data are currently available, there is an urgent need to increase data collection and analysis. This is particularly relevant to settings where issues of both access to, and excessive use of antibiotics are important public health concerns.

**Priority actions**

6a. Normative bodies should provide guidance for health technology assessment and evaluation of vaccine impact on AMR and antimicrobial use.

6b. Funders and researchers should analyse existing datasets from epidemiologic studies, trials and routine surveillance in order to estimate vaccine impact on AMR.

6c. When relevant, sponsors, funders and investigators conducting new trials and studies using existing and candidate vaccines should assess vaccine impact on AMR, including antimicrobial use.

6d. Public health authorities at the global, national and subnational levels should enhance surveillance data systems to link vaccination data with antimicrobial use and resistance data, with the greatest practicable level of geographic and demographic granularity to enable interventions that focus on the most vulnerable. In resource-limited settings, building capacity for data collection and analysis should be included in immunization and AMR country action plans.

6e. Researchers should continue to generate new evidence on:

- how to use vaccines with the specific aim of controlling drug-resistant pathogens when highly prevalent or causing epidemics;
- how vaccines can complement other infection control strategies and stewardship efforts to prolong or restore effective use of antibiotics against specific pathogens;
- socioeconomic and ethical aspects of vaccine impact on AMR.

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6f. Researchers and their sponsors should ensure that new data and evidence are made rapidly and publicly available through prompt public posting and scientific publications, preprints, and data-sharing platforms.

**Objective 7.**

Develop estimates of vaccine value to avert the full public health and socioeconomic burden of AMR

In a context of resource constraints, prioritization of investments should be informed by estimates of the value of existing and future vaccines in their ability to prevent and control AMR. Mathematical modelling, multi-criteria decision analysis and other methodologies including empirical approaches can be used to inform investment decision-making.

Beyond cost-effectiveness analyses, the full scope of investments needed and societal impact should be considered (impact on antibiotic use, direct medical costs, social care costs, loss in productivity, impact on social justice and equity, impact on education, consumption, leisure, savings and wealth, financial risk, impact on caregivers and households, and macroeconomic effects). Such analyses should inform both private and public funders, manufacturers, regulators and policy-makers, ministries of health, finance and agriculture, global AMR control and vaccine-financing bodies. Through an iterative process, modelling estimates should be regularly refined as empirical data emerge.

**Priority actions**

7a. Research funders should support researchers to develop and improve methodologies for estimating impact of vaccines on AMR. Factors such as individual protection, herd immunity, transmission patterns, pathogen carriage rates, bacterial population dynamics, vaccine-driven reductions in antibiotic use and the various molecular drivers of resistance should be considered. Models should account for replacement of vaccine-preventable serotypes by other serotypes of the targeted pathogen where applicable.

7b. Health delivery payers and investors in R&D should develop and use standardized health technology assessments and value-attribution frameworks to inform the estimation of the full value of vaccines to prevent and control AMR. Value can be articulated in terms of mortality and morbidity prevention, reduction of antibiotic use, economic and societal impact, and impact on equity, taking into account potential vaccine-preventable AMR-related social exclusion, poverty and disproportionate negative impacts on vulnerable groups.
4. Conclusions

Vaccines are already contributing to the battle against AMR through prevention of infections and an associated decrease in antibiotic use. The priority activities outlined in this document provide the opportunity for vaccines to contribute fully, sustainably and equitably to the prevention and control of AMR, as a complementary approach to other AMR-reduction efforts.

Increased investments from the private, philanthropic and public sectors are needed for existing vaccines to reach higher coverage, as well as to develop new vaccines.

Guidance provided to both the AMR and immunization communities should be updated and strengthened to reflect the vision expressed here. Regulatory and policy frameworks should be adapted to support efficient decision-making and to maximize vaccine-related opportunities and impact.

Among available vaccines, increased uptake of Hib, PCV, TCV, and influenza vaccines should be prioritized for impact on antibiotic use and AMR. Among disease areas for which vaccines are not available, but proof-of-concept evidence suggests that vaccine development is technically feasible, TB constitutes a major public health emergency and priority for investment. Vaccines against gonococcal infections and enteric diseases due to Shigella, E. coli and non-typhoidal Salmonella also constitute priority R&D opportunities.

Development should be accelerated of next-generation vaccines providing expanded strain coverage and durable protection against influenza and pneumococcus, as well as new vaccines against malaria, HIV, RSV and group A Streptococcus. It may be possible to develop vaccines against other important AMR pathogens such as S. aureus, P. aeruginosa, E. coli, Campylobacter, H. pylori, K. pneumoniae, Enterobacteriaceae, A. baumannii, E. faecium, C. difficile, Chlamydia and Candida, but confidence in feasibility needs to be built.

Across disease areas, key activities to maximize impact, including for AMR control, comprise: further development of innovative technologies, accelerated testing pathways, effectiveness evaluation through pilot implementation, new opportunities for immunization along the life course, access to high-risk groups, and market shaping.

Decisions should be based on evidence, and investments based on careful value-based prioritization. More and better collection and analysis of data on the role of vaccines against AMR across a variety of microbiological, health and economic sectors are critical. Modelling provides important opportunities to estimate the full value of vaccines against AMR, across a range of relevant criteria for prioritization.

Health interventions and policies depend on public confidence. Advocacy and targeted communication can contribute to increased knowledge and catalyse the action needed to better protect everyone against infections and curb the threat that AMR poses to individuals, societies and global health.
5. Useful links

The links below have been identified as useful sources of information about vaccines and AMR. WHO does not favour nor prioritise institutions listed below.

**AMR Control**
[http://resistancecontrol.info/](http://resistancecontrol.info/)
The AMR Control publication brings together high-level contributors from around the world to monitor and analyse the worrying challenge of AMR, as well as providing its readers with a coherent picture of the latest thinking on developments, solutions and policy.

**BMGF**
[https://www.gatesfoundation.org/](https://www.gatesfoundation.org/)
Bill & Melinda Gates Foundation (BMGF) is a global funder of health research with a focus on reducing mortality in children under five years old.

**CARB-X**
[https://carb-x.org/](https://carb-x.org/)
CARB-X (Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator) is a global non-profit partnership dedicated to accelerating antibacterial research to tackle the rising global threat of drug-resistant bacteria. Among the products that CARB-X funds are candidate vaccines against antimicrobial-resistant pathogens.

**CDC**
The US Centers for Disease Control and Prevention (CDC) website summarizes key information, challenges, research areas, policy, and funding in the AMR sector.

**CDDEP**
[https://cddep.org/research-area/antibiotic-resistance/](https://cddep.org/research-area/antibiotic-resistance/)
The Center for Disease Dynamics, Economics & Policy (CDDEP) produces independent, multidisciplinary research to advance the health and well-being of human populations around the world, with a focus on antimicrobial resistance.

**Chatham House**
[https://www.chathamhouse.org/about/structure/global-health-security/antimicrobial-resistance-project](https://www.chathamhouse.org/about/structure/global-health-security/antimicrobial-resistance-project)
Chatham House is a not-for-profit organization whose mission is to analyse and promote the understanding of major international issues and current affairs. This website summarizes their current work and perspectives in the AMR field.

**Coalition against Typhoid**
[https://www.coalitionagainsttyphoid.org/](https://www.coalitionagainsttyphoid.org/)
The Coalition against Typhoid (CaT) and the Typhoid Vaccine Acceleration Consortium (TyVAC) work on improving water, sanitation, and hygiene interventions to reduce the burden and impact of typhoid fever.

**COMBACTE**
[https://www.combacte.com/](https://www.combacte.com/)
COMBACTE fights antimicrobial resistance by speeding up the development of new antibiotics.

**European Commission**
The European Commission provides global funding opportunities in key research areas, including AMR.
**European Commission Joint Programming Initiative on Antimicrobial Resistance**

https://www.jpiamr.eu/

The Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), established by the European Commission, is a global collaborative platform that has engaged 28 nations to curb AMR with a One Health approach.

**FAO**


The Food and Agriculture Organization of the United Nations (FAO) website summarizes key challenges and workstreams around the use of antimicrobials in agriculture.

**Global AMR R&D Hub**

https://globalamrhub.org/

The Global AMR R&D Hub aims to plan, design, build and implement a dynamic online dashboard that will present all AMR R&D investments globally from public and private sources across the One Health continuum.

**IACG**


The Interagency Coordination Group (IACG) on Antimicrobial Resistance brings together partners across the UN, international organizations and individuals with expertise across human, animal and plant health, as well as the food, animal feed, trade, development and environment sectors, to formulate a blueprint for the fight against antimicrobial resistance.

**IFPMA**

https://www.ifpma.org/subtopics/antimicrobial-resistance/

The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) represents research-based biopharmaceutical companies to advocate policies and practices that encourage discovery and access to life-saving and life-enhancing medicines and vaccines, for people everywhere. Its website presents a summary of IFPMA's perspectives and workstreams on AMR.

**LSHTM AMR Centre**

https://www.lshtm.ac.uk/research/centres/amr/

The London School of Hygiene and Tropical Medicine (LSHTM) brings together inspiring innovation in AMR research through interdisciplinary and international engagements.

**OECD**

https://www.oecd.org/health/health-systems/antimicrobial-resistance.htm

The Organisation for Economic Co-operation and Development (OECD) offers a forum for discussion and provides countries with evidence to implement effective and cost-effective policies to tackle AMR, and promote effective use of antimicrobials and R&D in the antibiotic sector.

**OIE**

https://www.oie.int/en/for-the-media/amr/

The World Organisation for Animal Health (OIE) website describes coordinated actions between human and animal health as well as environmental sectors to ensure responsible and prudent use of antibiotics to safeguard their efficacy.
PATH
https://www.path.org/articles/drug-resistance-vaccines/
PATH’s article describes the potential of vaccines to combat AMR, the need to expand the reach of existing vaccines, and highlights the urgency to produce vaccines for emerging threats.

ReAct
https://www.reactgroup.org/
Created in 2005, ReAct is one of the first international independent networks to articulate the complex nature of antibiotic resistance and its drivers. ReAct’s goal is to serve as a global catalyst, advocating and stimulating global engagement on antibiotic resistance by collaborating with a broad range of organizations, individuals and stakeholders.

REPAIR Impact Fund
https://www.repair-impact-fund.com/
Novo Holdings established the REPAIR Impact Fund commissioned by the Novo Nordisk Foundation in February 2018. With a total budget of US$ 165 million, the Fund invests in companies involved in discovering and early-stage development of therapies targeting resistant microorganisms. The purpose of the REPAIR Impact Fund is to increase humanity’s therapeutic arsenal in the fight against antimicrobial resistance.

Vaccines Europe
http://www.vaccineseurope.eu/
Vaccines Europe represents major innovative research-based vaccine companies as well as small and medium-sized enterprises operating in Europe.

UNICEF
https://www.unicef.org/documents/time-running-out
This technical note reflects UNICEF’s response to the growing global threat of AMR to child survival, growth and development. It identifies UNICEF’s AMR-specific and AMR-sensitive actions in reducing infections, promoting access to and optimal use of antimicrobials, and increasing AMR awareness and understanding.

United Kingdom Government
The five-year action plan of the UK government articulates its ambitions and actions to tackle AMR for the years 2019-2024.

WHO and AMR
https://www.who.int/antimicrobial-resistance/en/
The WHO website is the key source of information on AMR. It contains fact sheets, the Global action plan on antimicrobial resistance, data collection platforms such as Global Antimicrobial Resistance Surveillance System (GLASS), and WHO resolutions regarding antimicrobial resistance.
Global and regional burden of attributable and associated bacterial antimicrobial resistance avertable by vaccination: modelling study

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NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
Abstract

Introduction: Antimicrobial resistance (AMR) is a global health threat with 1.27 million and 4.95 million deaths attributable to and associated with bacterial AMR respectively in 2019. Our aim is to estimate the vaccine avertable bacterial AMR burden based on existing and future vaccines at the regional and global levels by pathogen and infectious syndromes.

Methods: We developed a static proportional impact model to estimate the vaccination impact on 15 bacterial pathogens in terms of reduction in age-specific AMR burden estimates for 2019 from the Global Research on Antimicrobial Resistance project in direct proportion to efficacy, coverage, target population for protection, and duration of protection of existing and future vaccines.

Results: In the baseline scenario for vaccination of primary age-groups against 15 pathogens, we estimated vaccine-avertable AMR burden of 0.51 (95% UI: 0.49 - 0.54) million deaths and 28 (27 - 29) million DALYs associated with bacterial AMR, and 0.15 (0.14 - 0.17) million deaths and 7.6 (7.1 - 8.0) million DALYs attributable to AMR globally in 2019. In the high-potential scenario for vaccination of additional age groups against 7 pathogens, we estimated vaccine-avertable AMR burden of an additional 1.2 (1.18 - 1.23) million deaths and 37 (36 - 39) million DALYs associated with AMR, and 0.33 (0.32 - 0.34) million deaths and 10 (9.8 - 11) million DALYs attributable to AMR globally in 2019.

Conclusion: The AMR burden avertable by vaccination in 2019 was highest for the WHO Africa and South-East Asia regions, for lower respiratory infections, tuberculosis, and bloodstream infections by infectious syndromes, and for Mycobacterium tuberculosis and Streptococcus pneumoniae by pathogen. Increased coverage of existing vaccines and development of new vaccines are effective means to reduce AMR, and this evidence should inform the full value of vaccine assessments.
Key questions

What is already known on this topic

- There is some evidence on the impact of vaccines against *Haemophilus influenzae* type b, rotavirus, *Streptococcus pneumoniae*, *Salmonella* Typhi and influenza on antimicrobial resistance (AMR) in specific settings.

What this study adds

- To our knowledge, this is the first study to estimate attributable and associated bacterial AMR burden avertable by vaccination against 15 bacterial pathogens for a combined set of existing and new vaccines in the pipeline by pathogen, infectious syndrome, and region.
- The AMR burden avertable by vaccination in 2019 was highest for the WHO Africa and South-East Asia regions, for lower respiratory infections, tuberculosis, and bloodstream infections by infectious syndromes, and for *Mycobacterium tuberculosis* and *Streptococcus pneumoniae* by pathogen.

How this study might affect research, practice or policy

- Our model-based projections facilitate evidence-based decision-making for scaling up of existing vaccines to regions in most need with higher AMR burden and prioritise development of new vaccines with high potential for lowering AMR burden by pathogen, infectious syndrome, and region.
- Our study contributes to the WHO-led value attribution framework for vaccines against antimicrobial resistance, and specifically to the criterion focused on vaccine averted AMR health burden.
Introduction

Since the discovery of penicillin in 1928, antimicrobials have been used to treat bacteria, fungi, parasites, and viruses, saving countless lives [1]. However, antimicrobial resistance (AMR) is a growing global public health threat in the 21st century [2]. Resistance occurs through pathogen evolution, either naturally over time or acquired by the use of antimicrobial drugs, which render these drugs ineffective and increase the risk of morbidity and mortality. While access to antimicrobial drugs in low- and middle-income countries to treat infections continues to be a challenge, misuse and overuse of antimicrobials along with lack of access to clean water, sanitation and hygiene (WASH) and effective infection prevention and control (IPC) measures have fuelled the emergence and spread of AMR globally. The UK government commissioned review on AMR in 2014 projected that if AMR is not controlled, it would lead to significant impact on health with 10 million AMR-related deaths annually and macroeconomic consequences with a cumulative economic loss of US$ 100 trillion by 2050 [3].

Vaccination, when used in conjunction with other preventive measures, has the potential to significantly reduce AMR transmission through several pathways [4,5]. First, vaccination has a direct influence on the health burden of AMR by preventing the emergence and transmission of drug-resistant and drug-sensitive infections, and the associated antibiotic use. Second, vaccines have an indirect influence by reducing resistant infections in unvaccinated populations through herd immunity. Third, vaccination can prevent infections where antimicrobials are not indicated but often wrongly prescribed, such as primary viral infections, thereby reducing misuse and overuse of antimicrobials. Fourth, vaccines can also reduce the use of antimicrobials to treat secondary bacterial infections caused by viral diseases. Finally, vaccines can give longer-term health benefits in preventing infections and resistance to vaccines is rarely observed [6].

The Global Research on Antimicrobial Resistance (GRAM) project estimated the deaths and disability-adjusted life-years (DALYs) attributable to and associated with resistance by replacing all drug-resistant infections with susceptible infection or no infection, respectively. It estimated that 1.27 (95% UI: 0.91 - 1.7) million deaths and 47.9 (35 - 64) million DALYs were attributable to bacterial AMR and 4.95 (3.6 - 6.6) million deaths and 192 (146 - 248) million DALYs were associated with bacterial AMR in 2019 [7]. Despite the significant potential impact of vaccination in lowering AMR, evidence is limited due to the methodological difficulties and challenges in obtaining data on the health burden associated with AMR in order to calculate this impact [8–10]. Such evidence will be valuable to inform improvements in the coverage of existing vaccines and prioritise research and development of new vaccines.

To address this evidence gap, our aim is to analyse the findings from the GRAM project and estimate the vaccine-avertable bacterial AMR burden based on the profiles of existing and future vaccines by pathogen and infectious syndromes at the regional and global levels in 2019. Such pan-pathogen analyses using standardised approaches are critical to inform vaccine development, funding,
introduction and use. They also inform the WHO-led value attribution framework for vaccines against AMR [11], which includes five criteria: (i) vaccine averted AMR health burden, (ii) vaccine averted AMR economic burden, (iii) vaccine averted antibiotic use, (iv) sense of urgency to develop antimicrobial approaches, and (v) pathogen impact on equity and social justice. Our study contributes to the first criterion – vaccine-verted AMR health burden.
Methods

AMR burden data

We used the bacterial AMR burden estimates from the Global Research on Antimicrobial Resistance (GRAM) project which provided data for age-specific deaths and DALYs associated with and attributable to AMR by pathogen, infectious syndrome, and region for 2019 [7]. These comprehensive estimates of bacterial AMR burden were based on statistical predictive modelling of data from systematic reviews, surveillance systems, hospital systems, and other sources to generate estimates for 23 pathogens and 88 pathogen-drug combinations for 204 countries in 2019. The AMR burden estimates for *Neisseria gonorrhoeae* includes only morbidity and no mortality.

Two sets of estimates are presented – burden attributed to AMR, that is deaths and DALYs that could be averted if all drug-resistant infections would be replaced by drug-sensitive infections; and burden associated with AMR, that is deaths and DALYs that could be averted if all drug-resistant infections would be replaced by no infections. As vaccines prevent drug-resistant and drug-susceptible burden, we infer that the associated AMR burden is the appropriate metric for measuring the impact of vaccination on AMR burden.

Vaccine profiles

We focused our analysis on 15 pathogens – *Acinetobacter baumannii*, *Enterococcus faecium*, *Escherichia coli*, Group A *Streptococcus*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Mycobacterium tuberculosis*, *Neisseria gonorrhoeae*, non-typhoidal *Salmonella*, *Pseudomonas aeruginosa*, *Salmonella Paratyphi*, *Salmonella Typhi*, *Shigella* spp., *Staphylococcus aureus*, and *Streptococcus pneumoniae*. We selected pathogens that are part of the WHO evaluation of the value of vaccines in preventing AMR. We used vaccine profiles (see Table 1), which comprise the vaccine target population, efficacy, coverage, duration of protection, and disease presentation prevented.

For the existing vaccines against *H. influenzae* type b, *Streptococcus pneumoniae*, and *Salmonella Typhi*, the vaccine profiles expand coverage of the current vaccines in order to meet the strategic priority on coverage and equity of Immunisation Agenda 2030 [12]. For vaccines that are not yet available, hypothetical profiles were developed based on preferred product characteristics (PPCs) [13], target product profiles (TPPs), attributes of advanced vaccine candidates, and expert consultations with WHO working groups, PATH, and pathogen experts. Some pathogens have multiple disease presentations and would require different vaccines to prevent different disease presentations. As such, these pathogens have more than one vaccine profile.

Modelling process

We developed a static proportional impact model to estimate the vaccination impact in terms of reduction in age-specific AMR burden estimates for 2019 from the GRAM project. We estimated a counterfactual pre-vaccination scenario for diseases with current vaccinations and adjusted for...
disease type specification before applying the vaccine impact. We calculated the reduction in pre-vaccine AMR burden after vaccination in direct proportion to efficacy, coverage, target population for protection, and duration of protection of existing and potential future vaccines [14].

For ages that lie within the duration of protection since the time of vaccination:

\[
\text{AMR burden averted at age } i = \text{AMR burden at age } i \text{ pre-vaccination } \times \\
\text{vaccine efficacy } \times \\
\text{vaccine coverage}
\]

**Scenarios**

We estimated vaccine avertable deaths and DALYs attributable to and associated with AMR by region, infectious syndrome, and pathogen with 95% uncertainty intervals (UIs) for two scenarios — baseline scenario (for 15 pathogens) for primary vaccination of specific age-groups, and high-potential scenario (for a subset of 7 pathogens) that includes additional age groups at risk of infection based on expert opinion.

Vaccine profiles with the corresponding product characteristics for efficacy and duration of protection for vaccine-derived immunity, and coverage and target population for the baseline and high-potential scenarios are described in Table 1. In the baseline scenario, we estimated the vaccine avertable burden from the age of vaccination under the assumption that vaccine-derived immunity would sustain for the duration of protection of the corresponding vaccines. We did not consider vaccine waning dynamics due to limited evidence. For pathogens with a highly uncertain vaccine target population or feasibility of vaccine delivery, we estimated an additional high-potential scenario which assumed that individuals at risk (including additional age groups at risk) would be vaccinated to protect against corresponding disease presentations. This was applicable to vaccines against *Acinetobacter baumannii*, *Enterococcus faecium*, Extraintestinal Pathogenic *Escherichia coli* (ExPEC), *Klebsiella pneumoniae* (all syndromes), *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. For *Streptococcus pneumoniae*, we explored the high-potential scenario by administering a vaccine to an elderly population with the highest disease burden.

**Uncertainty analysis**

We conducted a Monte Carlo simulation of 400 runs (sufficient for results to converge) to propagate the uncertainty in the AMR burden, vaccine efficacy, and coverage through the model simulations to estimate the uncertainty in our projected outcomes of vaccination impact. We provide summary estimates in terms of vaccine-avertable deaths and DALYs attributable to and associated with AMR by region, infectious syndrome, and pathogen with 95% uncertainty intervals (UIs) for the baseline and high-potential scenarios. Additional details on the modelling process, scenarios, and uncertainty analysis are provided in the Appendix A1.
Results

Vaccine impact on global AMR burden

At the global level in 2019 for the baseline scenario, we estimated that vaccines against the 15 pathogens (analysed in this study) could avert 0.51 (95% UI: 0.49 - 0.54) million deaths and 28 (27 - 29) million DALYs associated with AMR, and 0.15 (0.14 - 0.17) million deaths and 7.6 (7.1 - 8.0) million DALYs attributable to AMR. In the high-potential scenario, we estimated that vaccines against a subset of 7 pathogens could avert an additional 1.2 (1.18 - 1.23) million deaths and 37 (36 - 39) million DALYs associated with AMR, and 0.33 (0.32 - 0.34) million deaths and 10 (9.8 - 11) million DALYs attributable to AMR globally in 2019.

Vaccine impact on AMR burden by pathogen

Figure 1a and Table 2a present the vaccine avertable burden attributable to and associated with AMR in 2019 for each of the pathogen-specific vaccine profiles at the global level for the baseline scenario. For pathogens with licensed vaccines, we estimated that vaccination against *Streptococcus pneumoniae* at 2019 coverage levels averted 44 (37 - 52) thousand deaths and 3.8 (3.3 - 4.5) million DALYs associated with AMR in 2019. By reaching the WHO recommended coverage level of 90% globally, 59 (50 - 69) thousand deaths and 5.1 (4.5 - 5.9) million DALYs associated with AMR could have been averted in 2019. Expanding the coverage to elderly populations would increase the vaccination impact to avert 71 (63 - 81) thousand deaths. We estimated that vaccination against *H. influenzae* at 2019 coverage levels averted 11 (9.7 - 13) thousand deaths and 0.98 (0.85 - 1.2) million DALYs associated with AMR in 2019. At 90% coverage globally, 13 (11 - 15) thousand deaths and 1.1 (0.96 - 1.3) million DALYs associated with AMR could have been averted. We estimated that wider introduction and scale-up of vaccination against *Salmonella* Typhi could have averted 34 (26 - 44) thousand deaths and 2.8 (2.2 - 3.6) million DALYs associated with AMR in 2019.

For pathogens with hypothetical vaccine profiles (developed by experts or provided in preferred product characteristics), we estimated that a vaccine against *Mycobacterium tuberculosis* that meets WHO’s PPC criteria of 80% efficacy, given to infants, with life-long immunity or boosting, would have averted 0.12 (0.11 - 0.13) million deaths and 4.5 (4.1 - 5.0) million DALYs associated with AMR. An improved vaccine against *Streptococcus pneumoniae* (70% efficacy against bloodstream infections (BSI), meningitis and other bacterial central nervous system infections (CNS), 50% efficacy against lower respiratory infection and all related infections in the thorax (LRI), given to 90% of infants at six weeks of life) would have a relatively highest impact by averting 99 (86 - 115) thousand deaths and 8.6 (7.5 - 10) million DALYs associated with AMR in 2019. An M72-like vaccine against *Mycobacterium tuberculosis* given to adolescents and older populations with life-long immunity or boosting would avert 71 (64 - 78) thousand deaths and 2.6 (2.3 - 2.8) million DALYs associated with AMR. A vaccine against all disease presentations of *Klebsiella pneumoniae* infection given to infants and elderly populations would avert 64 (59 - 72) thousand deaths and 3.7 (3.3 - 4.1) million DALYs
associated with AMR.

In the high-potential scenario (see Table 2b), we estimated that vaccination of at-risk individuals across all age groups against *E. coli* - non-diarrhogenic could avert 0.39 (0.37 - 0.40) million deaths and 13 (12 - 13) million DALYs associated with AMR in 2019. Vaccination of at-risk individuals against *Klebsiella pneumoniae* could avert 0.32 (0.31 - 0.34) million deaths and 14 (13 - 15) million DALYs associated with AMR, and vaccination against *Staphylococcus aureus* could avert 0.32 (0.31 - 0.33) million deaths and 11 (10 - 11) million DALYs associated with AMR.

### Vaccine impact on AMR burden by infectious syndrome

Figure 1b shows the vaccine avertable deaths and DALYs attributable to and associated with bacterial AMR for the different infectious syndromes in 2019 at the global level in the baseline scenario. We estimated vaccine avertable mortality associated with bacterial AMR to be highest for lower respiratory infections at 0.16 (0.14 - 0.17) million deaths and 11 (9.6 - 11) million DALYs for the baseline scenario, followed by tuberculosis at 0.12 (0.11 - 0.13) million deaths and 4.5 (4.1 - 5.0) million DALYs and bloodstream infections at 0.11 (0.10 - 0.12) million deaths and 5.6 (5.1 - 6.3) million DALYs in 2019. In the high-potential scenario, vaccine avertable deaths and DALYs were highest for lower respiratory infections, bloodstream infections, and intra-abdominal infections.

For each infectious syndrome, we stratified the vaccine avertable AMR burden for deaths and DALYs by pathogen in the baseline scenario, as shown in Figure 2 (and Figure A1 in the appendix).

*Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Klebsiella pneumoniae* account for most of the vaccine avertable AMR burden associated with lower respiratory infections. *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Escherichia coli* account for most of the vaccine avertable AMR burden associated with bloodstream infections.

### Vaccine impact on AMR burden at the regional level

Table 3 and Figure 1c show the vaccine avertable deaths and DALYs attributable to and associated with bacterial AMR at the regional levels in 2019 for the baseline scenario. We estimated the vaccine avertable burden associated with bacterial AMR to be highest in the WHO Africa region at 0.17 (0.15 - 0.18) million deaths and 12 (11 - 13) million DALYs, followed by the WHO South-East Asia region at 0.16 (0.15 - 0.18) million deaths and 7.5 (6.8 - 8.5) million DALYs in 2019. The vaccine avertable AMR burden for the WHO Africa and South-East Asia regions accounts for around two-thirds of the vaccine avertable AMR burden globally in 2019. In the high-potential scenario, we estimated that vaccines would avert an additional 0.19 (0.18 - 0.20) million deaths and 9.6 (8.8 - 11) million DALYs associated with AMR in the WHO Africa region, and 0.32 (0.30 - 0.33) million deaths and 11 (10 - 11) million DALYs associated with AMR in the WHO South-East Asia region.
Discussion

We estimated vaccine avertable disease burden attributable to and associated with AMR for existing and new vaccines in the pipeline by pathogen, infectious syndrome, and region based on the most recent, comprehensive estimates of the global burden of AMR. The AMR burden avertable by vaccination in 2019 was highest for the WHO Africa and South-East Asia regions, for lower respiratory infections, tuberculosis, and bloodstream infections by infectious syndromes, and for *Mycobacterium tuberculosis* and *Streptococcus pneumoniae* by pathogen.

Our estimates show the impact of existing vaccines for pneumococcal conjugate vaccine (PCV), *Haemophilus influenzae* type b (Hib), and typhoid conjugate vaccine (TCV) on reducing AMR burden attributable to and associated with *Streptococcus pneumoniae*, *H. influenzae*, and *Salmonella Typhi* respectively. We highlight the critical need to scale up existing vaccines to high and equitable immunisation coverage, and the acceleration of TCV introductions in high burden countries. Also, we show that vaccines can contribute towards preventing a significant proportion of the AMR burden for pathogens which have vaccines in late-stage clinical development with clear attributes or published preferred product characteristics or target product profiles, such as for ExPEC and *Mycobacterium tuberculosis*. Novel regulatory and policy mechanisms should be developed to accelerate the approval and use of these vaccines to prevent AMR. Based on the estimated high vaccine avertable burden associated with AMR for *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Acinetobacter baumannii*, we urgently call for studies to enhance biological understanding and improve the feasibility of developing vaccines for these pathogens. For the remaining pathogens that have vaccine candidates in the early stages of clinical development or no vaccines in the pipeline, we recommend investing in vaccine development to resolve biological challenges as well as feasibility in terms of product development, market access, and product implementation.

Our analysis included a baseline and high-potential scenarios. In the baseline scenario, we model vaccine delivery based on known vaccine attributes, including a defined target age group that has been immunised with a vaccine in the past, during clinical trials, or identified in vaccine target product profiles. In contrast, the high-potential scenario makes no assumptions about vaccine delivery and target age group and shows the highest probable vaccine impact, should there be a policy recommendation and feasibility of delivery to all who would benefit from a vaccine. We recognise that the high-potential scenario includes multiple challenges that need overcoming such as immunisation of adults and the elderly, timely immunisation to prevent nosocomial infections, vaccine efficacy in patients who are immunocompromised and with co-morbidities, vaccine demand, and financing.

Pan-pathogen analyses with standardised methodologies are critical to inform vaccine funding and development and should be followed up with detailed vaccine-specific analyses, considering pathogen biology and transmission, and accounting for varied disease burden patterns across the spatial and temporal scales. *Haemophilus influenzae* type b (Hib), rotavirus, pneumococcal, typhoid
and influenza vaccines have been directly associated with reduction of resistance, antibiotic use and related clinical complications [9,15–22], while Fu et al. modelled the global burden of drug-resistant tuberculosis avertable by a future TB vaccine [23].

Our study has limitations. First, since we included the direct effect of vaccination but excluded indirect effect and transmission dynamics of AMR pathogens, our vaccine impact estimates on averted AMR burden are conservative. Second, our analysis focused on 15 bacterial pathogens and additional pathogens included in the GRAM project such as Enterobacter spp., Group B Streptococcus, Enterococcus feacalis, Proteus spp., Citrobacter spp., and Morganella spp. were excluded. However, inclusion of these pathogens appears unlikely to significantly affect our overall inferences considering that the included 15 pathogens are responsible for the majority of the AMR burden. Third, while our analysis was based on the estimates generated by the GRAM project, which represents the most comprehensive estimates of bacterial AMR burden to date, limited input data to the GRAM project especially from low- and middle-income countries is a significant data gap that necessitates newer surveillance data and platforms to inform the updates, validity, and confidence in the estimates of the GRAM project. In particular, estimates from the GRAM project for tuberculosis do not include tuberculosis associated with HIV. Fourth, we did not consider the impact of viral vaccines on reducing the AMR drivers of antibiotic misuse and overuse [18,20,24,25]. Finally, we did not consider geographic and socioeconomic clustering of vaccination coverage, which could lead to heterogeneity in vaccination impact on lowering AMR burden with relatively less impact among subpopulations with higher risk of disease while also facing lower health care access including access to vaccination services [26].

The value of vaccines in preventing AMR should be systematically considered in the decision-making process during scale-up of existing vaccines and introduction of new vaccines. Vaccines should be explicitly incorporated as tools to combat AMR into National Action Plans on AMR [27] and National Immunisation Strategies [28]. For new vaccines in the pipeline and future vaccines, we recommend vaccine avertable burden of AMR to be included in the full value of vaccine assessments [29]. This evidence can support stakeholders in their decision-making process and priority setting throughout the end-to-end continuum from discovery and clinical development to investment, development, introduction, and sustainability of new vaccines with equitable access.
Ethics approval

This study was approved by the ethics committee (Ref 26896) of the London School of Hygiene & Tropical Medicine.

Data availability and code repository

We conducted our analysis using the R programming language for statistical computing [30], and the repository for the data and software code of this modelling study are publicly accessible at https://github.com/vaccine-impact/vaccine_amr.

Role of the funding source

This study was funded by the Bill & Melinda Gates Foundation (INV-006816). The funders were not involved in the study design, data collection, data analysis, data interpretation, writing of the report, and the decision to submit for publication. All authors had full access to all the data in the study and final responsibility for the decision to submit for publication.

Contributors

CK, MH, IF, MHA, and KA conceptualised and designed the study. IF and MHA compiled the data sets. CK developed the proportional impact model and software and conducted the analysis. CK and KA wrote the first draft, and all authors contributed to reviewing and editing of the manuscript and have approved the final version.

Acknowledgements

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Declaration of interests

We declare no competing interests. Where authors are identified as personnel of affiliated organisations, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policies, or views of their affiliated organisations.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

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Bibliography


27. WHO. Library of AMR national action plans. 2022 [cited 10 May 2022]. Available:


Table 1. Vaccine profiles. Product characteristics for efficacy and duration of protection for vaccine-derived immunity, and coverage and target population (age of vaccination) for current and future vaccines against bacterial pathogens. The baseline scenario includes 15 pathogens, and the high-potential scenario includes a subset of 7 pathogens.

(Bone and joint infections = infections of bones, joints, and related organs; BSI = bloodstream infections; cardiac infections = endocarditis and other cardiac infections; CNS infections = meningitis and other bacterial CNS infections; intra-abdominal infections = peritoneal and intra-abdominal infections; LRI and thorax infections = lower respiratory infections and all related infections in the thorax; bacterial skin infections = bacterial infections of the skin and subcutaneous systems; typhoid, paratyphoid, and iNTS = typhoid fever, paratyphoid fever, and invasive non-typhoidal Salmonella spp; UTI = urinary tract infections and pyelonephritis)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease presentation</th>
<th>Vaccine</th>
<th>Vaccination scenarios (age of vaccination)</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acinetobacter baumannii</strong></td>
<td>BSI</td>
<td>70</td>
<td>70</td>
<td>5 years, elderly age group with highest burden</td>
</tr>
<tr>
<td><strong>Enterococcus faecium</strong></td>
<td>All (Bacterial skin infections, BSI, Cardiac infections, LRI and thorax infections, UTI)</td>
<td>70</td>
<td>70</td>
<td>5 years, elderly age group with highest burden</td>
</tr>
<tr>
<td><strong>Enterotoxigenic Escherichia coli (ETEC)</strong></td>
<td>Diarrhoea</td>
<td>60</td>
<td>70</td>
<td>5 years, elderly age group with highest burden</td>
</tr>
<tr>
<td><strong>Extraintestinal Pathogenic Escherichia coli (ExPEC)</strong> - BSI</td>
<td>BSI</td>
<td>70</td>
<td>70</td>
<td>5 years, elderly age group with highest burden</td>
</tr>
<tr>
<td>Pathogen</td>
<td>Disease</td>
<td>Age</td>
<td>Duration</td>
<td>Group</td>
</tr>
<tr>
<td>----------</td>
<td>---------</td>
<td>-----</td>
<td>----------</td>
<td>-------</td>
</tr>
<tr>
<td><em>Escherichia coli</em> (ExPEC)</td>
<td>UTI</td>
<td>70</td>
<td>6 weeks, elderly age group with highest burden</td>
<td>All age groups</td>
</tr>
<tr>
<td><em>E. Coli</em> - non diarrheagenic</td>
<td>Bacterial skin infections, bone and joint infections, BSI, cardiac infections, CNS infections, intra-abdominal infections, LRI and thorax infections, and UTI</td>
<td>70</td>
<td>5 years</td>
<td>All age groups</td>
</tr>
<tr>
<td>Group A streptococcus (GAS)</td>
<td>All (Bacterial skin infections, Bone and joint infections, BSI, Cardiac infections)</td>
<td>70</td>
<td>5 years</td>
<td>6 weeks</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type B (Hib)</td>
<td>All (CNS infections, LRI and thorax infections)</td>
<td>59; 92; 93</td>
<td>5 years</td>
<td>6, 10, 14 weeks</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em> - BSI</td>
<td>BSI</td>
<td>70</td>
<td>6 months</td>
<td>0 weeks (maternal)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em> - all</td>
<td>All (Bacterial skin infections, Bone and joint infections, BSI, Cardiac infections, CNS infections, Intra-abdominal infections, LRI and thorax infections, UTI)</td>
<td>70</td>
<td>5 years</td>
<td>6 weeks, elderly age group with highest burden</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em> - M72*</td>
<td>Tuberculosis</td>
<td>50</td>
<td>10 years</td>
<td>10 years + boost every 10 years</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em> - Improved</td>
<td>Tuberculosis</td>
<td>80</td>
<td>10 years</td>
<td>0 weeks + boost every 10 years</td>
</tr>
<tr>
<td>Pathogen</td>
<td>Condition</td>
<td>Vaccine Status</td>
<td>Age</td>
<td>Duration</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------------------------------</td>
<td>----------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Neisseria gonorrhoeae</strong></td>
<td>Gonorrhoea</td>
<td>WHO</td>
<td>70</td>
<td>10 years</td>
</tr>
<tr>
<td>Non-typhoidal Salmonella</td>
<td>All (BSI, Cardiac infections, Diarrhoea, Typhoid, paratyphoid, and iNTS)</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td>80</td>
<td>5 years</td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa</strong></td>
<td>BSI, LRI and thorax infections</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td>70</td>
<td>5 years</td>
</tr>
<tr>
<td>Salmonella Paratyphi</td>
<td>Typhoid, paratyphoid, and iNTS</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td>70</td>
<td>5 years</td>
</tr>
<tr>
<td>Salmonella Typhi</td>
<td>All (BSI, Cardiac infections, Typhoid, paratyphoid, and iNTS)</td>
<td>Existing vaccine &amp; Expert opinion</td>
<td>85</td>
<td>15 years</td>
</tr>
<tr>
<td>Shigella</td>
<td>All (Diarrhoea)</td>
<td>WHO</td>
<td>60</td>
<td>5 years</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>All (Bacterial skin infections, Bone and joint infections, BSI, Cardiac infections, CNS infections, Intra-abdominal infections, LRI and thorax infections, UTI)</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td>60</td>
<td>5 years</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>BSI, CNS infections, Cardiac infections, LRI</td>
<td>Existing vaccine</td>
<td>29; 58; 58a (27 for LRI)</td>
<td>5 years</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae - Improved</strong></td>
<td>BSI, CNS infections, Cardiac</td>
<td>Hypothetical vaccine based on expert opinion</td>
<td>70 (50 for LRI)</td>
<td>5 years</td>
</tr>
</tbody>
</table>
The effects of these vaccines were not added to the aggregated impact of vaccination on AMR burden by region and by infectious syndrome.

Efficacy corresponding to first, second, and third doses respectively.
Table 2. Vaccine impact on AMR burden by vaccine profile. The estimates (median and 95% uncertainty intervals) of the vaccine avertable deaths and DALYs attributable to and associated with bacterial antimicrobial resistance in 2019 were aggregated by vaccine profile for the baseline (Table 2a) and high-potential (Table 2b) scenarios.

(Bone and joint infections = infections of bones, joints, and related organs; BSI = bloodstream infections; cardiac infections = endocarditis and other cardiac infections; CNS infections = meningitis and other bacterial CNS infections; intra-abdominal infections = peritoneal and intra-abdominal infections; LRI and thorax infections = lower respiratory infections and all related infections in the thorax; bacterial skin infections = bacterial infections of the skin and subcutaneous systems; typhoid, paratyphoid, and iNTS = typhoid fever, paratyphoid fever, and invasive non-typhoidal Salmonella spp; UTI = urinary tract infections and pyelonephritis)

Table 2a. Baseline scenario

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease presentation</th>
<th>Vaccine avertable deaths</th>
<th>Vaccine avertable DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Associated with resistance</td>
<td>Attributable to resistance</td>
</tr>
<tr>
<td>Acinetobacter baumannii - BSI</td>
<td>BSI</td>
<td>18,060 (13,305 - 25,668)</td>
<td>5,723 (4,142 - 8,442)</td>
</tr>
<tr>
<td>Acinetobacter baumannii - all</td>
<td>All (Bacterial skin infections, BSI, Cardiac infections, LRI and thorax infections, UTI)</td>
<td>34,327 (28,241 - 43,094)</td>
<td>10,799 (8,651 - 14,129)</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>All (Bone and joint infections, BSI, Cardiac infections, Intra-abdominal infections, UTI)</td>
<td>13,933 (12,268 - 16,025)</td>
<td>3,641 (3,094 - 4,469)</td>
</tr>
<tr>
<td>Enterotoxigenic Escherichia coli (ETEC)</td>
<td>Diarrhoea</td>
<td>2,779 (2,043 - 4,136)</td>
<td>784 (545 - 1,094)</td>
</tr>
<tr>
<td>Extraintestinal Pathogenic Escherichia coli (ExPEC) - BSI</td>
<td>BSI</td>
<td>15,316 (11,794 - 19,992)</td>
<td>3,938 (3,060 - 5,348)</td>
</tr>
<tr>
<td>Extraintestinal Pathogenic Escherichia coli (ExPEC) - UTI</td>
<td>UTI</td>
<td>6,727 (5,659 - 7,934)</td>
<td>1,787 (1,469 - 2,172)</td>
</tr>
<tr>
<td>E. Coli - non diarrheagenic</td>
<td>All (Bacterial skin infections, bone and joint infections, BSI, cardiac infections,</td>
<td>62,424 (56,454 - 68,555)</td>
<td>16,405 (15,090 - 18,344)</td>
</tr>
<tr>
<td>Organism</td>
<td>Infections</td>
<td>Cases (Min - Max)</td>
<td>Deaths (Min - Max)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Group A Streptococcus (GAS)</strong></td>
<td>All (Bacterial skin infections, Bone and joint infections, BSI, Cardiac infections)</td>
<td>792 (643 - 998)</td>
<td>82 (55 - 130)</td>
</tr>
<tr>
<td><strong>Haemophilus influenzae type B (Hib)</strong></td>
<td>All (CNS infections, LRI and thorax infections)</td>
<td>13,027 (11,058 - 15,180)</td>
<td>2,946 (2,412 - 3,622)</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae - BSI</strong></td>
<td>BSI</td>
<td>27,333 (22,045 - 34,905)</td>
<td>8,116 (6,508 - 10,273)</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae - all</strong></td>
<td>All (Bacterial skin infections, Bone and joint infections, BSI, Cardiac infections, CNS infections, Intra-abdominal infections, LRI and thorax infections, UTI)</td>
<td>64,484 (58,747 - 72,028)</td>
<td>19,397 (16,971 - 21,761)</td>
</tr>
<tr>
<td><strong>Mycobacterium tuberculosis - M72</strong></td>
<td>Tuberculosis</td>
<td>70,704 (64,053 - 77,951)</td>
<td>31,040 (26,956 - 37,850)</td>
</tr>
<tr>
<td><strong>Mycobacterium tuberculosis - Improved</strong></td>
<td>Tuberculosis</td>
<td>118,316 (107,061 - 130,567)</td>
<td>51,675 (45,223 - 61,401)</td>
</tr>
<tr>
<td><strong>Neisseria gonorrhoeae</strong></td>
<td>gonorrhoea</td>
<td>NA (NA - NA)</td>
<td>NA (NA - NA)</td>
</tr>
<tr>
<td><strong>Salmonella non-typhoidal</strong></td>
<td>All (BSI, Cardiac infections, Diarrhoea, Typhoid, paratyphoid, and iNTS)</td>
<td>1,820 (1,412 - 2,624)</td>
<td>396 (290 - 618)</td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa</strong></td>
<td>BSI, LRI and thorax infections</td>
<td>20,700 (18,148 - 23,443)</td>
<td>5,314 (4,633 - 6,081)</td>
</tr>
<tr>
<td><strong>Salmonella Paratyphi</strong></td>
<td>Typhoid, paratyphoid, and iNTS</td>
<td>1,463 (853 - 2,793)</td>
<td>301 (149 - 637)</td>
</tr>
<tr>
<td><strong>Salmonella Typhi</strong></td>
<td>All (BSI, Cardiac infections, Typhoid, paratyphoid, and iNTS)</td>
<td>34,478 (26,029 - 44,037)</td>
<td>6,630 (5,022 - 8,959)</td>
</tr>
<tr>
<td>Pathogen</td>
<td>Disease presentation</td>
<td>Vaccine avertable deaths</td>
<td>Vaccine avertable DALYs</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>--------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated with resistance</td>
<td>Attributable to resistance</td>
</tr>
<tr>
<td><strong>Shigella</strong></td>
<td>All (Diarrhoea)</td>
<td>4,133 (2,765 - 6,132)</td>
<td>860 (545 - 1,557)</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>All (Bacterial skin infections, Bone and joint infections, BSI, Cardiac infections, CNS infections, Intra-abdominal infections, LRI and thorax infections, UTI)</td>
<td>56,141 (50,768 - 62,454)</td>
<td>13,322 (11,924 - 15,169)</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>BSI, CNS infections, Cardiac infections, LRI</td>
<td>58,922 (50,170 - 69,048)</td>
<td>12,179 (10,178 - 14,772)</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae - Improved</strong></td>
<td></td>
<td>98,987 (86,231 - 115,406)</td>
<td>20,415 (17,330 - 24,803)</td>
</tr>
</tbody>
</table>

**Table 2b. High-potential scenario**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease presentation</th>
<th>Vaccine avertable deaths</th>
<th>Vaccine avertable DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Associated with resistance</td>
<td>Attributable to resistance</td>
</tr>
<tr>
<td><strong>Acinetobacter baumannii - BSI</strong></td>
<td>BSI</td>
<td>116,141 (105,342 - 128,342)</td>
<td>36,641 (33,081 - 41,272)</td>
</tr>
<tr>
<td><strong>Acinetobacter baumannii - all</strong></td>
<td>All (Bacterial skin infections, BSI, Cardiac infections, LRI and thorax infections, UTI)</td>
<td>216,584 (201,748 - 231,987)</td>
<td>67,905 (63,384 - 73,535)</td>
</tr>
<tr>
<td><strong>Enterococcus faecium</strong></td>
<td>All (Bone and joint infections, BSI, Cardiac infections, Intra-abdominal infections, UTI)</td>
<td>100,814 (95,339 - 105,798)</td>
<td>26,342 (24,611 - 28,209)</td>
</tr>
<tr>
<td><strong>Extrainestinal Pathogenic Escherichia coli (ExPEC) - BSI</strong></td>
<td>BSI</td>
<td>103,016 (93,650 - 114,889)</td>
<td>26,551 (24,078 - 29,292)</td>
</tr>
<tr>
<td><strong>Extrainestinal Pathogenic Escherichia coli (ExPEC) - UTI</strong></td>
<td>UTI</td>
<td>49,669 (46,732 - 52,824)</td>
<td>13,003 (12,189 - 13,885)</td>
</tr>
<tr>
<td><strong>E. coli</strong> - non-diarrhogenic</td>
<td>Bacterial skin infections, bone and joint infections, BSI, cardiac infections, CNS infections, intra-abdominal infections, LRI and thorax infections, and UTI</td>
<td>389,043 (373,393 - 404,859)</td>
<td>102,352 (97,917 - 106,919)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae - all</td>
<td>All (Bacterial skin infections, Bone and joint infections, BSI, Cardiac infections, CNS infections, Intra-abdominal infections, LRI and thorax infections, UTI)</td>
<td>321,242 (308,878 - 335,698)</td>
<td>97,026 (92,013 - 102,088)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>BSI, LRI and thorax infections</td>
<td>118,966 (113,054 - 125,950)</td>
<td>30,495 (28,728 - 32,634)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>All (Bacterial skin infections, Bone and joint infections, BSI, Cardiac infections, CNS infections, Intra-abdominal infections, LRI and thorax infections, UTI)</td>
<td>319,112 (307,397 - 331,431)</td>
<td>76,796 (73,583 - 80,782)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>BSI, CNS infections, Cardiac infections, LRI</td>
<td>71,341 (62,610 - 81,314)</td>
<td>14,728 (12,661 - 17,487)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae - Improved</td>
<td>BSI, CNS infections, Cardiac infections, LRI</td>
<td>118,645 (103,983 - 135,056)</td>
<td>24,471 (20,943 - 28,957)</td>
</tr>
</tbody>
</table>
Table 3. Vaccine avertable AMR burden globally and by WHO region. The estimates (median and 95% uncertainty intervals) for vaccine avertable disease burden attributable to and associated with bacterial AMR in 2019 is presented in terms of deaths and DALYs avertable by vaccination in the baseline scenario.

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Vaccine avertable deaths</th>
<th>Vaccine avertable DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Associated with resistance</td>
<td>Attributable to resistance</td>
</tr>
<tr>
<td>Africa</td>
<td>166,105 (154,785 - 180,343)</td>
<td>44,745 (40,658 - 49,196)</td>
</tr>
<tr>
<td>Americas</td>
<td>32,901 (30,020 - 35,892)</td>
<td>8,824 (7,949 - 9,939)</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>61,060 (56,445 - 66,784)</td>
<td>18,105 (16,426 - 20,194)</td>
</tr>
<tr>
<td>Europe</td>
<td>32,218 (29,145 - 37,168)</td>
<td>9,721 (8,646 - 11,126)</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>162,699 (147,461 - 179,566)</td>
<td>54,989 (47,336 - 64,667)</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>58,701 (52,392 - 67,736)</td>
<td>16,569 (14,593 - 19,491)</td>
</tr>
<tr>
<td>Global</td>
<td>514,631 (491,550 - 540,336)</td>
<td>153,009 (144,253 - 165,008)</td>
</tr>
</tbody>
</table>
Figures

Figure 1. Vaccine impact on AMR burden by pathogen, infectious syndrome, and region.

Figure 1a. Vaccine impact on AMR burden by pathogen-specific vaccine profile. The estimates (median and 95% uncertainty intervals) of the vaccine avertable deaths attributable to and associated with bacterial antimicrobial resistance in 2019 were aggregated by vaccine profile in the baseline scenario.
Figure 1b. Vaccine impact on AMR burden by infectious syndrome. The estimates (median and 95% uncertainty intervals) of the vaccine avertable deaths attributable to and associated with bacterial antimicrobial resistance in 2019 were aggregated by infectious syndrome in the baseline scenario. (Bone+ = infections of bones, joints, and related organs; BSI = bloodstream infections; cardiac = endocarditis and other cardiac infections; CNS = meningitis and other bacterial CNS infections; intra-abdominal = peritoneal and intra-abdominal infections; LRI+ = lower respiratory infections and all related infections in the thorax; skin = bacterial infections of the skin and subcutaneous systems; TF–PF–iNTS = typhoid fever, paratyphoid fever, and invasive non-typhoidal Salmonella spp; UTI = urinary tract infections and pyelonephritis.)
Figure 1c. Vaccine impact on AMR burden by WHO region. The estimates (median and 95% uncertainty intervals) of the vaccine avertable deaths attributable to and associated with bacterial antimicrobial resistance in 2019 were aggregated by WHO region in the baseline scenario.
Figure 2. Vaccine avertable AMR burden by infectious syndrome and pathogen. Vaccine avertable deaths associated with AMR by infectious syndrome and pathogen in the baseline scenario. (“Others” include infections of bones, joints, and related organs, bloodstream infections, endocarditis and other cardiac infections, meningitis and other bacterial CNS infections, peritoneal and intra-abdominal infections, lower respiratory infections and all related infections in the thorax, bacterial infections of the skin and subcutaneous systems, typhoid fever, paratyphoid fever, and invasive non-typhoidal Salmonella spp, and urinary tract infections and pyelonephritis)
Appendix

A1. Additional details of the modelling process

Estimating vaccine-avertable AMR burden of the target age group

The AMR burden data from the Global Research on Antimicrobial Resistance (GRAM) project was disaggregated by age and included the following categories – early neonatal (first week after birth), late neonatal (2-4 weeks of age), postneonatal (5 weeks to under 1-year of age), 1-4 years, 4-9 years, … , 90-94 years, and 95 years and beyond. We estimated the reduction in AMR burden in direct proportion to efficacy, coverage, target population for protection, and duration of protection of existing and potential future vaccines. We considered that immunised individuals would gain vaccine-derived immunity two weeks post-vaccination.

Estimating pre-vaccination burden for pathogens with existing vaccines

For the existing Hib and pneumococcal conjugate vaccines (PCVs), we estimated the pre-vaccination (i.e., no vaccination) burden associated and attributable to AMR in 2019 using the estimates of efficacy and coverage in 2019. We used the vaccine coverage for Hib and PCV from WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) [1] and demography data from the United Nations World Population Prospects (UNWPP) [2] to estimate the vaccine coverage at the regional level. We used the vaccine efficacy estimates for the first dose, second dose, and third doses scheduled at 6, 10, and 14 weeks for the Hib [3,4] and PCV vaccines [5,6]. By applying the vaccine efficacies and regional coverage to the AMR burden data in 2019, we estimated the increase in AMR burden for the counterfactual scenario of no vaccination in direct proportion to efficacy, coverage, target population for protection, and duration of protection. The global and regional coverage of typhoid conjugate vaccine and the post-vaccination impact was minimal in 2019 [7] and thereby did not warrant additional estimation for the counterfactual scenario of no vaccination.

The GRAM project estimates of AMR burden for *H. influenzae* were not stratified by serotypes. *H. influenzae* serotype b (Hib) was responsible for around 95% of all invasive *H. influenzae* disease burden among children younger than 5 years of age before the introduction of vaccines [8]. By applying the 95% Hib proportion to the total *H. influenzae* burden in the counterfactual scenario of no vaccination, we estimated the vaccine-preventable proportion of Hib-specific AMR burden of the total *H. influenzae* AMR burden in 2019.

Disease type specification of the AMR burden

The GRAM project’s AMR burden estimations do not differentiate between *Escherichia coli* strains. Instead, the AMR burden estimates were stratified by symptoms. Since enterotoxigenic *E. coli* (ETEC) and enteropathogenic *E. coli* (EPEC) are the two major *E. coli* strains that cause diarrhoea, we calculated the proportional contribution of ETEC to the AMR burden due to *E. coli* causing diarrhoea and then estimated the impact of the ETEC vaccine on reducing this burden (43.97%).
Estimating the aggregated vaccine avertable burden

To estimate the aggregate estimates on the impact of the vaccines by region and by infectious syndrome, we estimated the impact of all listed vaccines as long as the effects do not overlap to avoid double counting. When there were multiple vaccines which target the same disease, infectious syndrome, and age, we chose the vaccines with greater efficacy for these estimates. However, for vaccines against *Streptococcus pneumoniae*, we used the efficacy of the existing vaccine with increased coverage that met the strategic priority on coverage and equity of Immunisation Agenda 2030.

Scenarios for vaccine avertable AMR burden

We estimated vaccine avertable AMR burden for baseline and high-potential scenarios. We recognise that the high-potential scenario is optimistic given the unanswered questions about the feasibility of producing vaccines with long-term immunity and timely delivery to populations at risk, such as patients in hospitals undergoing elective surgeries. We included the high-potential scenario to highlight the potential impact vaccines could have if challenges around vaccine development and delivery were to be resolved.

Uncertainty analysis

Our estimations account for the uncertainties around AMR burden, efficacy, and coverage. Based on data examination, we applied the lognormal distribution to the mean, the 2.5th and 97.5th percentiles of the AMR burden to generate the randomly drawn values. For vaccine efficacy and coverage, we used the truncated normal distribution. For hypothetical vaccines, we applied ± 20% to the vaccine efficacy and coverage on the vaccine profile. For existing vaccines, we used confidence intervals of the vaccine efficacy from studies and applied ± 5% to vaccine coverage (that is, coverage of existing vaccines increased in order to meet the strategic priority on coverage and equity of Immunisation Agenda 2030). When estimating the impact of the existing vaccines with current coverage (that is, based on WUENIC estimates), we only included the uncertainty in efficacy as we used the point estimates of actual coverage.

Data availability and code repository

We conducted our analysis using the R programming language for statistical computing [28], and the repository for the data and software code of this modelling study are publicly accessible at [https://github.com/vaccine-impact/vaccine_amr](https://github.com/vaccine-impact/vaccine_amr).
Figure A1. Vaccine avertable AMR burden by infectious syndrome and pathogen. Vaccine avertable AMR burden (deaths and DALYs averted) by infectious syndrome and pathogen in the baseline scenario. (A) Vaccine avertable deaths attributable to AMR by infectious syndrome and pathogen. (B) Vaccine avertable DALYs associated with AMR by infectious syndrome and pathogen. (C) Vaccine avertable DALYs attributable to AMR by infectious syndrome and pathogen.
(B)

![Diagram showing the distribution of bacterial infections in LRI and thorax infections, bloodstream infections, and tuberculosis.](image)

LRI and thorax infections (37.7%)
- Staphylococcus aureus (17.15%)
- Pseudomonas aeruginosa (7.46%)
- Klebsiella pneumoniae (15.10%)
- Haemophilus influenzae (7.68%)
- Escherichia coli (9.26%)
- Acinetobacter baumannii (4.41%)
- Streptococcus pneumoniae (15.97%)

Bloodstream Infections (20.2%)
- Staphylococcus aureus (4.87%)
- Others (13.76%)
- Klebsiella pneumoniae (55.22%)
- Escherichia coli (18.52%)
- Acinetobacter baumannii (8.96%)

Tuberculosis (16.3%)
- Mycobacterium tuberculosis (100.00%)

Others (25.8%)

(100.00%)
Bibliography (for appendix)


The approach of World Health Organization to articulate the role and assure impact of vaccines against antimicrobial resistance

Isabel Frost, Anand Balachandran, Sarah Paulin-Descenau, Hatim Sat, Mateusz Haso-Agopsowicz

ABSTRACT
Antimicrobial resistance (AMR) is a growing global problem and there were an estimated 4.95 million deaths associated with bacterial AMR worldwide in 2019. Vaccines can impact AMR by preventing infections and reducing the need for antibiotics which will inadvertently slow the emergence of AMR. Effective infection prevention and control (IPC) has been identified as the cornerstone action to combat AMR by the World Health Assembly and the Global Action plan on AMR. Similarly, the Immunization Agenda 2030 highlights vaccines as critical tools to combat AMR. This article summarizes the strategy of the World Health Organization to understand, articulate and communicate the important role of vaccines in countering AMR. The work is organized around developing a strategy, understanding the pipeline of vaccines in development, articulating the value of vaccines against AMR, and assuring sustainable impact of vaccines at a country level to combat AMR.

Antimicrobial Resistance (AMR) occurs when bacteria, viruses, fungi and parasites no longer respond to antimicrobial agents. As a result of drug resistance, antibiotics and other antimicrobial agents become ineffective and infections become difficult or impossible to treat, increasing the risk of disease spread, severe illness and death. The prevalence of AMR is growing rapidly and pathogens resistant to all classes of antibiotics have been reported more frequently in recent years. As a consequence, many resistant infections are becoming more difficult to treat resulting in health, economic and societal loss. In 2019, 4.95 million deaths were associated with drug-resistant bacterial infections globally. The antimicrobial resistant infections are more expensive to treat, are associated with higher mortality and morbidity rates as well as high socioeconomic impact. Estimates suggest that 28 million people will fall into poverty worldwide due to AMR with an increase in health-care costs of up to US$1 trillion worldwide by 2050, with low-income countries expected to be the most impacted. A rapid and multifaceted response is needed to prevent the significant disease burden and socio-economic cost.

The Global Action Plan on AMR lists five strategic objectives to contain AMR: optimizing the use of antimicrobials, preventing infections (including the use of vaccines), strengthening surveillance and research, improving awareness and understanding of AMR, and investing in new medical products.

The Global Action Plan lays the blueprint for countries to develop country-specific National Action Plans on AMR. Vaccines play an important role in preventing infections (drug-susceptible and drug-resistant), and reducing antibiotic use, a key driver of AMR. Vaccines therefore can contribute to reducing selection for AMR in both the target pathogen (for bacterial vaccines) as well as in bacterial species that are not directly targeted by the used antibiotics (bystander effect) (Figure 1). A study of a pneumococcal conjugate vaccine (PCV) in South Africa observed a 67% reduction in penicillin-resistant invasive disease in the PCV-vaccinated group, and post-licensure PCV studies observe near elimination of resistant strains. Estimates suggest that pneumococcal and rotavirus vaccines prevent 23.8 million and 13.6 million episodes of antibiotic-treated illness, respectively, among children under five years of age in LMICs each year. Similarly, influenza vaccine has been shown to reduce days of antibiotic use among healthy adults, likely through reduction inappropriate empiric prescribing. Furthermore, typhoid conjugate vaccine, recently introduced to tackle drug-resistant typhoid in Pakistan, is expected to avert 895,000 of extensive drug resistant typhoid cases over the next ten years.

Immunization was highlighted as one of the tools to combat AMR in the Immunization Agenda 2030: A global strategy to leave no one behind. To develop a strategy on vaccines and AMR, the World Health Organization (WHO) has published an action framework - a technical annex to the Immunization Agenda 2030. The action framework describes a vision for vaccines to contribute fully, sustainably and equitably to the prevention and control of AMR by preventing
infections and reducing antimicrobial use. To achieve this vision, the document articulates a list of priority actions to be taken by AMR and immunization stakeholders in three areas: expanding the use of licensed vaccines to maximize impact on AMR, developing new vaccines that contribute to the prevention and control of AMR, and expanding and sharing knowledge about the impact of vaccines on AMR (Panel 1). This document aims to support alignment of activities among international, regional and national vaccine and AMR implementing partners, and to structure and articulate key priority actions needed to articulate the value of vaccines against AMR and lead to implementation and impact.

There is growing recognition that vaccines are powerful tools to combat AMR. For example, the Wellcome Trust recommends to increase uptake of vaccines for *Salmonella typhi*, *Streptococcus pneumoniae*, and *Hemophilus influenzae* type b; and to bring to market vaccines for *Shigella*, nontyphoidal *Salmonella*, and enteric *Escherichia coli*. Gavi, the Vaccine Alliance analyzed the value of vaccines against AMR to inform their Vaccine Investment Strategy in 2018. They found that pneumococcal, typhoid and malaria vaccines have the highest value against AMR. The WHO has identified 12 priority pathogens for which new antibiotics are most urgently needed and has recently
analyzed the preclinical and clinical pipeline for vaccines against these pathogens, in addition to *Clostridioides difficile* and *Mycobacterium tuberculosis*. The analysis builds on previous initiatives to evaluate the pipeline of antibacterials in preclinical and clinical development against the priority pathogens. In clinical development, 61 vaccine candidates were identified that target the priority pathogens, which were also classified into four groups (Figure 2). Group A, consisting of pathogens on the priority pathogen list for which vaccines already exist and includes *Salmonella enterica* ser. Typhi, *S. pneumoniae*, *Haemophilus influenzae* type b, and *M. tuberculosis*. Group B, consisting of pathogens with

<table>
<thead>
<tr>
<th>Pipeline Feasibility Group</th>
<th>Description</th>
<th>Pathogens</th>
<th>Recommendations</th>
</tr>
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</table>
| Very high | AMR priority pathogens for which licensed vaccines already exist | • *Salmonella enterica* ser. Typhi  
• *Streptococcus pneumoniae*  
• *Haemophilus influenzae* type b  
• *Mycobacterium tuberculosis* | Increase coverage of authorized vaccines in line with WHO immunization targets to maximise impact on AMR  
Accelerate the development of effective vaccines against TB. |
| High | AMR priority pathogens for which a vaccine candidate is in late-stage development (Phase 3) and vaccines would be suitable to target AMR infections caused by these priority pathogens in the coming years | • Extraintestinal pathogenic *Escherichia coli* (ExPEC)  
• *Salmonella enterica* ser. Paratyphi A  
• *Neisseria gonorrhoeae*  
• *Clostridioides difficile* | Accelerate the development of a vaccine for these pathogens |
| Moderate | AMR priority pathogens for which a vaccine candidate has either been identified in early clinical trials or been identified as a feasible vaccine target during expert review. Vaccines may be feasible solutions to target AMR infections, with moderate feasibility of vaccine development | • *Enterotoxigenic Escherichia coli* (ETEC)  
• *Klebsiella pneumoniae*  
• Non-typhoidal *Salmonella*  
• *Campylobacter* spp.  
• *Shigella* spp. | Continue the development of a vaccine for these pathogens and expand knowledge of potential for vaccine impact and other tools to combat the AMR threat |
| Low | AMR priority pathogens for which no vaccine candidate has been identified in clinical development and therefore vaccines are not a feasible solution to target AMR infections in the foreseeable future, hence vaccine development feasibility is low | • *Acinetobacter baumannii*  
• *Pseudomonas aeruginosa*  
• *Enterobacter* spp.  
• *Enterococcus faecium*  
• *Staphylococcus aureus*  
• *Helicobacter pylori* | Research and investment should explore alternative methods of control, including treatments and effective infection prevention, and should ensure access to clean water and adequate sanitation and hygiene facilities |

Figure 2. Summary of pipeline findings and recommendations for priority AMR pathogens.21
vaccines in advanced clinical development including extraintestinal pathogenic Escherichia coli, Salmonella enterica ser. Paratyphi A, Neisseria gonorrhoeae, and C. difficile. Group C, consisting of pathogens with vaccines in earlier phases of clinical development; enterotoxigenic E. coli, Klebsiella pneumoniae, non-typhoidal Salmonella, Shigella spp. and Campylobacter spp. Finally, Group D includes pathogens with either no candidates in clinical development or those assessed by expert consultations to have low development feasibility. These are Pseudomonas aeruginosa, Acinetobacter baumannii, Staphylococcus aureus, Helicobacter pylori, Enterococcus faecium, and Enterobacter spp. WHO published the analyses in a 2022 report (ref) calling for the rapid introduction and expansion of already existing vaccines at country level, acceleration of clinical trials for pathogens with vaccines in late-stage development, research to understand the value of vaccines against pathogens in early stages of clinical development, and alternative ways to tackle AMR for pathogens with no vaccines in clinical development.

Despite the aforementioned WHO, Wellcome Trust and Gavi reports and analyses, the impact of vaccines on AMR is often not incorporated into evaluations of vaccine value. This means vaccines are often undervalued in terms of their impact on AMR across the public health community. To systematically incorporate the impact of vaccines on AMR, a value attribution framework is needed to guide ways of articulating vaccine impact on AMR. To this end, WHO is developing a value attribution framework for the impact of vaccines on AMR. The document considers the value of vaccines for 30 pathogens including bacteria, viruses, fungi and parasites, across five criteria: (1) vaccine averted AMR health burden, (2) vaccine averted AMR economic burden, (3) vaccine averted antibiotic use, (4) sense of urgency to develop antimicrobial approaches, and (5) resistant pathogen impact on equity and social justice. The feasibility of vaccine development is being assessed for each of the 30 pathogens in scope. These pathogen-specific assessments will then be presented in the context of other available approaches to contain AMR. The overall goal of the value attribution framework is to support the prioritization of decisions and investments relating to vaccine development, introduction and use. The framework, once published, will be a platform to synthesize best available evidence for the impact of vaccines against AMR, and will highlight critical knowledge data gaps. Subsequently, this will also inform the development of a core set of evidence-based AMR interventions in the human health sector, including vaccines, that countries should consider in the revisions of their national action plans on AMR. In addition, the role of vaccines in preventing AMR will be included as a key intervention within the new “people-centered framework” for addressing AMR in the human health sector that is being developed by WHO.

To ensure vaccines are optimally utilized to reduce the emergence and spread of AMR, WHO is engaging stakeholders in policy and decision-making at global and national levels. At the global level, WHO will work closely with the Strategic Group of Experts on Immunization (SAGE) to ensure the value of vaccines against AMR is systematically considered whenever decisions relating to vaccine introduction and use are made. To drive impact at the country level, WHO is working with countries and implementing partners to consider scaling up investment in vaccines as part of their National Action Plans on AMR, and to include indicators on immunization coverage within their national action plan implementation monitoring and evaluation frameworks. The proposed indicators are based on the indicators included in the monitoring and evaluation framework of the Global Action Plan on AMR that monitor immunization coverage for pneumococcal conjugate vaccine (PCV), rotavirus vaccine, measles-containing vaccine, and Haemophilus influenzae type b containing vaccine (Hib). However, only a handful of national action plans on AMR appropriately include vaccines. To improve this, governance, coordination and implementation of the national action plans on AMR should be closely aligned with national immunization programs, budgets and strategies.

AMR is a complex global problem that requires multiple approaches to prevent and contain it, including vaccines. As such, WHO has outlined key strategies for vaccines to contribute fully to the prevention of AMR; evaluated the pipeline of vaccines in development for WHO priority pathogens; continues to estimate the value of vaccines in preventing AMR; and works with member states, academic institutions, non-governmental organizations, the pharmaceutical industry, and funders to better understand and communicate the impact of vaccines on AMR and implementation at country level. However, there remain challenges and opportunities for vaccines to achieve its full potential in preventing AMR. Expansion of equitable coverage to licensed vaccines should be accelerated; recommendations and guidance in vaccine and AMR sectors should include the role of vaccines in preventing AMR; and awareness of the role of vaccines in preventing AMR should be increased through communication, education and training; the funding for research and development (R&D) of new vaccines needs increasing; and lastly, research to produce data on vaccine impact on AMR, especially in low-resource settings should be prioritized.

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Disclaimer
The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

References


WHO Full Value of Vaccines Assessment (FVVA)

Draft template

‘Vaccines should be seen not only, or even primarily, as a cost that increases public health budget needs, but as an investment with sustainable, long term, and large-scale impact.

Accurately measuring the full public health value of vaccines will increase the likelihood of adopting this approach by increasing political will and allowing for more accurate prioritization of available resources’ (Gessner et al. 2017).

The purpose of this WHO Full Value of Vaccines Assessment (FVVA) is to describe the global public health rationale for developing vaccines against **pathogen(s) X**, to inform decision making regarding short- and long-term investment in their development. The FVVA can be used as a basis for the development of more detailed investment or business cases.

*This template has suggested headings and sections. For some vaccines, a partial FVVA can be performed and other sections can be added.*

*Guidance notes on possible content for each section are in brown italics and can be reduced in length.*

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1 Executive summary and public health value statement

Summarise key points and conclusions from the FVVA.

1.1 Public health value statement

Summarize the vaccine(s) in question.

Table 1. Key characteristics, features, values and beneficiaries of ***X*** vaccine

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<thead>
<tr>
<th>Vaccine characteristics</th>
<th>Notes</th>
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<tr>
<td></td>
<td>Some WHO PPCs and FVVAs will list more than one vaccine and/or more than one indication.</td>
</tr>
<tr>
<td>Value</td>
<td>Include which groups will benefit from the vaccine.</td>
</tr>
<tr>
<td>Status of development</td>
<td>Include whether the vaccine is being developed or tested in LMICs.</td>
</tr>
<tr>
<td>Market features</td>
<td></td>
</tr>
</tbody>
</table>
2  WHO public health value assessments for vaccines in early stage development

This will become standard text for future WHO Initiative for Vaccine Research (IVR) FVVAs. FVVAs developed in collaboration with other groups might have different content and focus. WHO FVVAs are evidence based and not uncritical advocacy documents. The definition and methodology for their creation is new for WHO and it is likely that they will evolve over the next few years.

World Health Organisation’s (WHO’s) FVVAs for vaccines are published by WHO Initiative for Vaccine Research (IVR).

The mission of WHO IVR is to accelerate the development and optimal use of safe and effective vaccines and related technologies. Priority research focus areas include

- Promotion and acceleration of vaccine candidates in early development, towards licensure;
- Research to generate evidence to inform policy recommendations for candidate vaccines at advanced stages of development.

WHO FVVAs describe for candidate vaccines in **early development**, the value of a vaccine for a wide range of possible stakeholders, with a particular focus on public health value, especially in low- and middle-income countries (LMICs). For WHO FVVAs, early development is defined as ‘up to and including phase II clinical trials’.

Evaluation of the public health value considers the population impact of a vaccine and encompasses measures of community benefits against a range of outcomes. (Gessner et al. 2017) These values might be broader than the claims of efficacy in a vaccine’s license.

Like most WHO preferred product characteristics (PPCs) for vaccines, WHO FVVAs for vaccines aim to summarise:

- The unmet public health need for a vaccine, but with more quantification and stratification (for example by gender, occupation, at country level) than is contained in the PPCs, especially for LMIC populations;
- The type of vaccines that are likely to be of highest value for global public health use, especially in LMICs, but FVVAs might contain a more detailed analysis;
- The value for different stakeholders, but with additional quantification and stratification of potential markets for the vaccine;
- The pipeline of vaccines in development, but FVVAs might include more detail than the PPC regarding the technical feasibility of development, including estimating timescales to licensure and considerations for uptake;
- Key issues in the development of the vaccine and important gaps in knowledge, but for different stakeholders. FVVAs can also describe research studies and analyses that might address some of these gaps.

Unlike PPCs, FVVAs aim to:

- Estimate the cost of vaccine R&D and then the costs of implementation for the vaccine;
- Provide some guidance about possible pricing of vaccines, based on stakeholder feedback and economic analysis;
- Estimate potential vaccine impact in relation to the PPCs.

WHO FVVAs complement, but do not supersede, existing WHO guidance on vaccine development.
WHO FVVAs do not necessarily aim to be as comprehensive and detailed as value assessments compiled by other organisations. They do aim to assess the global value assessments by including the value of LMIC markets.

They do not name, compare or rank individual candidate products or product developers.

2.1 Target audiences and use of WHO FVVAs

The primary target audience for WHO PPCs and FVVAs is any entity intending to eventually seek WHO policy recommendation and prequalification (PQ) for their products.

Communication of the potential value of vaccines, including public health value, can be useful to all those involved in vaccine development activities. This can include academic groups, small biotech companies and funders. If WHO FVVAs use only data and opinions in the public domain, WHO FVVAs can be shared widely and published online.

The WHO PPCs and WHO FVVAs, taken together, aim to encourage innovation and the development of vaccines for use in settings most relevant to global unmet public health need. They can help raise further interest and funding to address key gaps in knowledge and to support vaccine development, especially for LMIC use.

2.2 Criteria for selecting vaccines for FVVAs

Selected disease areas for WHO PPC and FVVA development are identified by the WHO Product Development for Vaccines Advisory Committee (PDVAC) based on an unmet public health need for vaccines, and a brief assessment of technical feasibility and suitability for use in LMICs.

2.3 Methodology for FVVA development

For most vaccines, a WHO PPC will have been prepared beforehand. FVVAs complement and extend the scope of WHO PPCs (see above) and will likely refine the guidance to be included in future PPC iterations.

WHO FVVAs are drafted by a WHO secretariat, based on literature review, input from meetings of experts and stakeholders, working groups and wider consultation, including by WHO committees such as PDVAC. WHO FVVAs can also be informed by specially commissioned short projects to address key and amenable gaps in knowledge. The detailed analysis, including methodology, to support the conclusions in a FVVA can be in standalone documents and, ideally, shared in the public domain including in peer-reviewed publications.

Both PPCs and FVVAs can be updated in the event of product or technology innovations, or any other change in the identified need or R&D landscape.
3 The global public health need for the vaccine

This section summarises the unmet public health need (i.e. burden of disease and available healthcare), where it is located, and important trends over time. It can introduce the level of complexity of the problem to be addressed by the vaccine.

It should summarise the problems to be addressed (referring to PPCs) and take note of expected future trends. It should cross-reference to the detailed analysis, including modelling, in later sections.

3.1 Disease description

The main features of the burden of disease with mechanisms and heterogeneity. For more detailed analysis, see Section 8.

Is this a candidate for eradication or elimination?

Table 2. Main features of the infection and disease

Suggested features are shown in the table. The notes could include whether the data are current and from the most appropriate sources or whether they need updating.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Summary and evidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age distribution</td>
<td></td>
<td>Comment on heterogeneity, including in transmission.</td>
</tr>
<tr>
<td>Anti-microbial resistance (AMR) issues</td>
<td></td>
<td>This might be in associated infections.</td>
</tr>
<tr>
<td>Disruption of health systems</td>
<td></td>
<td>Include humanitarian emergencies if relevant.</td>
</tr>
<tr>
<td>Epidemic and outbreak potential</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender distribution</td>
<td></td>
<td>Comment on heterogeneity, including in transmission.</td>
</tr>
<tr>
<td>Herd immunity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morbidity</td>
<td></td>
<td>Include severity and sequelae</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td>Include case fatality ratio (CFR).</td>
</tr>
<tr>
<td>Natural immunity</td>
<td></td>
<td>Include duration of protection.</td>
</tr>
<tr>
<td>Predictability of disease occurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmission</td>
<td></td>
<td>Include heterogeneity.</td>
</tr>
<tr>
<td>Types, strains and serotypes</td>
<td></td>
<td>After use of a vaccine, could there be pathogen replacement?</td>
</tr>
</tbody>
</table>
3.1.1 Key interactions with other infections or diseases/conditions

*Short statement of pathogens and conditions linked to the vaccine-preventable infection or disease, including*

- Socio-cultural determinants that have a significant impact on the condition. Refer to any systematic analyses of these;
- Causal associations that might be addressed by vaccination, e.g. viruses that predispose to bacterial disease; or associations between the infection and malnutrition or chronic diseases.

3.1.2 Other non-healthcare impacts of the infection, including equity

*If possible, introduce non-healthcare impacts of the infection or conditions, e.g. loss in productivity, requirements for additional childcare. These will be described in more detail in Section 11.3.*

Equity is a fair opportunity for everyone to attain their full health potential regardless of demographic, social, economic or geographic strata.\(^1\) Vaccination is also an essential element for promoting equity. (Gessner et al. 2017)

**Table 3. Equity issues**

<table>
<thead>
<tr>
<th>Equity</th>
<th>Evidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health equity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Economic equity</td>
<td>Such as reducing medical and nonmedical costs associated with cases of vaccine-preventable diseases.</td>
<td></td>
</tr>
<tr>
<td>Social equity</td>
<td>Such as access to the health care system.</td>
<td></td>
</tr>
<tr>
<td>Vertical equity</td>
<td>Such as vaccines for diseases of poverty.</td>
<td></td>
</tr>
</tbody>
</table>

3.1.3 Geographic differences in burden of disease and where need is unrecognised

*Summarize what is known.*

Does climate change play a role in epidemiology?

3.2 Current methods of surveillance, diagnosis, prevention and treatment

*Brief introduction to the healthcare use that is currently linked to the infection or associated condition. This can include surveillance; vaccine use or other prevention (could be anti-microbial use); treatment and care (of all kinds including chemotherapeutic prevention, palliative); behaviour change that requires healthcare input etc. Cross-reference to Section 0 where these will be covered in more detail.*

Comment if they are effective alternatives to the vaccine or could be used alongside it. Are they likely to be, able to address needs in LMICs?

If there are existing or related vaccines, why can’t they address all need (or not in specific contexts), especially in LMICs?

Table 4. Surveillance, diagnosis, prevention and treatment of **X**

<table>
<thead>
<tr>
<th>Status in LMICs</th>
<th>Status HICs</th>
<th>Extent to which they meet the global need</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance of infection and conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention of acquiring infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention of transmitting infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of symptoms</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.3 Key gaps in knowledge or research evidence

Table 5. Gap analysis and prioritization

<table>
<thead>
<tr>
<th>Area</th>
<th>Gap in knowledge</th>
<th>Notes and prioritization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>State the gap and comment on the impact on the development or use of the vaccine.</em></td>
<td><em>Include references where possible.</em></td>
</tr>
</tbody>
</table>
4 **X** vaccine - a strategic priority for WHO

This section summarises why the vaccine is important to the WHO and should include links to relevant global public health initiatives and documents. It might be useful to refer to the stakeholder analysis (Section 5).

Are there any strategic global health goals established for **X**?

Have any of the following global activities been completed, or are they underway or in planning:

- Portfolio management processes;
- Programmes for elimination or eradication;
- Prioritisation by other global organisations;
- Product development partnerships;
- Advanced market commitments;
- Other relevant WHO initiatives;
- Other relevant PPCs or FVVAs.

4.1 WHO Preferred Product Characteristics (PPCs)

Summarize key messages of the WHO PPCs for the vaccines, including over-arching goals, prioritised indications, target populations and prioritised outcomes. These could form an appendix.

Will the scope of this FVVA go beyond that of the PPCs and, if so, why? It might be because of a strong high-income country (HIC) market or the development of related vaccines with non-prioritised indications or target groups, for example travel vaccines.
5 Stakeholder analysis and involvement

List types of stakeholders likely to have special interests in the vaccine, and if known, strategies to engage with them in the process of defining PPCs or FVVAs. This can help WHO, and others, to identify key groups and individuals to contact. It can also help people define key messages and routes of communication.

Typical stakeholders for R&D (for vaccines) include

- Public and private funders and donors;
- Developers (large pharma, biotech and academic) and manufacturers;
- Global and national policymakers including WHO;
- National/global advocacy groups including in countries with high disease burden.

Other stakeholders:

- Households;
- Third-party payers;
- Government (such as ministries of health, finance, military);
- Donors;
- Innovators;
- Society as a whole.

Stakeholders can be sub-divided into:

- Global;
- WHO regional;
- Sub-regional;
- HICs, UMIC, LMIC and LICs;
- Individual countries.

Stakeholder interests can include

- Development of the vaccine;
- Procurement (in some cases including for stockpiles) and introduction;
- Sustaining the current investment;
- Demonstrating the vaccine’s return on investment.

5.1 Key gaps in knowledge or research evidence

Table 6. Gap analysis and prioritization

<table>
<thead>
<tr>
<th>Area</th>
<th>Gap in knowledge</th>
<th>Notes and prioritization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>State the gap and comment on the impact on the development or use of the vaccine.</td>
<td>Include references where possible.</td>
</tr>
</tbody>
</table>
6 Development of the vaccine

This section should review briefly the scientific feasibility of developing an effective vaccine of public health value. The next section will evaluate the status of the technology area. For both sections, it might be informative to refer to knowledge gained from related ‘benchmark’ vaccines.

6.1 Biology of the vaccine

This might include

- Does natural infection impart immunity (see Section 3.1)?
- Knowledge of pathology of the infection (see Section 3.1);
- Complexity of interactions with other pathogen (see Section 3.1.1);
- Mechanisms of protective immunity;
- Knowledge of molecular biology of the pathogen;
- Knowledge of target antigens;
- Future approaches, and general advances in vaccinology expected or possible.

6.2 Technical platforms under consideration

Summarize the advantages and disadvantages of different vaccine technology platforms that might be used for the vaccine (e.g. live-attenuated compared with inactivated vaccines; subunit compared with nucleic acid). Are adjuvants likely to be needed? Cross reference to Section 7, for assessment of the vaccine pipeline.

6.3 Preclinical development: key issues

Briefly identify some of the key strengths and challenges in preclinical development of the vaccine, for example:

- Animal models – are they good or bad models of disease, and useful as predictors of efficacy?
- Availability of harmonised assays and standard reagents.

6.4 Clinical development and regulatory pathway: key issues

Discuss the key factors that might assist or hinder clinical development of the vaccines, see Table 7.

Table 7. Key issues in clinical development

<table>
<thead>
<tr>
<th>Issues and evidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarkers</td>
<td></td>
</tr>
<tr>
<td>Clinical endpoints</td>
<td>For example, will some clinical endpoints require very large trial design.</td>
</tr>
<tr>
<td>Correlates of protection</td>
<td></td>
</tr>
</tbody>
</table>
6.5 Vaccine efficacy: key issues

*Summarise factors that might affect the efficacy of vaccines as measured in randomised controlled trials (RCTs; Table 8), (Gessner et al. 2017).*

**Table 8. Factors that can affect vaccine efficacy**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Issues and evidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local epidemiological situation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geography</td>
<td></td>
<td><em>For example, rotavirus vaccine trials in HICs compared with LMICs.</em></td>
</tr>
<tr>
<td>Inclusion and exclusion criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbial flora or parasite burden</td>
<td></td>
<td><em>Especially for enteric vaccines.</em></td>
</tr>
<tr>
<td>Pre-existing immunity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotype distribution of the pathogen</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6.6 Vaccine safety; key issues

Briefly summarize possible safety concerns, including potential rare safety issues that might not be identified in early-stage or short-term clinical trials, but might require post-marketing surveillance.

6.7 Implementation: key issues

Who are the likely target populations?

What are assumptions on use case? For example, will the vaccine be used for routine childhood immunisations, in mass vaccination (including campaigns and outbreak response), for adolescents, pregnant women, adults, travellers or older people (refer to Section 9).

What target coverage rates are needed to achieve desired outcomes? What are the challenges for reaching target coverage (refer to Section 9)?

What are the likely formulation, presentation and dosing schedules? What are the implications of these for use (cross-reference to later sections on costs)?

Will new or existing diagnostic tests be required?

Would the vaccine be best used as part of an integrated management strategy, for example with environmental control and hygiene measures (Gessner et al. 2017)? Might need to refer to Sections 10 and 11.

6.8 Key gaps in knowledge or research evidence

<table>
<thead>
<tr>
<th>Area</th>
<th>Gap in knowledge</th>
<th>Notes and prioritization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>State the gap and comment on the impact on the development or use of the vaccine.</strong></td>
<td>Include references where possible.</td>
</tr>
</tbody>
</table>
7 Assessment of the vaccine development pipeline

This section should review the status of the current vaccine development pipeline. Vaccines in clinical development should be included. It might also be appropriate to review the portfolio of candidates in preclinical development.

Describe the pipeline in only general terms. WHO does not aim to rank or prioritise individual vaccines in development. Target product profiles (TPPs) are not required but might be available and, if so, could be included or referenced, so they can be referred to by other sections.

Comparisons can be made:

- By strategy within the general area of vaccine development;
- By vaccine type for the indication, for example live compared with subunit vaccine, or by antigen selected;
- By indications: for example, prophylactic vaccines for infant or adolescent use compared with therapeutic vaccines for mainly adults.

It should identify, where possible:

- The number of candidates at each stage of the pipeline;
- Diversity and robustness of the portfolio;
- Have the current candidates been informed by what was learned in earlier studies?

In general terms, discuss who the developers are:

- Do they have capacity to take the vaccine to license and supply at scale?
- Are they all in HICs?
- The likely timeframe to license, and, where relevant to WHO PQ;
- The probability of success;
- The major risks and challenges in development and commercialization;
- What could de-risk development, e.g. further development of correlates and biomarkers; see also Section 11.5.

7.1 Pipeline summary

Figure 1. Current vaccine landscape by stage of development

It might also be informative to summarize the progress and stage of failure of candidates no longer in development.
Table 10. Summary of vaccine candidates no longer in development

<table>
<thead>
<tr>
<th>Vaccine name</th>
<th>Type and composition</th>
<th>Development stage reached</th>
<th>Summary of results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*It might also be informative to briefly discuss/illustrate the location of developers involved to highlight (lack of) LMIC involvement:*

Table 11. Portfolio of vaccines in development by country

<table>
<thead>
<tr>
<th>Vaccine name</th>
<th>Developer</th>
<th>Country involved and if in HIC or LMIC</th>
<th>Development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 7.2 Pathway and timescale to licensure

*Estimating the steps and time to licensure can provide an indication of the time horizons that might need to be considered for activities such as vaccine impact modelling (Section 9). This could be as a simple, top-level GANTT chart (Figure 2). It might be useful to briefly comment on benchmark vaccines and timelines for current or previous vaccines in the pipeline as supporting data for the timeline.*

**Figure 2. Top-level illustrative timelines for vaccine **X** development**

![GANTT chart](image)

### 7.3 Benchmarking against other vaccines

*Predicting development timelines is difficult. It can be useful, therefore, to see if lessons can be learned from other relevant vaccines. For some vaccines, where there might be limited direct data, it might be helpful to use benchmark vaccines as examples, explaining why they have been chosen and their possible strengths and weaknesses (Table 12). For example:*

---
• Refer to examples of vaccines that are relatively difficult to manufacture but are still produced at scale and are affordable;
• Refer to vaccines that have a similar mechanism of action, even if for a different pathogen, that have been developed and approved;
• Refer to vaccines that were initially expensive but are now much more affordable.

Table 12. Development of other vaccines with issues in common with vaccine **X**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Rationale for comparison</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 7.4 Probability of success

Briefly list major (and general) risks and challenges in development. Many of the risks will be candidate-specific so outside the scope of this WHO analysis.

Depending on the stage of development, it might be appropriate to list ways of de-risking development including

- Funding the earliest stages of development to increase the numbers and breadth of candidates that could enter the later stages;
- Developing novel clinical trials designs;
- Portfolio development to share and prioritize critical resources for the most promising candidates and to reduce the number of similar candidates being tested at the same time.

A qualitative discussion of the key hurdles facing development will probably be sufficient. If required, a quantitative method for estimating the probability of a candidate vaccine progressing through the various stages of development could be used or cited; for example, the Monte-Carlo simulation analysis tool. (AERAS and Tuberculosis Vaccine Initiative 2012)

### 7.5 Key gaps in knowledge or research evidence

Table 13. Gap analysis and prioritization

<table>
<thead>
<tr>
<th>Area</th>
<th>Gap in knowledge</th>
<th>Notes and prioritization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>State the gap and comment on the impact on the development or use of the vaccine.</td>
<td>Include references where possible.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
8 Estimation of disease burden and transmission

In addition to the introductory description of total disease burden in Section 3, more detailed data and/or estimates of the burden of disease could be included, relevant to the prioritised indications in the PPCs and in this FVVA.

The burden of disease can be reported in a number of ways, including deaths, cases, long-term sequelae or ‘outbreaks’.

The data can be stratified by geographic regions of interest or target populations, as informed by stakeholders.

8.1 Public health inputs and output for modelling

Inputs could include data from 183 countries (if appropriate) and for each year from 2020 to 2050.

8.2 Transmission modelling

This is used for some studies of the impact of vaccines (see Section 9).

8.3 Key gaps in knowledge or research evidence

Table 14. Gap analysis and prioritization

<table>
<thead>
<tr>
<th>Area</th>
<th>Gap in knowledge</th>
<th>Notes and prioritization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>State the gap and comment on the impact on the development or use of the vaccine.</td>
<td>Include references where possible.</td>
</tr>
</tbody>
</table>
9 Defining the market for the vaccine

A strategic market assessment, over a period of 10 to 20 years, could be provided. (AERAS and Tuberculosis Vaccine Initiative 2012) This is usually based on stakeholder interviews. It can describe potential LMIC markets, which might not be familiar to some developers used to targeting very defined markets, especially in only HICs. This information might be referred to in Section 12.

When available, quantitative data from market analysis can be useful in modelling the impact of use of the vaccine and for cost analyses.

To predict the market globally, or by WHO region, or individual country it can be useful to have:

1. A draft target product profile (see Appendix 4);
2. Location of developers of the vaccine – and their intentions for trial settings and licensing;
3. Possible acceptability issues, including safety;
4. Disease burden (Section 8);
5. Demographics;
6. The status of its health systems including capacity for introduction and use of the vaccine;
7. Awareness of the health issue, advocacy and political will;
8. Its history of adoption of similar vaccines;
9. Its gross national income per capita;
10. Its access to donor support (e.g. GAVI).

9.1 Potential market segments

World Bank income-based categories, and LMIC markets are typically used and can be further categorized into public and private. For some vaccines, other segments might include routine use, and travel and military markets. The vaccine characteristics might differ between markets and be different to those described in WHO PPCs.

9.2 Market validation

Validation of the concept of the vaccine against a number of potential markets is useful. Typically, public and private healthcare providers and their customers are interviewed (by survey, as individuals or in focus groups) and in several different countries of interest. This will develop an evidence base to encourage investment in R&D and, at a later stage, facilitate adoption and uptake.

9.2.1 Scenarios of use

The vaccine can be evaluated for different scenarios of use, including properties, target populations and immunisation delivery platform. Questions could be addressed such as:

- Benefits;
- Associated costs;
- How strong the potential market is for each scenario?
- Would existing healthcare spending be re-allocated to purchase the vaccine?
- Can any identified obstacles to use be overcome?
• Are various pricing ranges deemed affordable?
• Likely time to introduction after WHO PQ;
• Will in-country studies be needed before the vaccine was used?

People and stakeholders to be surveyed can include

• Ministry of health officials (department heads, preventive medicine, planning or finance, and program managers of immunization program);
• Ministry of finance officials;
• Professional associations;
• Leading academics and researchers;
• National Immunization Technical Advisory Groups (NITAGs);
• International technical agency officials;
• Health officials from local governments.

9.2.2 Settings for use

The settings most likely to license and use the vaccine, and to benefit from its use, need to be identified and summarized. This could be based on data on burden of disease.

9.2.3 Market-based efficacy thresholds and non-interference

Interviews with stakeholders can inform on the sensitivity of purchase intentions and vaccine uptake to different levels of vaccine efficacy.

9.2.4 Market penetration

Interviews with stakeholders can inform on the sensitivity of purchase intentions and vaccine uptake to different pricing levels. Estimates of sensitivity of uptake to price could be made and could consider when a WHO PQ vaccine might be available and recommended. The likelihood, and impact or a differential pricing approach could also be considered.

9.2.5 Hurdles in acceptability in key markets

Potential obstacles to introduction of the vaccine should be briefly summarized. These might include

• Low awareness of the disease burden and low demand for prevention;
• The need for complex dosing;
• Perceived (or actual) low or unpredictable efficacy;
• Pricing that might not seem affordable or competitive;
• Side effects and safety issues;
• Difficulty delivering the vaccine to the target population.

9.2.6 Forecast date of introduction

This is an estimate of the base year when a vaccine will be WHO PQ and available for public health use in LMICs, even though not all countries will immediately start to use the vaccine. Reasons for delayed introduction should be identified where possible, and might include
• Lack of capacity to introduce the vaccine and also carry out surveillance;
• Competing priorities, such as civil unrest and economic instability;
• Preference to focus health budgets on other priorities.

To predict rates of uptake, especially accelerated country introduction, a ‘looks-like’ analysis can be used, based on:

• Historical uptake of similar vaccines;
• Disease burden data;
• Capacity in the relevant health service;
• Political will.

Ideally, a base case and conservative case will be established, with the number of countries and whether they are HIC, UMIC, LMIC or LIC. Countries can be divided into:

• Early introduction countries: perhaps in first five years after WHO PQ. For vaccines, early adopters drive the majority of revenues within the global market. Some will use the vaccine in sub-populations only, for example in healthcare workers (HCWs), or high-risk populations.
• Mid-introduction countries: additional numbers in years 6 to 10;
• Late-introduction countries: after 10 years (or not at all).

Estimates for India and China are often determined and presented separately.

Summarize any other issues that might affect access and supply, for example the number and location of manufacturers.

### 9.3 Strategic vaccine demand forecast

The strategic demand forecast (number of doses per year, in what time frame) needs to determine whether it is possible to introduce an affordable vaccine with a sustainable supply. High initial demand can be challenging for manufacturers to meet, during scale up. Some demand forecasts estimate how many manufacturers, and working at what capacity, will be required to meet demand.

Report the assumptions used, which can include target population, introduction year, vaccine coverage rate, doses per course, wastage factor and countries’ willingness and ability to adopt.

#### Table 15. Likely timescale for introduction of the vaccine

<table>
<thead>
<tr>
<th>Country</th>
<th>Year of introduction</th>
<th>Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 9.4 Key gaps in knowledge or research evidence

#### Table 16. Gap analysis and prioritization

<table>
<thead>
<tr>
<th>Area</th>
<th>Gap in knowledge</th>
<th>Notes and prioritization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area</td>
<td>Gap in knowledge</td>
<td>Notes and prioritization</td>
</tr>
<tr>
<td>------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td></td>
<td><em>State the gap and comment on the impact on the development or use of the vaccine.</em></td>
<td><em>Include references where possible.</em></td>
</tr>
</tbody>
</table>
10 Impact of the vaccine on burden of disease and transmission

Where available, summarise the conclusions of modelling the impact of use of the vaccine on preventable burden of disease and other factors. Where no formal modelling has been performed, a list of factors (and possible ranges) that influence vaccine impact could be included. Cost effectiveness and economic aspects will be covered in Section 11.

Health impact of the vaccine can be reported as: deaths averted, cases and sequelae averted or DALYs averted, by the numbers vaccinated per year.

Include the factors included and assumptions made, which can include incidence rate, CFR, direct vaccine efficacy rate, herd effects, coverage rate, vaccine duration and frequency, target populations.

10.1 Measurement of vaccine benefits

The benefits of vaccines can be measured in several ways (see Section 11 for economic measurements): extended cost effective analysis (ECEA); incremental cost effectiveness ratio (ICER); multi-criteria decision-making processes; quality adjusted life years (QALY); social rates of return; social welfare function. (Gessner et al. 2017). Summarize the measures used and the data available (Table 17).

Table 17. Measures used to assess vaccine benefits

<table>
<thead>
<tr>
<th>Measure</th>
<th>Data</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine effectiveness (VE)</td>
<td></td>
<td>The percentage of an outcome reduced by the vaccine. Can be used to calculate VPDI when multiplied by background disease incidence.</td>
</tr>
<tr>
<td>Vaccine preventable disease incidence (VPDI)</td>
<td></td>
<td>Also known as the vaccine attributable rate reduction or the incidence rate reduction.</td>
</tr>
<tr>
<td>Number needed to vaccinate (NNV)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10.2 Key gaps in knowledge or research evidence

Table 18. Gap analysis and prioritization

<table>
<thead>
<tr>
<th>Area</th>
<th>Gap in knowledge</th>
<th>Notes and prioritization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>State the gap and comment on the impact on the development or use of the vaccine.</td>
<td>Include references where possible.</td>
</tr>
</tbody>
</table>
11 Economic analysis of the value of the vaccine

WHO is developing an Accounting Framework for Economic Evaluation, with an adaptation for vaccines and immunization programmes in preparation. This can be used to guide the choice of methodology for economic analysis.

Types of analyses reviewed include

- Budget impact analysis (BIA);
- Cost benefit analysis (CBA);
- Cost-effectiveness analysis (CEA);
- Cost of illness study (COI);
- Costing studies;
- Economic surplus analysis;
- Effectiveness studies;
- Extended cost-effectiveness analysis (ECEA);
- Fiscal impact modelling;
- Optimization modelling;
- Investment cases.

The following questions should also be considered when assessing the public health value of vaccines: (1) what evaluations should be considered? (2) when should they be done pre- or post-licensure? and (3) who will see this as their responsibility? (Gessner et al. 2017)

11.1 Economic analysis: methodology

Summarize the methodologies used and the rationale for their selection.

11.2 Economic analysis: summary of findings

This section of the FVVA will summarise key conclusions, probably using a selection of figures; these should be understandable by a broad audience. The following section headings might be useful:

11.2.1 Disease burden costs

Can refer to the earlier section on health burden (Section 8). The costs can be direct or indirect.

11.2.2 Development costs

Summarize total R&D, manufacturing and marketing costs (Table 19). These include

- The cost of discovery research;
- Clinical trials;
- Process development;
- Manufacturing;

2 Raymond Hutubessy, WHO IVB, personal communication.
• Regulatory processes;
• Marketing and post-marketing activities.

For vaccines, estimating development costs is very challenging; there is no known reliable method. Benchmarking to other, similar, vaccines might be useful.

Table 19. Estimated costs of **X** vaccine development

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cost (US$)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery and pre-clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 1 (or 1 and 2a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 2 (or 2b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process development</td>
<td></td>
<td>Could include early process development as well as development and scale-up of the final process.</td>
</tr>
<tr>
<td>Regulatory filings and approvals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post marketing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Some estimations of development costs can include the total R&D expenditure of the organization, including development costs of candidates that fail. It should be clear what is included in the estimation.

Some economic evaluation methods will not include R&D costs, regarding them as ‘sunk costs’ and, therefore, not relevant to the calculation.

11.2.3 Delivery costs

This taken to mean the costs associated with getting a vaccine to the recipient. They can also be referred to as: deployment costs; health systems cost of delivering the vaccine, and operational cost. Typically, they include costs associated with:

• Cold chain;
• Training and supervision;
• Vehicles and transport;
• Social mobilization and awareness raising;
• Surveillance;
• Monitoring and evaluation;
• Waste management;
• Overhead.
Estimates can be derived from models such as Global Immunization Vision and Strategy (GIVS), which is based on target countries’ financial sustainability plans or comprehensive multi-year plans (cMYPs).

11.2.4 Vaccine price

Pricing is a key driver for future revenue by developers of vaccines and also as part of the calculation of total procurement costs. The estimated prices can be derived from two sources:

- A review of historical prices for similar vaccines launched in HICs, middle income countries (MICs), and low income countries (LICs). This can be used as an indicator of ‘what the market will bear’;
- Crude estimates of the vaccine’s ‘cost of goods’ (COGs), based upon the technology and manufacturing processes used in its production.

Alternatively, an estimate can be made for a solution space, defined as prices that represent a good investment case for donors and countries and at the same time are a good business case for suppliers.3

Prices can be summarised as price per schedule or per dose.

11.2.5 Strategic demand forecast

Summarize the number of vaccine doses demanded, with assumptions about the target population, vaccine coverage rate and the country’s willingness to pay and ability to adopt the new vaccine. Demand can be summarised as doses per year by a specified date and stratified by target group.

11.2.6 Cost of goods estimates

Broad assumptions about manufacturing costs can be made. For example, manufacturing using cell culture can double the COGs compared with using recombinant technology in bacteria. (AERAS and Tuberculosis Vaccine Initiative 2012) It is still difficult, however, to make accurate estimates for COGs when the final commercial manufacturing process has not been defined; which is the case for vaccines at early stages of development. Factors to consider include

- Fixed, variable and semi-variable costs;
- The utilization rate of the production plant;
- How long the plant is amortized (depreciation of valuation spread over time).

11.3 Impact of investment

These can be health, economic and broader public health benefits (Table 20).

Table 20. Potential broader impacts of the infection/condition and vaccine use

<table>
<thead>
<tr>
<th>Impact</th>
<th>Evidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-microbial resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consumer prices</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3 [http://www.preventpneumo.org](http://www.preventpneumo.org)
<table>
<thead>
<tr>
<th>Impact</th>
<th>Evidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term/on-going disability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease control cost</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educational and cognitive outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expenditure equity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family integrity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial protection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross domestic product (GDP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross national income (GNI);</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health care utilization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health equity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herd immunity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household integrity, disruption of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect effects on other infections or conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macroeconomic impact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outbreak control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Political disruption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public sector budget impact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual and reproductive health (SRH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social disruption absenteeism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synergy with other health interventions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word loss</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
11.3.1 Health gain

Direct and indirect, using dynamic models.

11.3.2 Health-systems strengthening

11.3.3 Healthcare costs averted

11.4 Estimation of cost effectiveness

11.4.1 Cost-benefit analysis

A cost-benefit analysis could be based on:

- Developers’ perspective: for example, costs incurred would be vaccine development costs, and the benefits would be health benefits based on vaccine impact estimate;

- Societal perspective: for vaccines, costs incurred are vaccine deployment costs. Benefits are health and economic, based on a vaccine impact estimate model. A decision could be made to exclude vaccine development costs.

Costs could be presented as:

- Cost per case averted;
- Cost per death averted;
- Cost per DALY averted.

11.4.2 Vaccine cost-effectiveness

11.4.3 Multi-criteria decision-making processes

A tool such as the Strategic Multi-Attribute Ranking Tool (SMART), as used by the US Institute of Medicine for vaccine prioritization, could be applied. Vaccine attributes are divided into eight categories. Three core values are highlighted: (a) mortality and severity of the disease, (b) vaccine safety considerations, and (c) an economic evaluation that captures the full benefits of vaccination. (Barocchi, Black, and Rappuoli 2016)

11.4.4 Summary

Typically, economists aim to compute an incremental cost effectiveness ratio (ICER), against a benchmark or threshold, to allow comparisons across competing programs. (Gessner et al. 2017)

A Social Welfare Function (SWF) and Social Rates of Return (SRR) framework could replace the QALYs and ICERs framework (Gessner et al. 2017).
### 11.5 Key gaps in knowledge or research evidence

**Table 21. Gap analysis and prioritization**

<table>
<thead>
<tr>
<th>Area</th>
<th>Gap in knowledge</th>
<th>Notes and prioritization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>State the gap and comment on the impact on the development or use of the vaccine.</em></td>
<td><em>Include references where possible.</em></td>
</tr>
</tbody>
</table>
12 Financing the development of the vaccine

Estimate, where possible, the total funding required globally for the development of the vaccine. Describe possible sources of funding and the overall funding landscape, which might include the entities listed below and in Table 22:

- Major funding institutions and agencies, from information in the public domain. These might include industry (big pharma and smaller biotech); government support; not for profit foundations:
  - Is there diversity?
  - How many are based in emerging markets, EU, India, China etc.?
  - What is the level of advocacy for the disease area?
  - Does the vaccine fit with poverty-related and neglected disease (PRND)?
- Multi-lateral initiatives, including with WHO and in product development partnerships (PDPs);
- Funding for capacity building for clinical trials, and manufacture of the vaccine. Is there funding available to support or promote commercial production in LMICs?

Table 22. Global funding landscape

<table>
<thead>
<tr>
<th>Funder (dates)</th>
<th>Basic science, discovery and preclinical development</th>
<th>Early-stage clinical development</th>
<th>Late-stage clinical development</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

12.1 Likely gaps in funding for development for use in LMICs

Provide a general description of whether current funding is sufficient to develop a vaccine with WHO PPCs and in a timely manner.

Funding might be available for the development of related vaccines with different indications, which could be adapted for use in LMICs.

Factors to consider include

- Total commercial market for the vaccine: for example, expressed in US$ over 10 years. This can help attract the attention of financing partners;
- Blended capital: public (or philanthropic) funds can be targeted at the highest risk points in development, with private sector contributing more to the most expensive parts;
- Partnership approach to financing: including PDPs;
- Expansion of public-private partnerships (PPPs);
- Incentives to target developed economies;
- Rational portfolio management approach;
• Push mechanisms to phase I trials: grants, pharma-cost sharing, venture philanthropy, and prizes. For example, technology transfer to developing countries vaccine manufacturers (DCVMs);

• Valley of death of funding into phase III trials: grant cost-sharing (through portfolio manager), debt financing, late-stage equity (impact investors);

• Pull mechanisms into licensure: market-enhancing mechanisms such as pre-advanced market commitment (AMC), with pre-defined TPPs; debt finance; evidence-based health economic data;

• Other ways to minimize development costs for manufacturers.

There might be insufficient data or opinion to describe (or publish in the public domain) the potential sources of financing the development of the vaccine. It might be necessary or useful to benchmark other similar vaccines.

12.2 Key gaps in knowledge or research evidence

Table 23. Gap analysis and prioritization

<table>
<thead>
<tr>
<th>Area</th>
<th>Gap in knowledge</th>
<th>Notes and prioritization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>State the gap and comment on the impact on the development or use of the vaccine.</td>
<td>Include references where possible.</td>
</tr>
</tbody>
</table>
13 Conclusions and recommendations

This section could include

- A summary of the estimated or perceive public health value of the vaccine;
- The commercial viability of the vaccine. Would the aim be to commercialize at least one vaccine?
- Need or desirability for a portfolio management approach, and who could do this?
- Likely portfolio development costs.

Additional detail and recommendations could include

- The potential for development and impact;
- A summary of work and data gathering in progress;
- Next steps for investors;
- Next steps for donors;
- Priority for development;
- Monitoring and data;
- Need for advocacy, especially the need for political commitment, good communication, and evidence-based decisions (e.g. technical aspects of vaccines, vaccine hesitancy and confidence); (Gessner et al. 2017)
- Need for more refined analysis.

13.1 Next steps

Provide more detail (if needed) on the key areas from the list above. Possible example headings are:

13.1.1 Activities proposed or underway to provide data for the FVVA

This section should summarise known WHO projects, requests for proposals (RFPs) and also work by other groups and funders that will generate data relevant to the FVVA.

Table 24. Activities underway or in planning linked to the FVVA

<table>
<thead>
<tr>
<th>Project area</th>
<th>Brief scope</th>
<th>Timescale to delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology: burden of disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modelling vaccine impact</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
14 References

Include peer-reviewed publications, systematic reviews, meta-analyses, other data sources, etc.


14.1 Further reading

Update and expand/reduce this list as appropriate:


Guidance about the WHO Prequalification (PQ) process and criteria by which vaccine quality, safety, efficacy and suitability for use in low and middle-income countries are assessed, in Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification: http://apps.who.int/iris/bitstream/10665/76537/1/WHO_IVB_12.10_eng.pdf

Guidance from WHO on regulatory expectations regarding clinical evaluation of vaccines can be found within Guidelines on clinical evaluation of vaccines: regulatory expectations: http://www.who.int/biologicals/expert_committee/WHO_TRS_1004_web_Annex_9.pdf?ua=1
Appendix 1. Abbreviations

To be completed.
Appendix 2. Glossary

Beneficiary
An individual, group of individuals, organisation or system who/that will benefit in any way from the vaccine being developed or used.

Business case
Similar to an investment case, a quantitative justification for investment in a fixed time period but with the justification targeted towards stakeholders with a profit interest in realizing the value. It focuses primarily on net revenues to establish its case and, secondarily, on the public health rationale. The pharmaceutical industry tends to focus on probability-weighted net present value, which will be very difficult or impossible for WHO to determine for vaccines at an early stage of development.

Disease burden
An indicator of health outcome. It can be expressed in many ways, such as the number of cases (e.g. incidence or prevalence), deaths, or disability-adjusted life years lost (DALYs) associated with a given condition. Preventable burden of disease: the proportion of the burden that the vaccine could prevent.

Integrated product development plan (IPDP)
Developed from the TPP, the IPDP summarizes all the multidisciplinary activities required to complete clinical and non-clinical development of the candidate product, as well as chemistry, manufacturing and controls (CMC) and regulatory activities. Definition of the targets and key claims of the product. The IPDP includes the estimated timelines and budgets for all activities.

Investment case
There are many definitions and uses of investment case, from the very general to specific economic evaluation methodology. In brief, investment cases can communicate information that facilitate the understanding of relevant costs, benefits, risks and other various factors associated with the investment. As applied to immunization, they usually include a description of disease and economic burden; vaccine price and quantity demanded; cost of investment; impact of investment (health, economic and broad), and other considerations.

Landscape analysis
Part of a business case. Typically, it uses literature searches and information obtained under confidential disclosure agreements (CDAs) between the authors/readers and the developers. Candidates are ranked using defined criteria, and there can be site visits and also financial or managerial due diligence. Pre-defined PPCs (or a TPP) are needed for ranking.

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4 http://www.who.int/immunization/monitoring_surveillance/burden/estimates/en/
5 Adapted from http://resources.rhoworld.com/blog/bid/159899/How-to-Use-Your-Target-Product-Profile-to-Create-an-Integrated-Product-Development-Plan
6 Literature review 2018. Raymond Hutubessy, personal communication
**Outcome**

A measurable event within a clinical trial or epidemiological study; this can be a direct effect of the vaccine or an indirect one.

**Portfolio management**

An approach for managing a portfolio of candidate vaccines for a given set of goals. It stretches from discovery to late-stage development of a vaccine. It is, preferably, independent of in-built biases towards particular approaches and candidates. Decisions are evidence-based and can expand, re-direct or terminate product development. Decisions are based on a comprehensive, strategic and well-defined approach. It can introduce new ideas, for example ways of testing and comparing candidates, and there can be overall R&D cost efficiencies. Agreeing a TPP is key to this approach and there can be priorities for development, including based on public health impact. Cost efficiencies can be based on milestone-based funding and ‘Go/No go’ criteria.

**Public health**

The science and art of preventing disease, prolonging life and promoting human health through organized efforts and informed choices of society, organizations, public and private, communities and individuals. Health takes into account physical, mental and social well-being; it is not merely the absence of disease or infirmity. In common usage, it tends to be used for population-level approaches to health improvement rather than at an individual level, especially those delivered by governments.

A public health paradigm in the context of value can consider the population impact of a vaccine and encompasses measures of community benefits against a range of outcomes. (Gessner et al. 2017)

**Public welfare interest**

Realization of non-monetary public benefits (such as improved quality of life).

**Push and pull mechanisms**

In vaccine R&D, refers to economic incentives that facilitate the development of vaccines perceived to be market failures or, where there is commercial viability, when the scientific risk and uncertainty are very high.

Push mechanisms for vaccine R&D can provide direct funding through grants that pay for research inputs; pull mechanisms that pay for research outputs increase the monetary rewards for the development of an effective vaccine.

**Return on Investment (ROI)**

A key part of a business or investment case. In R&D, it is the benefit (profits) to an investor resulting from an investment in R&D. A high ROI means the gains compare favourably to its cost. As a performance measure, ROI is used to evaluate the efficiency of an investment or to compare the efficiencies of several different investments.

**Roadmap**

Description of the process of development of a product or group of products.
Stage-specific gating strategy

Used in R&D management to review product development. At various gateway points (there can be more than one per development stage), candidates can be either selected for further development or terminated. Changes can also be made in resources and costs. The criteria are agreed in advance. The need for data and its quality tends to increase with stage of product development to reflect the increase in resources needed for later stages. For vaccines, characteristics can include production process; product characterisation and quality; safety; immunogenicity; protection and efficacy; clinical; regulatory and business. Each characteristic will have objectives and criteria to pass. (Barker, Hessel, and Walker 2012)

Standard care package

Part of the analysis of healthcare costs, it uses clinical guidelines and clinical norms to estimate maximum likely costs, even if individuals do not have full access to the care package or actually seek care.

Target product profile (TPP)

Definition of the targets and key claims of the product. The TPP provides a statement of the overall intent of the drug development program and gives information about the drug at a particular time in development. For vaccines, usually, the TPP is organized according to the key sections in the eventual vaccine label (FDA 2007).

Technical feasibility

A process of validating the technology assumptions and design of a product or project.

Tiered pricing

The prices paid by different market segments typically vary. For vaccines, there is often a wide range of prices paid by different countries and in the public or private sector. There can also be different prices for the same product for infant and adult use. It can help low-resource countries to afford a vaccine.

Vaccine introduction costs

The total costs of implementing a vaccine in a health system. WHO has guidelines on how to calculate these, (Biologicals 2002) including using a costing tool such as WHO’s OneHealth. Key data include the immunisation platform to be used, target coverage, and number of doses per person.

Vaccine pricing

The likely price of vaccines in development can be estimated using: knowledge of the cost of goods of vaccines using similar technology, pre-negotiated pricing scenarios (tiered pricing), or by benchmarking to vaccines with similar characteristics. The cost of goods is difficult to estimate for vaccines at an early-stage of development.

Guidance for Industry and Review Staff Target Product Profile — A Strategic Development Process Tool

Value
The monetary or other worth of a vaccine as perceived by an individual, group organisation or society. It can be measured in health outcomes per unit of currency spent, or the health gain, cost saving and/or benefit to society. Public health value can be measured by the extent to which a vaccine addresses an unmet public health need.

Value driver
A key factor that determines the value of a vaccine to a specified stakeholder. For vaccines, it could be the price, efficacy or indirect impact.

WHO preferred product characteristics (PPCs)
Definition of the desired characteristics of vaccines to address public health need, and usually with a LMIC focus. These characteristics include indications, target populations, implementation strategies, safety and efficacy requirements. PPCs don’t aim to and capture or quantify, to the same extent as a WHO Full Value of Vaccines Assessment (FVVA) the likely economic or public-health value of the vaccines in question or the likely costs of development. For vaccines, one pathogen area might have more than one set of PPCs.

WHO Full Value of Vaccine Assessment
A value assessment can be defined as ‘a promise of value to be delivered’ or a review and analysis of costs and benefits to be delivered by a proposed investment, from a variety of perspectives: who, for whom and for what purpose. See Section 2 for a description. See also the definitions for: business case; investment case; and WHO preferred product characteristics (PPCs).

WHO public health value statement
A short description of the vaccine in question, with a summary of its indications, for what target group(s), what stage of development it is, key features and value to different beneficiaries and stakeholders. This can be based on the WHO PPCs for the vaccine.
Appendix 3. Overview of the product development process

The development of the vaccine can be divided into distinct phases (see Section 6):

- **Discovery and pre-clinical stage 1**: includes basic research and discovery, assay development, animal testing and early process development, leading to selection of the product candidate;
- **Pre-clinical development (stage 2)**: includes further assay development, Good Manufacturing Practice (GMP) pilot-scale manufacturing, Good Laboratory Practice (GLP) toxicology testing, and regulatory filing to conduct the first safety trial in humans;
- **Phase 1 and 2a clinical trials**: phase 1 includes the first testing in humans, starting with a small group of adult subjects to assess safety (and, for vaccines, immunogenicity). It can also, for vaccines, include age-de-escalation studies to reach the target age group. In Phase 2a, individuals can belong to groups at risk of acquiring the disease;
- **Phase 2b clinical trials**: these involve a much larger number (for example, low thousands) of healthy volunteers to assess safety. For vaccines, they also test for immunogenicity and preliminary data on efficacy. These studies are randomized and double blinded. Due to their size, they often include multiple sites in different disease-endemic countries;
- **Phase 3 clinical trials**: successful candidate(s) from Phase 2b trials enters even larger trials (for example tens of thousands) of people, to assess the safety and efficacy in a large group of people;
- **Pre-commerce**: involves the introduction of the vaccine to the market. Successful introduction is achieved by developing a comprehensive data package that makes a public health and economic case for adoption of the vaccine into national programs. Often a WHO recommendation is required as a prerequisite for adoption in LMICs. Comprehensive data packages include
  - Evidence for policy development, advocacy and communication at global and country levels;
  - Financing mechanisms to support comprehensive vaccination programs;
  - Health infrastructure required for delivery.
- **Commercialization**: further work on the value assessment of the added benefit of a new vaccine. Activities include
  - Ensuring logistical, regulatory, financing, and policy issues are in place;
  - Accurate supply chain forecasting;
  - Management of supply and demand to guarantee the vaccine is available when countries are ready;
  - Review of health infrastructure to support uptake;
  - Monitoring and surveillance systems.
- **WHO prequalification**.
Appendix 4. Draft target product profile (TPP)

*For use in stakeholder interviews and for market analysis.*

## Table 25. Draft TPP for **X** vaccines

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Minimum acceptable target</th>
<th>Optimistic target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product/vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strain/type coverage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target populations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunogenicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety, tolerability and reactogenicity</td>
<td></td>
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</tr>
<tr>
<td>Dosing schedule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Route of administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stability and shelf-life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protection threshold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of goods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO PQ date</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 5. Authors, advisors and stakeholders interviewed

Authors

Scientific Advisory Group (SAG)

WHO Secretariat

Stakeholders interviewed
List stakeholder names with organisation, under headings.
For example:

- **Vaccine developers**: for a range of opinions it can be useful to interview people from large vaccine manufacturers, biotechnology companies, not-for-profit organisations, governmental and academic-based R&D, independent consultants and regulatory agencies;
- **Global demand**: it can be useful to interview experts at BMGF, GAVI, PATH, UNICEF, WHO and World Bank;
- **In-country demand**: useful to interview people in Ministries of Health (or public health), academic settings and private practice in priority and large-population countries;
- **Knowledge/opinion: supply**: people who know about the supply chain;
- **Knowledge/opinion: epidemiology**: useful to interview people working on modelling.
Session 6

Vaccine impact modelling (IA2030 and VIMC)
Vaccine Impact Modelling session

for the IVIR-AC meeting, February 2023

15 February 2023
Agenda

1. **Introduction**  -  Yoonie Sim (WHO IVB)

2. **Main presentation: VIMC analysis on impact of COVID-19 related disruptions for immunization**  -  Dr. Katy Gaythorpe (Vaccine Impact Modelling Consortium – VIMC)

3. **Brief updates: approaches to adding polio and influenza to IA2030 vaccine impact estimates**  -  Austin Carter/Yoonie Sim (IA2030 vaccine impact estimates project team)

4. **Q&A and discussion**  -  with IVIR-AC members
The Vaccine Impact Modelling Consortium (VIMC) comprises 21 modelling groups on 12 diseases, with its secretariat based at Imperial College London.

Funded by the Bill & Melinda Gates Foundation, Gavi, the Vaccine Alliance, and the Wellcome Trust, VIMC has established a strategic plan for the next five years (2023-2027).

Core aims for immunization:
- to provide reliable and accessible estimates of vaccine impact across the Gavi portfolio
- To address critical modelling-related vaccine policy questions raised by stakeholders who will be dynamically engaged in our work
- to translate the Consortium’s modelling to real-world policy that improves health outcomes
- to foster a diverse international community of vaccine impact modellers, inclusive of modellers in low- and middle-income countries (LMICs)
- to provide training in infectious disease modelling and its application to vaccine-preventable diseases for both modellers and policymakers.

VIMC also established a new research program on the impact of climate change on climate-sensitive VPDs.
Background: IA2030 vaccine impact estimates

- IA2030 vaccine impact estimates project was launched in August 2020 to generate modelled vaccine impact estimates for WHO’s 194 member states

- Three use cases
  - **Advocacy and target setting:** “50 million lives saved during 2021–2030”
  - **Monitoring and reporting:** Impact Goal Indicator 1.1 as part of IA2030 M&E framework
  - **Other strategic purpose:** Input into WHO’s second investment case, advocacy for the African Vaccination Week 2022, etc.

- Planned activities for 2023
  - Improve tools, platforms and communication strategies for annual reporting of IG 1.1
  - Improve underlying models and methods
  - Expand the scope of pathogens and impact measures
Background: WHO IVB's collaboration with VIMC

• IVB and VIMC collaborated closely on **IA2030 vaccine impact estimates (194 member states, 14 pathogens)** which leverage VIMC’s impact estimates for their model runs for 110 countries and 10 pathogens.

• We have recently formalized this relationship by developing a joint work plan under the **WHO Collaborating Centre for Infectious Disease Modelling agreement** with Imperial College London to collaborate on:
  • 1) Mid-point target updates for IA2030 vaccine impact estimates (impact goal indicator 1.1) by 2025
  • 2) Modelling analyses to answer priority questions raised by WHO IVB and IA2030 partners
    • including main presentation for today’s session to inform global, regional and country efforts for catch-up, recovery and intensification
Previous IVIR-AC sessions

Vaccine Impact Modelling Consortium (VIMC)

- March 2021
  Weekly epidemiological record, 30 April 2021, No 17, 2021, 96, 133–144

- September 2021
  Weekly epidemiological record, 26 November 2021, No 47, 2021, 96, 569–584

- March 2022
  Weekly epidemiological record, 06 May 2022, No 18, 2022, 97, 173–184

- September 2022
  Weekly epidemiological record, 25 Nov 2022, No.47, 2022, 97, 599–620

IA2030 vaccine impact estimates

- September 2020
  Weekly Epidemiological Record, 4 December 2020, vol. 95, 49 (pp. 609–628)

- March 2021
  Weekly epidemiological record, 30 April 2021, No 17, 2021, 96, 133–144

- September 2021
  Weekly epidemiological record, 26 November 2021, No 47, 2021, 96, 569–584

- March 2022
  Weekly epidemiological record, 06 May 2022, No 18, 2022, 97, 173–184

- September 2022
  Weekly epidemiological record, 25 Nov 2022, No.47, 2022, 97, 599–620
Joint session for IVIR-AC February 2023: VIMC + IA2030 vaccine impact estimates

Main presentation

VIMC analysis on the impact of COVID-19 related disruptions for immunization shows

• Request for IVIR-AC to review and provide feedback on the final results from the analysis on the impact of COVID-19 disruptions for immunization, particularly around communicating results

Brief updates

IA2030 vaccine impact estimates project team’s plan to expand the scope of pathogens and include polio and influenza

• The project team to provide updates on the plan add polio and influenza to the existing analytical framework
VIMC presentation by Dr. Katy Gaythorpe
IA2030 vaccine impact estimates
Expanding the scope of pathogens for mid-point target updates

- Need for expanding the scope of pathogens and impact measures (e.g. DALYS) to fully describe the value of vaccines included in the national immunization schedule

- Based on consultation with the IA2030 vaccine impact estimates project – Stakeholder Committee, four pathogens were selected to be prioritized for updating targets for the midpoint of IA2030 in 2025

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>New high impact vaccine</td>
</tr>
<tr>
<td>Covid-19</td>
<td>Current global priority</td>
</tr>
<tr>
<td>Polio</td>
<td>Historically high impact vaccine</td>
</tr>
<tr>
<td>Influenza</td>
<td>High impact life course vaccine</td>
</tr>
</tbody>
</table>

The list of next target pathogens include Varicella, dengue, mumps, rabies, HepA and HepE based on the scoring criteria developed in 2020.
Ideal approach to leveraging existing dynamic transmission models for polio and influenza

• "Modelling hub approach" to establish a process for engaging modelling groups in the submission of estimates:
  • IA2030 vaccine impact estimates project team could use impact ratios generated from these estimates for novel coverage scenarios and historical estimates of impact based on updated vaccination coverage
  • The project team is currently in discussion with VIMC regarding technical support and infrastructure
Pathogen expansion: Influenza

**Inputs**

- **Coverage**: OECD Health care utilization survey for 65+ vaccine coverage 2000–2021
- **Burden**: Multiple sources, including CDC, Global Pandemic Mortality Project (GLaMOR), and GBD. Generally, GBD estimates are lower
- **Vaccine effectiveness**: Annual studies, compiled by CDC

**Table 2.** Global Influenza-Associated Mortality Estimates According to Age Group, Multiple Countries, 1980–2016

<table>
<thead>
<tr>
<th>Age Group</th>
<th>CDC</th>
<th>GLaMOR</th>
<th>IHME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>95% Crl</td>
<td>Rates Per 100,000</td>
</tr>
<tr>
<td>All ages</td>
<td>409,111</td>
<td>291,243, 645,832</td>
<td>5.6</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>175,303</td>
<td>67,225, 342,576</td>
<td>2.6</td>
</tr>
<tr>
<td>≥65 years</td>
<td>244,012</td>
<td>188,261, 330,694</td>
<td>40.2</td>
</tr>
</tbody>
</table>

Abbreviations: CDC, US Centers for Disease Control and Prevention; Crl, credible interval; GLaMOR, Global Pandemic Mortality Project; IHME, Institute for Health Metrics and Evaluation;
Pathogen expansion: Polio

Inputs

- **Coverage**: WUENIC
  - IPV1 – At least one dose of inactivated polio vaccine
  - POL3 – 3rd dose of polio containing vaccine, which may be either oral or inactivated polio vaccine

- **Burden**: Polio Information System (POLIS) with reported cases split by wild and vaccine-derived, as well as instances of acute flaccid paralysis (AFP)
Next Steps

1. Connect with modeling groups and scope out best approach for each pathogen
2. Clarify which aspects of modeling will be managed by WHO, modeling groups, and possible collaboration with VIMC
3. Develop preliminary estimates for review
4. Integrate additional impact estimates into mid-point target updates
Thank you
### Project team

*Changes in the coming year 2022–2023*

<table>
<thead>
<tr>
<th>Function</th>
<th>Name</th>
<th>Affiliation</th>
<th>Location/time zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytics</td>
<td>Austin Carter</td>
<td>Independent consultant for WHO IVB; University of Washington</td>
<td>Portland, USA</td>
</tr>
<tr>
<td>VIMC liaison</td>
<td>Katy Gaythorpe</td>
<td>Imperial College London Vaccine Impact Modelling Consortium (VIMC)</td>
<td>London, UK</td>
</tr>
<tr>
<td>Project management</td>
<td>So Yoon (Yoonie) Sim</td>
<td>WHO Department of Immunization, Vaccines and Biologicals (IVB)</td>
<td>Geneva, Switzerland</td>
</tr>
<tr>
<td>Supervision</td>
<td>Philipp Lambach a.i. Value of Vaccines, Economics and Modelling team lead (Raymond Hutubessy)</td>
<td>WHO Department of Immunization, Vaccines and Biologicals (IVB)</td>
<td>Geneva, Switzerland</td>
</tr>
</tbody>
</table>

- Additional team member: One consultant will join the project team for 2022–2023
- The project team will coordinate closely with WHO IVB’s IA2030 focal points:

  - **Alba Maria Ropero**, Senior Lead, Immunization Agenda 2030
  - **Erlyn Macarayan**, M&E Specialist, Immunization Agenda 2030
  - **Carolyn Inae Kim**, Data analyst, Immunization Agenda 2030
  - **Jan Grevendonk**, Co-Chair of I2030 M&E WG & Technical Officer, Immunization Information Systems
Stakeholder Committee membership

*New members of the Stakeholder Committee (2022–2023)

<table>
<thead>
<tr>
<th>Representative</th>
<th>Organization, consortium or committee</th>
<th>Location/time zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Niket Thakkar (Emily Dansereau)</td>
<td>The Bill &amp; Melinda Gates Foundation (BMGF)</td>
<td>Seattle, USA</td>
</tr>
<tr>
<td>2 Todi Mengistu*</td>
<td>Gavi, the Vaccine Alliance (Gavi)</td>
<td>Geneva, Switzerland</td>
</tr>
<tr>
<td>3 Jon Mosser</td>
<td>Institute for Health Metrics and Evaluation (IHME)</td>
<td>Seattle, USA</td>
</tr>
<tr>
<td>4 Walt Orenstein</td>
<td>Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC)</td>
<td>Atlanta, USA</td>
</tr>
<tr>
<td>5 Katy Gaythorpe</td>
<td>Vaccine Impact Modeling Consortium (VIMC)</td>
<td>London, UK</td>
</tr>
<tr>
<td>6 Ulla Griffiths</td>
<td>United Nations International Children’s Emergency Fund (UNICEF)</td>
<td>New York, USA</td>
</tr>
<tr>
<td>7 Dimitri Prybylski*</td>
<td>US Centers for Disease Prevention and Control (US CDC)</td>
<td>Atlanta, USA</td>
</tr>
<tr>
<td>8 William Msembali*</td>
<td>WHO Division of Data, Analytics and Delivery for Impact (DDI)</td>
<td>Geneva, Switzerland</td>
</tr>
<tr>
<td>9 Naor Bar-Zeev Unit head, IAI*</td>
<td>WHO Department of Immunization, Vaccines and Biologicals (IVB)</td>
<td>Geneva, Switzerland</td>
</tr>
<tr>
<td>10 Philipp Lambach Team Lead a.i., VoV* (Raymond Hutubessy)</td>
<td>WHO Department of Immunization, Vaccines and Biologicals (IVB)</td>
<td>Geneva, Switzerland</td>
</tr>
</tbody>
</table>

Please find the presentations, notes and background materials from the previous meeting in [the shared folder](#).
VIMC analysis on impact of COVID-19 related disruptions for immunization

IVIR-AC meeting
February 2023

Dr. Katy Gaythorpe
This presentation

Three aims of VIMC analysis on impact of COVID-19 related disruptions for immunization are to model vaccine impact estimates (deaths, cases and DALYs averted) that show:

- Where the 2020-2021 disruption has left us
- What can be done to recoup losses in coverage
- What could be achieved if we met aspirational goals (with and without disruption)
Methods and coverage assumptions
Methods

We present the headline results of the 2022 modelling exercise based on the central estimates, provided by 10 modelling groups, shown by calendar year for 112 countries.

We also present interim update results by year of vaccination.

Where average disease-specific estimates are presented, these reflect the mean estimate across both modelling groups.

Full estimates, including uncertainty through the stochastics submitted by each group, will be discussed in the corresponding manuscript.
### Brief summary of coverage assumptions

**Table:** Brief summary of coverage assumptions. Introductions are determined by DTP1 coverage levels, in line with IA2030 projection methodology. Acronyms: 1 WHO/UNICEF estimates of national immunisation coverage; 2 Autoregressive integrated moving average; 3 Immunisation Agenda 2030.

<table>
<thead>
<tr>
<th>Scenario name</th>
<th>Routine assumptions</th>
<th>Campaign assumptions</th>
<th>Catchup assumptions</th>
<th>Motivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No-vaccination</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Baseline counterfactual</td>
</tr>
<tr>
<td>Default-update</td>
<td>Follows WUENIC$^1$ up to 2021 (incl.), assumes nonlinear recovery until 2025 and then projects towards default endpoints in 2030</td>
<td>Follows WHO immunisation repository up to 2021 (incl.) then best-practice/guidelines until 2030</td>
<td>None</td>
<td>Best estimate of existing and conservative estimate of future coverage</td>
</tr>
<tr>
<td>Default-nocovid</td>
<td>Follows WUENIC up to 2019 (incl.) then projects coverage in 2020 &amp; 2021 using ARIMA$^2$, then projects towards default endpoints in 2030</td>
<td>Follows WHO immunisation repository up to 2019 (incl.), incorporates projected and planned campaigns for 2020 &amp; 2021 using the WHO campaign tracker and then best-practice/guidelines until 2030</td>
<td>None</td>
<td>Projection of coverage in the absence of 2020-2021 disruption</td>
</tr>
<tr>
<td>Default-update-catchup</td>
<td>Same as default-update</td>
<td>Same as default-update</td>
<td>Catch-up activities for missed cohorts in 2023, 2024 and 2025</td>
<td>Best estimates of current coverage with theoretical catch-up activities and conservative estimate of future coverage</td>
</tr>
<tr>
<td>IA2030-update</td>
<td>Follows WUENIC up to 2021 (incl.), assumes nonlinear recovery until 2025 and then projects towards IA2030$^3$ endpoints in 2030</td>
<td>Follows WHO immunisation repository up to 2021 (incl.) then best-practice/guidelines until 2030</td>
<td>None</td>
<td>Best estimates of current coverage with IA2030$^3$ targets by 2030</td>
</tr>
<tr>
<td>IA2030-update-catchup</td>
<td>Same as IA2030-update</td>
<td>Same as IA2030-update</td>
<td>Catch-up activities for missed cohorts in 2023, 2024 and 2025</td>
<td>Best estimates of current coverage with IA2030 targets by 2030 and theoretical catch-up activities</td>
</tr>
</tbody>
</table>

**Figure:** Diagram of projected routine immunisation coverage in the situation where there is disruption in 2020 and 2021 (A), there is not any disruption in 2020 and 2021 (B), and (C) where the no-COVID scenario is projected for 2020 and 2021 using ARIMA. Areas shaded in blue correspond to information provided by WUENIC 2022, areas in yellow highlight the recovery period if there has been disruption, areas in green show the scale-up towards the 2030 endpoints and areas in pink highlight periods projected using ARIMA.
Coverage: catch-up activities

- We assume catch-up activities take the form of intensified routine immunisation similar to PIRI (periodic intensification of routine immunization).

- These activities target missed or affected vaccine cohorts where affected cohorts are defined as those individuals who would have received routine immunisation in the `no-covid` scenario but did not in the `default-update` scenario.

- Vaccine cohorts are targeted in the recovery years in stages, see table:

<table>
<thead>
<tr>
<th>Vaccination year</th>
<th>Affected/missed vaccine cohorts targeted</th>
</tr>
</thead>
<tbody>
<tr>
<td>2023</td>
<td>2020 and 2021</td>
</tr>
<tr>
<td>2024</td>
<td>2022 and 2023</td>
</tr>
<tr>
<td>2025</td>
<td>2024</td>
</tr>
</tbody>
</table>
Interim update

 Extrapolates the impact from one coverage set to another using impact ratios.

 Impact ratios here are calculated from the 2021 VIMC model runs as the burden averted per vaccine dose and are stratified by vaccine, country, modelling group and activity type.

 There was no routine-intensified activity type in the 2021 model runs, therefore we do not extrapolate impact for groups who did not rerun in 2022.
Results

Preliminary results focused on the central estimates only. Uncertainty quantification is in preparation.
Past
Past: Where has the 2020-2021 disruption left us?

- We project 48,109 additional deaths will occur between calendar years 2020 and 2030 as a result of COVID-related disruption in measles, rubella, HPV, HepB, MenA and YF vaccination coverage assuming coverage does not return to pre-COVID levels until 2025 and no catch-up activities are undertaken.
- The vast majority, 91%, of these are projected to be due to measles.

<table>
<thead>
<tr>
<th>Disease</th>
<th>AFRO</th>
<th>EMRO</th>
<th>EURO</th>
<th>PAHO</th>
<th>SEARO</th>
<th>WPRO</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HepB</td>
<td>303</td>
<td>16</td>
<td>1</td>
<td>2</td>
<td>130</td>
<td>71</td>
<td>523</td>
</tr>
<tr>
<td>HPV</td>
<td>95</td>
<td>0</td>
<td>1</td>
<td>13</td>
<td>-85</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>Measles</td>
<td>26,252</td>
<td>2,907</td>
<td>636</td>
<td>1,392</td>
<td>12,838</td>
<td>197</td>
<td>44,222</td>
</tr>
<tr>
<td>MenA*</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Rubella</td>
<td>8</td>
<td>0</td>
<td>70</td>
<td>6</td>
<td>30</td>
<td>0</td>
<td>114</td>
</tr>
<tr>
<td>YF</td>
<td>3,034</td>
<td>174</td>
<td>-</td>
<td>15</td>
<td>-</td>
<td>-</td>
<td>3,223</td>
</tr>
<tr>
<td>Total</td>
<td>29,692</td>
<td>3,097</td>
<td>708</td>
<td>1,428</td>
<td>12,913</td>
<td>271</td>
<td>48,109</td>
</tr>
</tbody>
</table>

Additional deaths in calendar years 2020-2030 due to COVID-19 related disruption to vaccination coverage. *MenA was run for five countries only. There are 42 VIMC countries in AFRO, 14 VIMC countries in EMRO, 15 VIMC countries in EURO, 15 VIMC countries in PAHO, 10 VIMC countries in SEARO and 16 VIMC countries in WPRO.
Past: Where has the 2020-2021 disruption left us?

- We project 790,105 additional deaths will occur between 2020 and 2100 as a result of COVID-related disruption in **years of vaccination** 2020 - 2030 assuming coverage does not return to pre-COVID levels until 2025 and no catch-up activities are undertaken.
- The majority of these are due to HPV.
- In this analysis we assume impact scales linearly with coverage.
- This analysis is less effective at projecting dynamic model results.

Interim update projected numbers of additional deaths due to coverage disruption between **years of vaccination** 2020 and 2030. Each square represents 1,000 additional deaths.
Present
Present: What can be done to mitigate losses in coverage?

We project 18,521 deaths could be mitigated between calendar years 2020 and 2030 as a result of catch-up activities.

<table>
<thead>
<tr>
<th>Disease</th>
<th>AFRO</th>
<th>EMRO</th>
<th>EURO</th>
<th>PAHO</th>
<th>SEARO</th>
<th>WPRO</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HepB</td>
<td>208</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>58</td>
<td>38</td>
<td>315</td>
</tr>
<tr>
<td>HPV</td>
<td>142</td>
<td>0</td>
<td>1</td>
<td>23</td>
<td>96</td>
<td>4</td>
<td>266</td>
</tr>
<tr>
<td>Measles</td>
<td>7,086</td>
<td>1,506</td>
<td>86</td>
<td>337</td>
<td>7,080</td>
<td>158</td>
<td>16,253</td>
</tr>
<tr>
<td>MenA*</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Rubella</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>YF</td>
<td>1,641</td>
<td>0</td>
<td>-</td>
<td>41</td>
<td>-</td>
<td>-</td>
<td>1,682</td>
</tr>
<tr>
<td>Total</td>
<td>9,080</td>
<td>1,517</td>
<td>88</td>
<td>402</td>
<td>7,235</td>
<td>200</td>
<td>18,521</td>
</tr>
</tbody>
</table>

Mitigated deaths per WHO region from calendar years 2020-2030 due to catch-up activities. *MenA was run for five countries only. There are 42 VIMC countries in AFRO, 14 VIMC countries in EMRO, 15 VIMC countries in EURO, 15 VIMC countries in PAHO, 10 VIMC countries in SEARO and 16 VIMC countries in WPRO.
Present: What can be done to mitigate losses in coverage?

→ illustrates the additional deaths per country and disease due to disruption between calendar years 2020 and 2030 as well as the proportion of those additional deaths that would be mitigated by catch-up activities.

It also highlights that catch-up activities, given the timing we have modelled, will mitigate less than half of these additional deaths over the decade in these countries.

Note: in the above we mention mitigating deaths; however, this is an aggregate quantity over the decade.
Future
Future: What could be achieved if we met our aspirational goals?

There would be large, year on year, gains in deaths averted if the aims of the IA2030 are met over the coming decade.

HPV has a notable contribution to the potential gains in impact, followed by YF, measles and HepB.

Note: in EURO and WPRO the overall numbers of deaths are small and thus the figures for those regions should be interpreted with caution.

Difference (%) in deaths averted per year between aspirational IA2030 scenario and default scenario per calendar year. There are 42 VIMC countries in AFRO, 14 VIMC countries in EMRO, 15 VIMC countries in EURO, 15 VIMC countries in PAHO, 10 VIMC countries in SEARO and 16 VIMC countries in WPRO.
Future: What could be achieved if we met our aspirational goals?

We compare the aspirational, IA2030, scenario with the default and no-COVID scenarios across all vaccines.

It highlights that the overall deaths averted in the aspirational scenario are higher than those in the default or no-COVID scenarios.

Interim update projected deaths averted (100K) per scenario for years of vaccination 2020-2030. Each square represents 100,000 deaths averted for all 14 diseases.
Conclusions

And next steps
Conclusions

- Between calendar years 2020 and 2030 we project a notable increase in deaths (48,109) due to disruptions in vaccination coverage to measles, rubella, menA, YF, HepB and HPV.
  - Majority due to measles and occur in the AFRO WHO region.

- For vaccine activities occurring between 2020 and 2030 we project approximately 790,000 additional deaths occurring over the lifetime of vaccinees for all VIMC vaccines plus DTP.
  - Primarily due to coverage drops between 2020 and 2025 relative to the no-COVID scenario.

- The catch-up scenario we modelled leads to mitigation of some of these additional deaths over the decade.
  - However, for measles and YF, the additional burden occurs quickly following coverage disruption.
Conclusions

- For diseases with burden occurring later in life, such as for HPV, catch-up activities may mitigate additional deaths due to coverage disruption.

- The catch-up activities themselves had variable impact ratios, i.e., burden averted per dose.

- As we look towards the end of the decade, reaching the IA2030 targets will reduce overall burden.
Next steps

- Quantifying uncertainty
- Preparing for publication
- Communication of results
- Preparing for the next round of full model runs
Questions/ Discussion points

- When preparing this work for publication we will focus on the first two aims initially ie. without the “future” section - are there any limitations of this approach?

- Are there any sensitivities in communication that we should bear in mind?
Thank you to all our members and funders
Supplementary slides
In the default no-COVID scenario we project routine immunisation coverage for each country/vaccine for 2020 and 2021 using ARIMAs with logit transform in a manner similar to Evans 2022.

For campaigns or SIAs we refer to the WHO campaign tracker and our own full model runs to assess which campaigns were planned but disrupted beyond 2021 due to COVID; we then include these campaigns in the `no-COVID` scenario but omit them in the default-update scenario unless they have subsequently taken place (according to the WHO immunisation repository).
Coverage: functional forms

• Non-linear recovery to pre-pandemic levels of routine coverage

\[ y = cov_{21} + \frac{cov_{25} - cov_{21}}{1 + \exp(-k(x - m))} \]

Where \( y \) is coverage in year \( x \), \( cov_z \) is the coverage in year \( z \), \( m \) is the midpoint and \( k \) is the rate of coverage increase. In our analysis \( m = 2023 \) and \( k = 3 \) so that the greatest recovery occurs in 2023.

• Non-linear scale-up of routine vaccination coverage towards 2030 endpoints

\[ cov_t = 1 - (1 - cov_{t_0}) \exp \left( \log \left( \frac{1 - cov_t}{1 - cov_{t_0}} \right) \frac{t - t_0}{T - t_0} \right) \]

Where \( t_0 \) and \( T \) are the baseline and target years, \( t \) is the current year and \( cov \) is the coverage.
Methods: Modelling groups for urgent commission

<table>
<thead>
<tr>
<th>Disease</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>LSHTM-Jit</td>
</tr>
<tr>
<td>Measles</td>
<td>PSU-Ferrari</td>
</tr>
<tr>
<td>Rubella</td>
<td>UKHSA-Vynnycky</td>
</tr>
<tr>
<td>Rubella</td>
<td>JHU-Winter</td>
</tr>
<tr>
<td>HPV</td>
<td>LSHTM-Jit</td>
</tr>
<tr>
<td>HPV</td>
<td>Harvard-Kim</td>
</tr>
<tr>
<td>MenA</td>
<td>Cambridge-Trotter</td>
</tr>
<tr>
<td>HepB</td>
<td>IC-Hallett</td>
</tr>
<tr>
<td>YF</td>
<td>IC-Gaythorpe</td>
</tr>
<tr>
<td>YF</td>
<td>UND-Perkins</td>
</tr>
</tbody>
</table>

A full list of all modelling groups in the VIMC can be found at: modellers
Session 7

Typhoid Conjugate Vaccine Micro Array Patches (TCV-MAP) FVVA
TCV-MAP Full Vaccine Value Assessment
Equity Analysis Methodology
IVIR-AC Feb 2023
The TCV-MAP FVVA evaluates the potential broad socio-economic and public health impact of TCV-MAPs

The Vaccine Innovation Prioritisation Strategy (VIPS) Alliance – an initiative bringing together Gavi, WHO, UNICEF, BMGF and PATH – and Wellcome have partnered to develop a Full Vaccine Value Assessment (FVVA) of a microarray patches (MAPs) for typhoid conjugate vaccine (TCV) with the objectives to:

- Evaluate the potential broad socio-economic and public health impact of microarray patches (MAPs) for typhoid conjugate vaccine (TCV) delivery from the perspective of countries (including LMICs), funders and industry.
- Inform potential future investments in the development of TCV-MAPs for vaccine delivery.
- Develop a methodology that could be replicated for other vaccine product delivery innovations.
A new component has been added to the FVVA structure: the equity impact analysis

- This presentation will focus on the methodology proposed for the analysis of equity impact which will be conducted as part of the socioeconomic and public health impact analyses.
- The equity analysis is a new addition to the FVVA methodology that has not been included in prior vaccine FVVAs.
- The TCV-MAP FVVA is modelled on the WHO FVVA framework and shares a similar structure FVVAs reviewed by IVIR-AC including the MR-MAP iFVVA in 2022.
Requested feedback from the IVIR-AC

1. Review of the methodology proposed for the equity analysis.

2. Recommendations to improve the robustness of the methodology.

3. Guidance to align the equity aspects of the analysis to concerns around disparities to the global health community.
Three sets of analyses will be combined to assess the health and socioeconomic impact of TCV-MAPs

- **Disease transmission analysis**: Predicts country and age specific typhoid incidence and mortality with MAPs versus vials.
- **Costing analysis**: Estimates the supply chain and delivery costs for TCV in vials vs. MAP which will be used as inputs into the extended cost-effectiveness analysis (ECEA).
- **Health and socioeconomic impact evaluation (Extended cost-effectiveness analysis)**: Compares MAP to vial presentation and evaluates health impact and cost, to identify factors impacting the potential value of TCV-MAPs.
The extended CEA will compare the impact of the addition of TCV-MAPs following TCV introduction.

- The extended cost effectiveness analysis will compare the impact of introduction of TCV-MAPs to immunization programmes at a national level relative to the use of conventional TCV in a 5-dose vial presentation.

- The difference in presentation is expected to have differing impact on sub-groups of the population based on socioeconomic indicators such as access to health care and disease-specific risk factors.

- An equity analysis seeks to quantify this impact.
Schematic to estimate infection risk by wealth strata

Wealth Quintiles

1. Vaccine Coverage
2. Risk of Disease
3. Access to Healthcare

Population segmentation:
- Wealth Quintile 1: Highest Vaccine Coverage, Lowest Risk of Disease, Lowest Access to Healthcare
- Wealth Quintile 2: Highest Access to Healthcare
- Wealth Quintile 3: Highest Vaccine Coverage, Lowest Risk of Disease
- Wealth Quintile 4: Highest Risk of Disease
- Wealth Quintile 5: Lowest Vaccine Coverage, Highest Risk of Disease

Equity Considerations
- Vaccinated
- Susceptible (S)
- Infected (I)
- Recovered (R)

Equity considerations are accounted for in the extended cost-effectiveness analysis at different points within the disease transmission model.
Methods for calculating incidence of typhoid by wealth strata

**Key assumptions**
- Social contact data among wealth quintiles is not available – simple mixture model assumed
- All wealth quintiles contribute to the force of infection
- Wealth quintiles get infected at a rate proportional to their exposure to risk factors

### Incidence of Typhoid by risk factors for Typhoid (sanitation, water)

- **Poor sanitation**
  - 200 typhoid cases per 100,000*

- **Adequate sanitation**
  - 100 typhoid cases per 100,000*

*Values for illustration purposes

### Proportion of population exposure to risk factors by wealth strata

<table>
<thead>
<tr>
<th>Wealth Strata</th>
<th>Adequate Sanitation</th>
<th>Poor Sanitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wealth Q5 - highest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wealth Q4 - fourth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wealth Q3 - middle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wealth Q2 - second</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wealth Q1 - lowest</td>
<td></td>
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</tr>
</tbody>
</table>

### Incidence of typhoid by wealth strata

<table>
<thead>
<tr>
<th>Wealth Strata</th>
<th>Incidence per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wealth Q5 - highest</td>
<td>200 typhoid cases</td>
</tr>
<tr>
<td>Wealth Q4 - fourth</td>
<td>150 typhoid cases</td>
</tr>
<tr>
<td>Wealth Q3 - middle</td>
<td>100 typhoid cases</td>
</tr>
<tr>
<td>Wealth Q2 - second</td>
<td>50 typhoid cases</td>
</tr>
<tr>
<td>Wealth Q1 - lowest</td>
<td>0 typhoid cases</td>
</tr>
</tbody>
</table>

*Values for illustration purposes*
Illustrative health impact and cost outcomes of TCV-MAPs across wealth quintiles

**Health impact for wealth quintile 1 (lowest)**

- Higher cost incurred to reach each case in wealth quintile 1
- More treatment costs averted for wealth quintile 1

**Health impact for wealth quintile 5 (highest)**

- Lower cost incurred to reach each case in wealth quintile 5
- Less treatment costs averted for wealth quintile 5

**Analysis Outputs**

1. Identifying differential distribution of benefits in the typhoid interventions
2. Identifying impact of TCV-MAPS to address inequities
Questions for the IVIR-AC

1. Is the approach described sufficiently informative to assess the potential impact of TCV-MAPs on health equity?

2. Does this analysis address the issues the global health community is most interested in when assessing the potential equity impact of vaccine innovations?

3. Are there other data sources that could be leveraged to provide inputs for the analysis?

4. Are there similar analyses in the gray literature that could be shared to inform this analysis?
Thank You