World Health Organization

Department of Immunization, Vaccines and Biologicals (IVB)

IVIR-AC – March 2022

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

MICROSOFT TEAMS - VIRTUAL MEETING

WHO HEADQUARTERS, GENEVA, SWITZERLAND

07 – 11 March 2022

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)
07-11 March 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

Walter Orenstein (Chair), Professor**,** Emory Global Health Institute, Emory University, Atlanta, **United States of America**
Habib Hasan Farooqui, Additional Professor, Public Health Foundation of India, Delhi, **India**
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**
Mark Jit, Professor Vaccine Epidemiology, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London, **United Kingdom of Great Britain & Northern Ireland**
Sun-young Kim, Global Health, School of Public Health, Seoul National University, Seoul, **Republic of Korea**
Julie Leask, Proferssor, Susan Wakil School of Nursing and Midwifery, Sydney Nursing School, Faculty of Medicine and Health, Camperdown NSW 2050, Sydney, **Australia**
Jean-Daniel Lelièvre, Department of Clinical Immunology INSERM, CHU Henri Mondor 51 avenue Maréchal de Lattre de Tassigny, 94010 Créteil Cedex, **France**

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Paula M. Luz, Professor, Evandro Chagas Clinical Research Institute (IPEC/ FIOCRUZ), Av. Brasil 4365, Manguinhos, 21040-360 Rio de Janeiro, **Brazil**
Dafrossa C. Lyimo, Programme Manager, Immunization and Vaccines Development, Ministry of Health, Community Development, Gender, Elderly & Children, Dar es salaam, **United Republic of Tanzania**
Victoria Nankabirwa, Professor, Department of Epidemiology and Biostatics, School of Public Health, College of Health Sciences, Makerere University, Kampala, **Uganda**
Virginia Pitzer, Associate Professor, Yale School of Public Health, P.O. Box 208034, 60 College St, New Haven, CT 06511, **United States of America**
Sheetal Silal, Modelling and Simulation Hub, Africa (MASHA), University of Cape Town, Cape Town, **South Africa**
Stéphane Verguet, Assistant Professor, Department of Global Health and Population, Harvard T.H. Chan School of Public Health, 665 Huntington Avenue, Boston, MA 02115, **United States of America**
Xuan-yi Wang, Research Scientist, Shanghai Medical College, Fudan University, **China**
Joseph Wu, Professor, Division of Epidemiology and Biostatistics, School of Public Health, The University of Hong Kong, Pok Fu Lam, **Hong Kong SAR, China**

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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-implementation-research-advisory-committee-(ivir-ac)

World Health Organization

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. <u>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.</u>**

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

<u>CONSENT TO DISCLOSURE</u>. 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.

<u>DECLARATION</u>. 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:
Addis Ababa – Accra – Atlanta - Amman – Bangkok – Beirut - Brazzaville – Cairo – Copenhagen – Dakar – Geneva – Jakarta - Johannesburg – Hanoi - Libreville – London – Manila – Nairobi – Paris – Rome

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.

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* *The travel allowance for New York is $ 78.*
For a return trip, travel allowances are payable on both ways. e.g. departure Washington - $47, arrival Geneva - $47, departure Geneva - $47, arrival Washington - $47, total travel allowance - US$ 188)

World Health Organization

Agenda and List of Participants

World Health Organization

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

Microsoft Teams - Virtual Meeting

WHO Headquarters, Geneva, Switzerland

7-11 March 2022

Background reading materials **available at the following link:**

Meeting of the Advisory Committee on Immunization and Vaccines-related Implementation Research

Chair: Walt Orenstein

7 March

Duration	Title	Content and key questions to IVIR-AC	Purpose	Proposed speaker
13:00 - 13:05 5’	Opening of Meeting	• Update on global strategies and issues of relevance to WHO	For information	K. O’Brien, Director, Department of Immunization, Vaccines and Biologicals
13:05 - 13:20 15’	Introduction/ Objectives of the meeting	• Administrative issues • Objectives of IVIR-AC meeting and outline of the 1st day		P. Lambach W. Orenstein
Session postponed: COVID 19 vaccine impact modelling				
To accommodate to the timeline of the SAGE working group subgroup on COVID 19 vaccine impact modelling, this session is being postponed to take place in form of an ad hoc meeting or as session of the next IVIR-AC meeting				
Session 1: Measles Case Fatality Ratio estimation				
13:20 - 13:25 5’	Background	• Robust, transparent, and dynamic age- and country-specific measles case fatality ratios (CFRs) are critical for updating WHO’s measles mortality estimates. A recent review published results of an updated literature search and predictive model to estimate measles CFR, with noted limitations in data availability. In 2021, IVIR-AC recommended continued updates of measles CFR estimates with increased transparency and systematic covariate selection.	For decision	P. O’Connor

		• IVIR-AC is now asked to advise on the conceptual framework, preliminary modeling results, ongoing primary data needs, and best practices on promoting the longevity and utility of dynamic measles CFR estimates moving forward. ***Background reading materials**: See Sharepoint*		
13:25 - 13:45 20’	Update on methods, data and estimates available	• To build upon recommendations from IVIR-AC, the London School of Hygiene and Tropical Medicine and Harvard University, on behalf of a working group of experts, presented a conceptual framework of factors related to measles CFR and preliminary estimates from a new methodology and expanded literature review.		A. Sbarra, A. Portnoy, M. Jit, M. Ferrari

13:45 - 14:10
25’
	Q&A and discussion to inform IVIR-AC recommendations	• Questions to IVIRAC
		  • Has the updated effort, which reflects the available evidence of factors related to CFR, sufficiently responded to the recommendations from IVIR-AC?
		  • Are there additional methodological considerations that need to be taken into account for the proposed CFR modelling study?
		  • How can the transparency and sustainability of this work be promoted in this update with an eye to continuing this work in future iterations?
				P. Luz, X. Wang,
				V. Pitzer

14:10 - 14:20 10’	Wrap up	• Summarize day’s findings and request any follow up from WHO Secretariat/IVIR-AC FPs for closed session	For information	W. Orenstein, Chair

8 March				
Duration	**Title**	**Content and key questions to IVIR-AC**	**Purpose**	**Proposed speaker**
12:00 - 12:05 5’	Introduction	• Recap of previous day and objectives for the day	For information	W. Orenstein, Chair
Session 2: Behavioural and social drivers of vaccination				

12:05 - 12:10 5’	Background	• Introduction to the topic and summary of previous discussion at IVIR-AC • Questions to IVIR-AC: • Request to provide guidance on how to support routine data collection in-country • Feedback on proposed approach to data harmonization at a national and global level from multiple sources	For information	J. Leask
12:10 – 12:25 15’	Presentation	• Update on plans to support gathering and use of data on behavioural and social drivers of vaccination (BeSD) • Outline of global data management planning and proposed processes for supporting data sharing and use		L. Menning
12:25 – 12:55 30’	Q&A and discussion to inform IVIR-AC recommendations	• IVIR-AC discusses presentation and clarifies on content. Gives general feedback and input on the questions raised		V. Nankabirwa, D. Lyimo, S. Kim
12:55 - 13:20 25’	Break			
Session 3: Developing a guidance on methodologies to measure the impact of vaccines in preventing antimicrobial resistance (AMR)				

13:20 - 13:40
20’
	Background and Methodology	• Developing a guidance on methodologies to measure the impact of vaccines on antimicrobial resistance (AMR)
		  o Scope in terms of included vaccine/pathogen targets, types of trial, types of study, and indicators to consider.
		  o Proposed methodology for needs analysis and landscape analysis
		• ***Background reading materials***: *See SharePoint*
			For decision	I. Frost

13:40 - 14:00 10’	Technical presentation	• Case study: methodologies to measure the impact of typhoid conjugate vaccines on AMR		M. Carey
14:00 - 14:20 20’	Q&A and Discussion	• IVIR-AC discusses presentation, clarifies on content and acknowledges main issues; • Questions to IVIR-AC (tentative):		S. Flasche, P. Luz, H. Farooqui

		• Is the methodological approach to developing the guidance appropriate? • Does IVIR-AC agree with the proposed scope in terms of pathogens, classes of pathogens, and study types?		
14:20 - 14:30 10’	Wrap up	• Summarize day’s findings and request any follow up from WHO Secretariat/IVIR-AC FPs for closed session	For information	W. Orenstein, Chair

9 March

Duration	Title	Content and key questions to IVIR-AC	Purpose	Proposed speaker
12:00 - 12:05 5’	Introduction	• Recap of previous day and objectives for the day	For information	W. Orenstein, Chair
Session 4: Evaluation of a modelling approach to assess the public health value and preferred product characteristics of a therapeutic vaccine for human papillomavirus (HPV)				
12:05 - 12:15 10’	Background	• Defining the potential role of a therapeutic HPV vaccine to reduce cervical cancer mortality amongst women in LMICs	For information	S. Gottlieb/ H. Prudden
12:15 - 12:35 20’	Technical presentation	• Modelling to understand the potential value of therapeutic HPV vaccines, and to help define preferred product characteristics ***Background reading materials***: *See SharePoint*		K. Canfell

12:35 - 12:55
20’
	Q&A and Discussion	• IVIR-AC discusses presentation, and obtains clarification on content;
		• Questions to IVIR-AC:
		  • Is the modelling approach appropriate for guiding decision making about therapeutic HPV vaccine development and preferred attributes?
		  • Does IVIR-AC agree with the inclusion of the different modelling scenarios and related assumptions?
				M. Jit, X. Wang,
				S. Silal

		• Does IVIR-AC agree with the proposed modelling plan/steps in the modelling process?		
12:55 - 13:20 25’	Break			
Session 5: Evaluation of morbidity associated with enteric pathogens; for review and decision				
13:20 - 13:35 15’	Background	• The need to measure and articulate the full value of enteric vaccines.	For decision	M. Hasso-Agopsowicz
13:35 - 14:10 35’	Technical presentation	• The proposed approach to measure the morbidity associated with enteric infections: prioritised workstreams and pathogens, expected results ***Background reading materials***: *See SharePoint*		M. Hasso-Agopsowicz E. Rogawski

14:10 - 14:40
30’
	Q&A and Discussion	• IVIR-AC discusses presentation, clarifies on content and acknowledges main issues
		• Questions to IVIR-AC:
		  • Does IVIR-AC agree with the approach to prioritise the list of pathogens for the assessment of morbidity?
		  • Does IVIR-AC agree with the proposed analyses to measure the impact of enteric infections on long term morbidity?
		  • Does IVIR-AC agree with the proposed approach to systematic reviews to measure the morbidity burden of enteric infections?
				S. Flasche, J Leask, JD Lelievre

14:40- 14:50 10’	Wrap up	• Summarize day’s findings and request any follow up from WHO Secretariat/IVIR-AC FPs for closed session	For information	W. Orenstein, Chair

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10 March

Duration	Title	Content and key questions to IVIR-AC	Purpose	Proposed speaker
Session 6: VIMC				
12:00 - 12:15 15’	Background	• This for information session serves to update the IVIRAC on new models and ongoing projects of VIMC	For information	R. Hutubessy /Y. Sim
12:15 – 12:35 20’	Presentation on updates	• Update the IVIRAC on ongoing projects of VIMC ***Background reading materials***: *See SharePoint*		K. Gaythorpe
12:35 - 12:55 20’	Q&A and Discussion	• IVIR-AC discusses presentation, clarifies on content and acknowledges main issues		J. Wu and J.D. Lelièvre
12:55 - 14:00 65’	Break			
Session 7: IA2030				
14:00 - 14:10 10’	Background	• In September 2021, IVIR-AC reviewed the current status of work on validation of the first iteration of death averted estimates for high-income countries and uncertainty analysis. IVIR-AC provided feedback on the effectiveness of the proposed uncertainty methodology, its utility with respect to the vaccine impact estimates, and the appropriateness of their planned validation approach • The project team will present updates based on the previous recommendations and request further feedback from the committee	For information	Y. Sim
14:10 - 14:20 10’	Technical presentation	• The project team will present the results of their uncertainty and sensitivity analyses, highlighting the impact of draw-level propagation of uncertainty on the magnitude of prediction intervals for deaths		W. Msemburi, A. Carter

		averted. In addition, the team will follow-up on previous recommendations regarding the validation of deaths averted estimates in high-income countries and the incorporation of SIA for measles in response to COVID interruptions. • Questions to IVIRAC: o Do the estimated predication intervals align with expectations about the level of uncertainty surrounding the vaccine impact metric? o Do the visualizations we shared effectively communicate uncertainty to the broader audience for our estimates? o Does the presented validation exercise for high-income estimates address concerns about the extrapolation from low- and middle-income economies? o Do the updated estimates of measles vaccine impact after incorporation of SIA seem credible? ***Background reading materials***: *See SharePoint*		
14:20 - 14:40 20’	Q&A and Discussion	• IVIR-AC discusses presentation, clarifies on content and acknowledges main issues		S. Verguet and J. Wu
14:40 - 14:50 10’	Wrap up	• Summarize day’s findings and request any follow up from WHO Secretariat/IVIR-AC FPs for closed session	For information	W. Orenstein, Chair

11 March	
Closed session: IVIR-AC members only	
12:00 - 16:00	**IVIR-AC reporting/recommendations**

Meeting of the Advisory Committee on Immunization and Vaccines-related Implementation Research (IVIR-AC)
Microsoft Teams - Virtual Meeting
WHO Headquarters, Geneva, Switzerland 7 - 11 March 2022

Draft list of participants

Advisory Committee Members

Habib Hasan Farooqui, Public Health Foundation of India, Gurugram, Haryana, **India**

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**

Mark Jit, Department of Infectious Disease Epidemiology, London School of Hygiene and 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**

Jean-Daniel Lelièvre, Department of Clinical Immunology, National Institute of Health and Medical Research (INSERM), CHU Henri Mondor, Créteil, **France**

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**

Victoria Nankabirwa, Department of Epidemiology and Biostatics, School of Public Health, College of Health Sciences, Makerere University, Kampala, **Uganda**

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**

Stéphane Verguet, Department of Global Health and Population, Harvard T.H. Chan School

of Public Health, Boston, **United States of America**

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

Karen Canfell, The Daffodil Centre, Faculty of Medicine and Health, The University of Sydney Cancer Council Australia, Sydney, **Australia**

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

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

Matthew Ferrari, Center for Infectious Disease Dynamics; Huck Career Development Professor; Professor of Biology, **United States of America**

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**

Patrick O'Connor, Centers for Disease Control and Prevention, Atlanta, **United States of America**

Allison Portnoy, Harvard University, Center for Health Decision Science, Harvard T. H. Chan School of Public Health, Boston, **United States of America**

Holly Prudden, Consultant, Sexual Health and Reproductive Cancers, World Health Organization, London, **United Kingdom of Great Britain and Northern Ireland.**

Alyssa Sbarra, London School of Hygiene & Tropical Medicine, London**, United Kingdom of Great Britain and Northern Ireland**

Observers/Standing participants

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

Eduardo Azziz Baumgartner, Centers for Disease Control and Prevention, Atlanta,

United States of America

IFPMA representative (TBC)

Logan Brenzel, Bill and Melinda Gates Foundation, Seattle, **United States of America**

Joseph Brezee, Partnership for Influenza Vaccine Introduction, Georgia, **United States of America**

Hsiu-Hsi Chen, Institute of Epidemiology and Preventive Medicine, College of Public Health, NTU

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

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

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

Michael Lynch, Centers for Disease Control and Prevention, Atlanta, **United States of America**

Meg McCarron, 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**

Rajinder Suri, Developing Countries Vaccine Manufacturers Network International (DCVMN), Geneva, **Switzerland**

Nicolas Theopold, Bill and Melinda Gates Foundation, Seattle, **United States of America**

Kirsten Vannice, Bill and Melinda Gates Foundation, Seattle, **United States of America**

Elizabeth Tacket Rogawski McQuade, Emory University, **United States of America**

Regional and Country Offices

Sweetc Alipon, World Health Organization, Regional Office for the Western Pacific, Manila, **Philippines**

Don Ananda Chandralal Amarasinghe, World Health Organization, Regional Office for the Western Pacific, Manila, **Philippines**

Syeda Kanwal Aslam, World Health Organization, Islamabad Country Office, Islamabad**, Pakistan**

Tigran Avagyan, World Health Organization, Regional Office for the Western Pacific, Manila, **Philippines**

Sunil Kumar Bahl, World Health Organization, Regional Office for South-East Asia, New Delhi, **India**

Jarbas Barbosa, World Health Organization, Regional Office for the Americas, Washington DC, **United States of America**

Nyambat Batmunkh, World Health Organization Regional Office for the Western Pacific, Manila, **Philippines**

Ado Bwaka, World Health Organization, Burkina Faso Country Office, Ouagadougou, **Burkina Faso**

Heeyoun Cho, World Health Organization, Regional Office for the Western Pacific, Manila, **Philippines**

Brett Janson Craig, World Health Organization, Regional Office for Europe, Copenhagen**, Denmark**

Eltayeb Elfakki, World Health Organization, Regional Office for the Eastern Mediterranean, Cairo**, Egypt**

Kamal Fahmy, World Health Organization, Regional Office for the Eastern Mediterranean, Cairo**, Egypt**

Andrés de Francisco, World Health Organization, Regional Office for the Americas, Washington DC, **United States of America**

Margherita Ghiselli, World Health Organization, Regional Office for the Americas, Washington DC, **United States of America**

Varja Grabovac, World Health Organization, Regional Office for the Western Pacific, Manila, **Philippines**

José Hagan, World Health Organization, Regional Office for Europe, Copenhagen**, Denmark**

Quamrul Hasan, World Health Organization, Regional Office for the Eastern Mediterranean, Cairo**, Egypt**

Sudhir Khanal, World Health Organization, Regional Office for South-East Asia, New Delhi, **India**

Emmaculate Jepkorir Lebo, World Health Organization, Zimbabwe Country Office, Harare, **Zimbabwe**

Balcha Girma Masresha, World Health Organization, Zimbabwe Country Office, Harare, **Zimbabwe**

Balcha Masresha, World Health Organization, Regional Office for Africa, Brazzaville, **Republic of the Congo**

Osama Mere, World Health Organization, Regional Office for the Eastern Mediterranean, Cairo**, Egypt**

Richard Mihigo, World Health Organization, Regional Office for Africa, Brazzaville, **Republic of the Congo**

Nasrin Musa, World Health Organization, Regional Office for the Eastern Mediterranean, Cairo**, Egypt**

Siff Malue Nielsen, World Health Organization, Regional Office for Europe, Copenhagen**, Denmark**

Lucia De Oliveira, World Health Organization Regional, Office for the Americas, Washington DC, **United States of America**

Desiree Pastor, World Health Organization Regional, Office for the Americas, Washington DC, **United States of America**

Roberta Pastore, World Health Organization, Regional Office for Europe, Copenhagen**, Denmark**

Gloria Rey, World Health Organization, Regional Office for the Americas, Washington DC, **United States of America**

Nora Rodriguez, World Health Organization, Regional Office for the Americas, Washington DC, **United States of America**

Alba Maria Ropero, World Health Organization, Regional Office for the Americas, Washington DC, **United States of America**

Gerald Sume, World Health Organization, Regional Office for the Eastern Mediterranean, Cairo**, Egypt**

Masamitsu Takamatsu, Consultant, World Health Organization Regional Office for the Western Pacific, Manila, **Philippines**

Yoshihiro Takashima, World Health Organization, Regional Office for the Western Pacific, Manila, **Philippines**

Patricia Tanifum, World Health Organization, Gabon Country Office, Libreville, **Gabon**

Maite Vera, World Health Organization, Regional Office for the Americas, Washington DC, **United States of America**

Martha Velandia, World Health Organization, Regional Office for the Americas, Washington DC, **United States of America**

WHO Secretariat

Shirley Bennett, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Melanie Bertram, Economic Evaluation and Analysis, World Health Organization, **Switzerland**

Adwoa Bentsi-Enchill, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Austin Carter, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

Diana Chang-Blanc, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

Natasha Crowcroft, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

Tessa Edejer, Economic Evaluation and Analysis, World Health Organization, **Switzerland**

Isabel Frost, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

Marta Gacic-Dobo, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

Deepa Gamage, Consultant, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

Tracey Goodman, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

Sami Lynne Gottlieb, Sexual Health and Reproductive Cancers, World Health Organization, **Switzerland**

Santosh Gurung, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

Lee Lee Ho, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

Joachim Hombach, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Mateusz Hasso-Agopsowicz, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

Raymond Hutubessy, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Maarten Jansen, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Anna-lea Kahn, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Philipp Lambach, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Ann Lindstrand, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Kathleen Morales, **C**onsultant to WHO, **Czech Republic**

William Msemburi, Division of Data, Analytics and Delivery for Impact, World Health Organization, **Switzerland**

Melanie Marti, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Ann Moen, Global Infectious Hazard Preparedness, World Health Organization, **Switzerland**

William Msemburi, Division of Data, Analytics and Delivery for Impact, World Health Organization, Switzerland

Katherine O'Brien, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Minal Patel, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

William Perea, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

Alex Rosewell, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

Shalini Desai, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

Maryam Sadeghimehr, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

Stephanie Shendale, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

So Yoon Sim, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Dijana Spasenoska, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Annelis Wilder-Smith, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Karene Yeung, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

World Health Organization

WER summary of last IVIRAC

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

26 NOVEMBER 2021, 96th YEAR / 26 NOVEMBRE 2021, 96e ANNÉE
No 47, 2021, **96**, 569–584
http://www.who.int/wer

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Sommaire

Meeting of the Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC), September 2021

The IVIR-AC recommendations are based on discussions during a virtual meeting of the IVIR-AC held 30 August–4 September 2021.

COVID-19 vaccine impact modelling

The COVID-19 Vaccine Impact Modelling Subgroup of the WHO Strategic Advisory Group of Experts on Immunization (SAGE) Working Group on COVID-19 vaccines, provides modelling guidance to inform global policy recommendations related to prioritization and use of COVID-19 vaccines. In March 2021, IVIR-AC advised[1] the subgroup on additional modelling questions to prioritize beyond those included in the Request for Proposals (RFP) issued in January 2021.[2] In preparation for the upcoming SAGE meeting in October 2021, the 8 modelling groups selected from the RFP presented their findings and methodologies to address the RFP questions. IVIR-AC was asked to provide feedback on the work of each modelling group, including their key messages to SAGE, and to provide recommendations on the type and degree of future modelling support to inform SAGE, WHO, and countries in their COVID-19 vaccination decision-making.

[1] See No. 17, 2021, pp.133–143.

[2] Modeling epidemiological, social and economic impacts of COVID-19 vaccination strategies (https://www.ungm.org/Public/Notice/120376, accessed 16 September 2021).

Réunion du Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC), septembre 2021

Les recommandations de l'IVIR-AC présentées dans le présent document se fondent sur les discussions qui ont eu lieu lors d'une réunion virtuelle du Comité qui s'est tenue du 30 août au 4 septembre 2021.

Modélisation de l'impact des vaccins contre la COVID-19

Le sous-groupe chargé de la modélisation de l'impact des vaccins anti-COVID-19, qui fait partie du groupe de travail sur les vaccins anti-COVID-19 du Groupe stratégique consultatif d'experts sur la vaccination (SAGE) de l'OMS, fournit des conseils en matière de modélisation afin d'éclairer les recommandations stratégiques mondiales relatives à l'établissement des priorités et à l'utilisation des vaccins contre la COVID-19. En mars 2021, l'IVIR-AC a conseillé[1] au sous-groupe d'aborder de nouvelles questions prioritaires de modélisation, au-delà de celles figurant déjà dans l'appel à propositions émis en janvier 2021.[2] En prévision de la réunion du SAGE d'octobre 2021, les 8 groupes de modélisation sélectionnés à l'issue de l'appel à propositions ont présenté leurs résultats et les méthodes employées pour répondre aux questions énoncées dans l'appel à propositions. Il a été demandé à l'IVIR-AC d'émettre des commentaires sur les travaux de chaque groupe de modélisation, y compris sur les informations clés à communiquer au SAGE, et de formuler des recommandations sur le type et l'étendue des activités de modélisation qui seront nécessaires à l'avenir pour orienter les décisions du SAGE, de l'OMS et des pays en matière de vaccination contre la COVID-19.

[1] Voir N° 17, 2021, pp. 133-143.

[2] Modeling epidemiological, social and economic impacts of COVID-19 vaccination strategies (https://www.ungm.org/Public/Notice/120376, consulté le 16 septembre 2021).

Summary of IVIR-AC feedback and recommendations

IVIR-AC focused on critical modelling elements of relevance across the modelling groups and recommended:

- to incorporate different levels of health systems and vaccine delivery constraints into the models – factors which influence rapid and equitable distribution of vaccines;
- to standardize model input parameters and datasets to enable direct comparison of model outputs and outcomes;
- to provide evidence to support model inputs, while also stating whether the inputs are based on expert opinion, data, or a combination of both;
- to indicate which vaccine(s) and variant(s) are assumed in each model, as well as any vaccine specific details (e.g. brand and type) and characteristics (e.g. mRNA vaccines, dosing intervals, and variations in efficacy);
- to make clear and transparent the current limitations of assumptions that use presumed immunological correlates of protection;
- to include the impact of vaccination and natural infection on transmission, including exploring the robustness of conclusions to different assumptions about the presumed correlates of protection (e.g. how antibody levels correlate with protection against infection and disease);
- to incorporate the overall impact – including economic and societal effects – of infections which lead to long-term adverse impact on health and quality of life (e.g. long COVID);
- to perform modelling exercises at the regional level (e.g., as conducted by the Institute for Clinical Effectiveness and Health Policy[3]);
- to strengthen engagement with policy-makers at the national and regional levels;
- to consider variations in public health and social measures – also known as non-pharmaceutical interventions – which may be felt more intensely in disadvantaged population groups, thus exacerbating inequities.

IVIR-AC further suggested that all modelling groups involved in the RFP make a fully commented version of their code available through open access, to ensure full transparency and replicability. IVIR-AC reiterated their role to organize, support, and propose modelling in support of SAGE policy recommendations. To that end, IVIR-AC:

- highlighted the importance of maintaining future engagement and support to the subgroup;
- proposed hosting a small symposium for all modelling groups to engage in smaller group discussions, to resolve and present discrepancies in diverging

[3] ICES: https://www.iecs.org.ar/en/ (accessed September 2021).

Résumé des observations et des recommandations de l'IVIR-AC

L'IVIR-AC s'est concentré sur les éléments essentiels de modélisation qui étaient pertinents pour l'ensemble des groupes de modélisation et a recommandé:

- d'intégrer dans les modèles différents niveaux de contraintes liées aux systèmes de santé et à l'administration des vaccins, car ces dernières sont des facteurs qui influent sur la distribution rapide et équitable des vaccins;
- de standardiser les paramètres et les données d'entrée des modèles pour permettre une comparaison directe des produits et des résultats de modélisation;
- de fournir des preuves à l'appui des intrants de la modélisation, en précisant également si ces derniers se fondent sur des avis d'experts, sur des données ou sur une combinaison des deux;
- d'indiquer quel(s) vaccin(s) et variant(s) sont pris en compte dans chaque modèle, ainsi que les détails relatifs à chaque vaccin (marque et type, par exemple) et à ses caractéristiques (par exemple, vaccins à ARNm, intervalles d'administration et variations de l'efficacité);
- d'indiquer de manière claire et transparente les limites actuelles des hypothèses reposant sur des corrélats immunologiques présumés de la protection;
- d'inclure l'impact de la vaccination et de l'infection naturelle sur la transmission, y compris en examinant la fiabilité des conclusions obtenues à partir de différentes hypothèses relatives aux corrélats présumés de la protection (par exemple, corrélation entre les niveaux d'anticorps et la protection contre l'infection et la maladie);
- de tenir compte de l'impact global, y compris sur le plan économique et sociétal, des infections qui ont des effets négatifs à long terme sur la santé et la qualité de vie (notamment les formes prolongées de COVID-19);
- de mener des exercices de modélisation à l'échelle régionale (tels que ceux réalisés par l'Institute for Clinical Effectiveness and Health Policy,[3] par exemple);
- de renforcer la collaboration avec les décideurs politiques aux niveaux national et régional;
- de tenir compte de la variabilité des mesures sociales et de santé publique – aussi appelées interventions non pharmaceutiques – dont les effets peuvent être ressentis de manière plus intense par les groupes de population défavorisés, exacerbant ainsi les inégalités.

L'IVIR-AC a également suggéré que tous les groupes de modélisation ayant participé à l'appel à propositions fournissent en accès libre une version entièrement commentée de leur code de modélisation, afin de garantir une transparence et une reproductibilité complètes. L'IVIR-AC a réaffirmé sa mission consistant à organiser, soutenir et proposer des travaux de modélisation afin de guider l'élaboration de recommandations stratégiques par le SAGE. À cet effet, l'IVIR-AC:

- a souligné qu'il est important que ses activités de soutien et de collaboration avec le sous-groupe se poursuivent;
- a proposé d'organiser un colloque restreint réunissant tous les groupes de modélisation pour qu'ils puissent mener des discussions en petits groupes, présenter et résoudre

[3] IECS: https://www.iecs.org.ar/en/ (consulté en septembre 2021).

results, to look deeper at country-specific data, and to consider future priorities (such as modelling vaccinations in children or adolescents, or boosters);

- proposed development of slide templates using the model features and input parameter template presented by the modelling groups in order to harmonize across groups;

- stressed the importance of IVIR-AC's involvement in the subgroup of the SAGE working group on COVID-19 vaccines to ensure consistent and quick evaluation of COVID-19 vaccine models and to translate information into useful policy recommendations, without waiting for publications. The involvement of IVIR-AC in the COVID-19 vaccine modelling subgroup could aim:

  – to orientate the next RFP for country groupings (specific countries) to be studied;

  – to pose the next major modelling questions and approaches to answer them;

  – to provide a forum for IVIR-AC and the COVID-19 vaccine modelling community to maintain this important exchange on models for the greatest global health problem in 100 years;
  – to identify or propose publications to support the estimates in the model parameters.

IVIR-AC stressed that future work be coordinated with the COVID-19 Multi-model Comparison Collaboration[4] and the COVID-19 vaccine modelling subgroup of the SAGE working group on COVID-19 vaccines.

Centers for Disease Control and Prevention (CDC) measles immunity profiles

Measles remains a worldwide infectious disease causing unpredictable and explosive epidemic outbreaks in endemic settings. As a component of country risk assessments, Gavi, the Vaccine Alliance,[5] WHO regions, and the WHO measles outbreak strategic response plan (MOSRP)[6] rely on immunity profiles[7] to identify immunity gaps in the population. These gaps guide strategic decision-making around vaccine implementation and prioritization, including mobilization to prevent anticipated

[4] Clapham H, et al. Assessing fitness-for-purpose and comparing the suitability of COVID-19 multi-country models for local contexts and users [version 1; peer review: 1 approved, 1 approved with reservations]. Gates Open Res. 2021; 5:79 (https://doi.org/10.12688/gatesopenres.13224.1, accessed September 2021).

[5] Gavi the Vaccine Alliance: https://www.gavi.org (accessed September 2021).

[6] Measles outbreaks strategic response plan: 2021–2023: measles outbreak prevention, preparedness, response and recovery. Geneva: World Health Organization, 2010 (https://apps.who.int/iris/handle/10665/340657, accessed September 2021).

[7] Cutts FT, et al. Using models to shape measles control and elimination strategies in low- and middle-income countries: A review of recent applications. Vaccine. 2020; 38,5: 979–992 (https://doi.org/10.1016/j.vaccine.2019.11.020, accessed September 2021).

les divergences apparues dans les résultats, examiner de manière plus approfondie les données relatives à chaque pays et réfléchir aux priorités futures (comme la modélisation de la vaccination des enfants et des adolescents ou de la vaccination de rappel);

- a proposé que des diapositives types soient élaborées sur la base du modèle présenté par les groupes de modélisation, contenant les caractéristiques de modélisation et les paramètres d'entrée, à des fins d'harmonisation entre les différents groupes;
- a souligné qu'il est important que l'IVIR-AC soit impliqué dans les travaux du sous-groupe du SAGE chargé de la modélisation de l'impact des vaccins anti-COVID-19 pour favoriser une évaluation harmonisée et rapide des modèles relatifs aux vaccins contre la COVID-19 et la transposition des informations obtenues en recommandations stratégiques utiles, sans attendre leur publication. La collaboration de l'IVIR-AC avec le sous-groupe chargé de la modélisation de l'impact des vaccins anti-COVID-19 pourrait être axée autour des objectifs suivants:
  – orienter l'élaboration du prochain appel à propositions ciblant des groupes de pays (pays spécifiques) à étudier;
  – formuler les prochaines grandes questions de modélisation et définir les approches à adopter pour y répondre;
  – offrir un forum permettant à l'IVIR-AC et à la communauté de modélisation de l'impact des vaccins anti-COVID-19 de poursuivre leurs précieux échanges sur la modélisation face au plus grand problème de santé publique qu'ait connu le monde depuis 100 ans;
  – identifier ou proposer des publications pour étayer les estimations des paramètres de modélisation.

L'IVIR-AC a souligné que les travaux futurs devront être coordonnés avec le consortium de comparaison multi-modèles pour la COVID-19[4] et le sous-groupe chargé de la modélisation de l'impact des vaccins anti-COVID-19 du groupe de travail du SAGE sur les vaccins anti-COVID-19.

Profils immunitaires contre la rougeole des Centers for Disease Control and Prevention (CDC)

La rougeole est une maladie infectieuse qui reste présente à l'échelle mondiale, entraînant des flambées épidémiques imprévisibles et foudroyantes dans les zones d'endémie. Afin d'évaluer les risques dans les pays, l'Alliance Gavi,[5] les Régions de l'OMS et le Plan stratégique de riposte aux flambées de rougeole (MOSRP) de l'OMS[6] se servent des profils immunitaires[7] pour identifier les lacunes de l'immunité au sein de la population. Ces lacunes éclairent la prise de décisions stratégiques sur la mise en œuvre de la vaccination et l'établissement des priorités,

[4] Clapham H, et al. Assessing fitness-for-purpose and comparing the suitability of COVID-19 multi-country models for local contexts and users [version 1; peer review: 1 approved, 1 approved with reservations]. Gates Open Res. 2021; 5:79 (https://doi.org/10.12688/gatesopenres.13224.1, consulté en septembre 2021).

[5] Gavi, l'Alliance du Vaccin : https://www.gavi.org/fr (consulté en septembre 2021).

[6] Measles outbreaks strategic response plan: 2021–2023: measles outbreak prevention, preparedness, response and recovery. Genève: Organisation mondiale de la santé, 2010 (https://apps.who.int/iris/handle/10665/340657, consulté en septembre 2021).

[7] Cutts FT, et al. Using models to shape measles control and elimination strategies in low- and middle-income countries: A review of recent applications. Vaccine. 2020; 38,5: 979–992 (https://doi.org/10.1016/j.vaccine.2019.11.020, consulté en septembre 2021).

pated outbreaks. Measles immunity profiles estimate immunity gaps using readily available data such as annual number of births and previously collected vaccination coverage data – cost–effective alternatives to resource and time-intensive serosurveys. CDC presented the static model currently used to identify immunity gaps followed by Pennsylvania State University, who presented an alternative model incorporating population immunity impact (from infection) and vaccination coverage. IVIR AC was asked to review and provide feedback on the 2 methodologies when applied to assessing the measles risk at the country level.

Summary of IVIR-AC feedback and recommendations

IVIR-AC highlighted the importance of immunity profiles as a component of risk assessments and confirmed support of the CDC methodology for describing immunity profiles at the country level. IVIR-AC acknowledged the proposed enhancements to the methodology, including the degree to which MCV2[8] and supplementary immunization activity (SIA) doses reach children previously reached by MCV1;[8] incorporation of non-overlapping SIAs and phased SIAs by population segment; and age-dependent vaccine effectiveness, which will likely produce more robust and useful measles immunity profiles. Further to this, IVIR-AC:

- approved the use of the programming language R/Python[9] as platforms for sharing publicly accessible codes and for higher precision, more realistic assumptions, and improved efficiency in generating profiles for WHO Member States;
- recommended the development of the methodology for subnational immunity profiles and risk assessments to the extent possible, to allow for a more spatially precise analysis of risk;
- highlighted that prioritization of interventions towards high-risk locations may increase the health and economic value of SIAs and outbreak response actions; even still, targeted SIAs may be equally effective and lead to fewer disruptions to routine immunization programmes;
- acknowledged that the reliability of subnational immunity profiles and risk assessments will depend on the availability of good-quality data at this scale;
- supported conducting a formal quantitative validation of the immunity profiles by comparing to a gold-standard, such as serosurveys, and then reporting back to IVIR-AC in the future with the results of these formal quantitative validations;

[8] MCV1: first dose of measles-containing vaccine; MCV2: second dose of measles-containing vaccine.

[9] See https://www.r-project.org

y compris les efforts de mobilisation nécessaires pour prévenir les flambées épidémiques attendues. Les profils immunitaires contre la rougeole permettent d'estimer les lacunes immunitaires à l'aide de données aisément disponibles, comme le nombre annuel de naissances et les données antérieures sur la couverture vaccinale. Cette approche constitue une alternative économiquement avantageuse aux enquêtes sérologiques, lesquelles exigent beaucoup de temps et de ressources. Les CDC ont décrit le modèle statique actuellement employé pour identifier les lacunes immunitaires, puis la Pennsylvania State University a présenté un nouveau modèle intégrant l'impact de l'immunité de la population (induite par l'infection) et la couverture vaccinale. Il a été demandé à l'IVIR-AC d'examiner ces 2 méthodes et d'émettre des commentaires sur leur application à l'évaluation des risques de rougeole à l'échelle des pays.

Résumé des observations et des recommandations de l'IVIR-AC

L'IVIR-AC a souligné que les profils immunitaires sont d'un apport important dans l'évaluation des risques et a confirmé son appui à la méthodologie appliquée par les CDC pour décrire les profils immunitaires au niveau national. L'IVIR-AC a salué les améliorations proposées à cette méthodologie, notamment la prise en compte du niveau de couverture du MCV2[8] et des activités de vaccination supplémentaire (AVS) parmi les enfants préalablement vaccinés par le MCV1,[8] l'incorporation d'AVS non chevauchantes et d'AVS échelonnées par segment de population, et l'efficacité vaccinale en fonction de l'âge, et a estimé que ces améliorations permettront probablement d'obtenir des profils plus rigoureux et plus utiles de l'immunité contre la rougeole. En outre, l'IVIR-AC:

- a approuvé l'utilisation du langage de programmation R/Python[9] pour fournir une plateforme de partage de codes accessibles au public et permettre la formulation d'hypothèses plus précises et plus réalistes, ainsi qu'une production plus efficace des profils pour les États Membres de l'OMS;
- a recommandé de développer la méthodologie pour permettre la génération des profils d'immunité et l'évaluation des risques au niveau infranational dans la mesure du possible, de sorte que les risques puissent être analysés avec une plus grande précision géographique;
- a souligné que le fait d'intervenir en priorité dans les zones à haut risque peut accroître l'utilité sanitaire et économique des AVS et des mesures de riposte aux flambées épidémiques; pour autant, la mise en œuvre d'AVS ciblées peut être tout aussi efficace et occasionner moins de perturbations des programmes de vaccination systématique;
- a reconnu que la fiabilité des profils immunitaires et des évaluations des risques au niveau infranational dépendra de la disponibilité de données de qualité à cette échelle;
- a préconisé de procéder à une validation quantitative formelle des profils immunitaires en les comparant à des profils de référence, comme ceux issus des enquêtes sérologiques, et de communiquer les résultats de ces validations à l'IVIR-AC à l'avenir;

[8] MCV1: première dose de vaccin à valence rougeole; MCV2: deuxième dose de vaccin à valence rougeole.

[9] Voir https://www.r-project.org

- highlighted that it is critical to pull from multiple sources of data when interpreting immunity profiles; this could include a historical comparison of multiple data sources to determine the value of each source and inform the need for additional data;
- suggested that to strengthen and inform immunity profiles and/or to supplement estimated immunity profiles in countries with poor information, the team could use vaccination coverage data beyond WHO and UNICEF Estimates of National Immunization Coverage (WUENIC) data,[10] case-surveillance data to inform age-distribution of cases, cohort analysis of case-surveillance data to inform on the fraction of vaccination among cases in comparison to that of the source population, or cohort studies/serosurveys to estimate immunity profiles from infection and immunization;
- recognized the importance of immunity from prior infections, but stressed the need for good quality data to make use of such data worthwhile;
- highlighted that incorporating the impact of infections on population immunity will be most informative where measles is endemic and vaccine coverage is low, and where immunity from infections will continue to play a role among older individuals, as cohorts age;
- pointed out that case surveillance data may improve priority-setting by WHO regions or within regions as the identification of high-risk countries for training, resource allocation and resource mobilization, thus aiding the mission of MOSRP to guide and inform comprehensive outbreak response efforts.

IVIR-AC suggested that future modelling efforts work towards distinguishing infection immunity from vaccination immunity and suggested the development of a rating system for evaluating the quality of the data used to inform immunity profiles.

Vaccine delivery cost projections

In March 2018, IVIR-AC requested that WHO develop normative guidance on *vaccine delivery costing*.[11] WHO subsequently discovered multiple organizations working to develop such guidance; hence, discussions among them led to a consensus statement and comprehensive review of 11 existing guidance documents and costing tools. The review identified 4 workstreams with a gap in vaccine delivery cost projections (one of the types of vaccine delivery costings). IVIR-AC was asked to review a proposed systematic literature review protocol on vaccine delivery cost projections.

- a souligné qu'il est essentiel d'avoir recours à plusieurs sources de données lors de l'interprétation des profils d'immunité; cela pourrait impliquer une comparaison historique de multiples sources de données pour établir l'utilité de chaque source et déterminer les besoins en données supplémentaires;
- a suggéré que pour améliorer et étayer les profils immunitaires et/ou pour compléter les estimations des profils immunitaires dans les pays pour lesquels les informations sont insuffisantes, l'équipe pourrait utiliser des données de couverture vaccinale autres que les estimations OMS/UNICEF de la couverture vaccinale nationale (WUENIC),[10] des données de surveillance des cas pour connaître la répartition par âge des cas, des analyses de cohorte des données de surveillance des cas pour déterminer le taux de vaccination des cas par rapport à celui de la population concernée, ou des études de cohorte/enquêtes sérologiques pour estimer les profils immunitaires à partir d'informations sur l'infection et la vaccination;
- a reconnu que l'immunité résultant d'infections passées joue un rôle important, mais a souligné la nécessité de disposer de données de qualité à ce sujet pour pouvoir en tirer parti;
- a souligné que la prise en compte de l'impact des infections sur l'immunité de la population sera particulièrement pertinente dans les zones où la rougeole est endémique et la couverture vaccinale est faible, et où l'immunité induite par l'infection demeurera un facteur important chez les personnes plus âgées, à mesure que les cohortes vieillissent;
- a fait remarquer que les données de surveillance des cas peuvent aider les Régions de l'OMS à mieux définir les priorités à l'échelle régionale ou infrarégionale en identifiant les pays à haut risque à cibler en termes de formation, d'allocation des ressources et de mobilisation des ressources, contribuant ainsi à la mission du MOSRP, qui est de guider et d'orienter les efforts globaux de riposte aux flambées.

L'IVIR-AC a préconisé que les modélisations futures s'efforcent de distinguer l'immunité induite par l'infection de l'immunité induite par la vaccination et a suggéré d'élaborer un système de notation permettant d'évaluer la qualité des données utilisées pour établir les profils immunitaires.

Projections des coûts de distribution des vaccins

En mars 2018, l'IVIR-AC a demandé à l'OMS d'élaborer des orientations à caractère normatif sur *l'établissement des coûts de distribution des vaccins*.[11] Par la suite, l'OMS a identifié plusieurs organisations œuvrant à l'élaboration de telles orientations ; des discussions entre ces organisations ont ainsi abouti à une déclaration consensuelle et à l'examen complet de 11 documents d'orientation et outils d'établissement des coûts existants. Cet examen a permis d'identifier 4 axes de travail présentant des lacunes dans les projections des coûts de distribution des vaccins (l'une des approches employées pour établir les coûts de distribution des vaccins). Il a été demandé à l'IVIR-AC d'examiner une proposition de protocole pour la conduite d'une revue systématique de la littérature sur les projections des coûts de distribution des vaccins.

[10] See https://www.doc.ic.ac.uk/~rak/papers/WUENIC%20JURASIN.pdf

[11] See No. 24, 2018, pp. 345–356.

[10] Voir https://www.doc.ic.ac.uk/~rak/papers/WUENIC%20JURASIN.pdf

[11] Voir N° 24, 2018, pp. 345-356.

Summary of IVIR-AC feedback and recommendations

IVIR-AC commended the group's effort in bringing together multiple partners to develop a consensus statement and clarified that this workstream can now be ended, and subsequent work can shift towards filling identified gaps. IVIR-AC stressed:

- the importance of including country representatives to ensure work plans meet their needs;
- the need to clarify the main purpose of future work in collaboration with partners (i.e. to obtain a final set of harmonized, comprehensive recommendations with possible sign-off from all partners);
- the importance of close communication with key global health partners and funders to avoid "reinventing the wheel";
- that WHO consider updating the 2002 guidelines on the costs of new vaccine introduction[12] and ensure that there is adequate time and resources to conduct this major exercise;
- the need to clarify use case(s) for any outcomes (e.g. cost estimates) generated from the literature review, as well as any future guidance;
- the systematic literature review on vaccine delivery cost projection as a useful way to fill a key evidence gap;
- the need to include all relevant vaccines in the search strategy;
- that the search strategy evaluates all adequate databases and includes sufficiently broad search terms.

CAPACITI: Decision–Making Resource Catalogue

IVIR-AC previously reviewed and recommended CAPACITI (Country-led Assessment for Prioritization on Immunization),[13] a decision-support tool for countries to prioritize and select between multiple vaccination products, services, or strategies. A complementary tool, the Decision–Making Resource Catalogue (not publicly available), supports end-users in: a) selecting decision criteria; and b) collecting high-quality evidence – 2 crucial steps when utilizing the CAPACITI decision-support tool. IVIR AC was requested to provide expert review on the user-friendliness, completeness and correctness of the Decision–Making Resource Catalogue as a repository of already existing tools, databases, and reports.

Résumé des observations et des recommandations de l'IVIR-AC

L'IVIR-AC a salué les efforts déployés par le groupe pour rassembler plusieurs partenaires en vue de formuler une déclaration consensuelle et a précisé que cet axe de travail peut désormais être considéré comme clos et que les travaux futurs devront se concentrer sur la résolution des lacunes identifiées. L'IVIR-AC a souligné:

- l'importance d'inclure des représentants des pays pour veiller à ce que les plans de travail répondent à leurs besoins;
- la nécessité de définir clairement l'objectif principal des travaux à venir en collaboration avec les partenaires (en vue d'obtenir un ensemble final de recommandations harmonisées et complètes, approuvées dans la mesure du possible par tous les partenaires);
- l'importance d'une communication étroite avec les principaux bailleurs de fonds et partenaires mondiaux dans le domaine de la santé pour éviter de «réinventer la roue»;
- la nécessité pour l'OMS d'envisager une mise à jour des lignes directrices de 2002 sur l'estimation des coûts liés à l'introduction de nouveaux vaccins[12] et de veiller à la disponibilité des ressources et du temps nécessaires pour mener à bien ce travail important;
- la nécessité de préciser le(s) scénario(s) d'utilisation des résultats issus de la revue de la littérature (estimation des coûts, par exemple), ainsi que les orientations susceptibles d'être formulées à l'avenir;
- la contribution utile apportée par la revue systématique sur la projection des coûts de distribution des vaccins pour combler un manque important de données;
- la nécessité d'inclure tous les vaccins pertinents dans la stratégie de recherche;
- la nécessité de veiller à ce que la stratégie de recherche porte sur toutes les bases de données pertinentes et que les termes de recherche employés soient suffisamment larges.

CAPACITI: Catalogue de ressources pour la prise de décision

Lors d'une réunion précédente, l'IVIR-AC avait examiné et recommandé l'outil d'aide à la décision CAPACITI (Country-led Assessment for Prioritization on Immunization),[13] conçu pour aider les pays à établir des priorités et opérer une sélection entre différents produits, services ou stratégies de vaccination. Un outil complémentaire, le Catalogue de ressources pour la prise de décision (non accessible au public), permet aux utilisateurs de a) sélectionner les critères de décision et b) recueillir des données de qualité – 2 étapes essentielles lors de l'utilisation de l'outil CAPACITI d'aide à la décision. Il a été demandé à l'IVIR-AC de fournir un avis d'expert sur la convivialité, l'exhaustivité et la fiabilité de ce catalogue de ressources pour la prise de décision, en tant que répertoire des outils, bases de données et rapports existants.

[12] Guidelines for estimating costs of introducing new vaccines into the national immunization system (No. WHO/V&B/02.11). Geneva: World Health Organization, 2002 (https://apps.who.int/iris/bitstream/handle/10665/67342/WHO_V-B_02.11_eng.pdf;sequence=1, accessed September 2021).

[13] See No. 49, 2020, pp. 609–628.

[12] Guidelines for estimating costs of introducing new vaccines into the national immunization system (No. WHO/V&B/02.11). Genève: Organisation mondiale de la santé, 2002 (https://apps.who.int/iris/bitstream/handle/10665/67342/WHO_V-B_02.11_eng.pdf;sequence=1, consulté en septembre 2021).

[13] See N° 49, 2020, pp. 609-628.

Summary of IVIR-AC feedback and recommendations

Overall, IVIR-AC found the resource catalogue to be a useful compilation of available tools, databases, and reports to support decision-makers assembling the evidence for programme evaluation under the CAPACITI decision-support tool and beyond. IVIR-AC found particularly helpful the organization of resources into relevant criteria including a side-by-side comparison of available resources within each category. Going forward, IVIR-AC stressed that:

- future efforts should focus on promoting and supporting use of the CAPACITI decision-support tool in countries, and gathering feedback to refine the tool based on user experience;
- development of a web-based platform should be prioritized to facilitate navigation of resources specific to user needs. A homepage menu should allow users to filter available resources to those that are more general, versus those specific to their needs (e.g. evaluation of a particular vaccine programme).
- CAPACITI[14] should liaise with WHO disease focal points and research partners to identify and build resources specific to each vaccine-preventable disease.
- The resource catalogue should aim to be as user-friendly as possible so as not to require additional training materials.
- CAPACITI should consider how the decision-support tool can be used to support decisions regarding emergency-use vaccines (e.g. COVID-19, Ebola) for which less information is available.
- The CAPACITI decision-support tool and Decision–Making Resource Catalogue should aim to accelerate the decision-making process and should facilitate changes to policy as more information becomes available (e.g. if recommendations need to be changed).

Immunization Agenda 2030 (IA2030) – vaccine impact modelling

In September 2020, IVIR-AC first reviewed the proposed analytical framework and methodologies for estimating the impact of vaccination, as part of the Immunization Agenda 2030: A Global Strategy to Leave No One Behind.[15] In March 2021, IVIR-AC provided detailed recommendations on the statistical modelling methodology, on communication and presentation of results, and

[14] See https://decidehealth.world/en/capaciti

[15] Immunization Agenda 2030: A Global Strategy to Leave No One Behind (https://www.who.int/teams/immunization-vaccines-and-biologicals/strategies/ia2030, accessed September 2021).

Résumé des observations et des recommandations de l'IVIR-AC

Dans l'ensemble, l'IVIR-AC a jugé que le catalogue de ressources constituait un répertoire utile des outils, bases de données et rapports disponibles pour aider les décideurs à rassembler les données probantes nécessaires à l'évaluation des programmes, que ce soit dans le cadre de l'outil d'aide à la décision CAPACITI ou dans d'autres contextes. L'IVIR-AC a trouvé particulièrement judicieux que les ressources soient organisées en fonction de critères pertinents, permettant notamment une comparaison côte à côte des ressources disponibles dans chaque catégorie. Pour la suite, l'IVIR-AC a souligné que:

- les activités futures devront se concentrer sur la nécessité de promouvoir et d'appuyer l'adoption de l'outil CAPACITI d'aide à la décision dans les pays et de recueillir des retours d'informations pour perfectionner l'outil sur la base des expériences des utilisateurs;
- la priorité devra être accordée à l'élaboration d'une plateforme en ligne permettant aux utilisateurs de naviguer plus facilement parmi les ressources en fonction de leurs besoins spécifiques. Il convient que la page d'accueil contienne un menu permettant aux utilisateurs de filtrer les résultats pour distinguer les ressources plus générales de celles qui répondent spécifiquement à leurs besoins (par exemple, évaluation d'un programme de vaccination particulier);
- une liaison devrait être établie entre CAPACITI[14] et les services de coordination de l'OMS chargés des différentes maladies, ainsi que les partenaires dans le domaine de la recherche, afin d'identifier et de rassembler des ressources spécifiques pour chaque maladie à prévention vaccinale;
- l'utilisation du catalogue de ressources devrait être aussi conviviale que possible afin de ne pas nécessiter de matériel de formation supplémentaire;
- il convient d'étudier comment l'outil d'aide à la décision CAPACITI peut être employé pour guider les décisions relatives aux vaccins destinés à une utilisation d'urgence (par exemple contre la COVID-19 ou la maladie à virus Ebola), pour lesquels les informations disponibles sont plus limitées;
- l'outil d'aide à la décision CAPACITI et le Catalogue de ressources pour la prise de décision doivent viser à accélérer le processus décisionnel et à faciliter les changements de politique lorsque de nouvelles informations deviennent disponibles (par exemple, si une modification des recommandations s'avère nécessaire).

Programme pour la vaccination à l'horizon 2030 (IA2030) – modélisation de l'impact des vaccins

En septembre 2020, l'IVIR-AC a procédé à un premier examen des méthodes et du cadre analytique proposés pour estimer l'impact de la vaccination, dans le cadre du Programme pour la vaccination à l'horizon 2030: Une stratégie mondiale pour ne laisser personne de côté.[15] En mars 2021, l'IVIR-AC a formulé des recommandations détaillées sur les méthodes de modélisation statistique, sur la communication et la présentation des résultats et sur les moyens d'extrapoler les résultats aux pays à

[14] Voir https://decidehealth.world/en/capaciti

[15] Programme pour la vaccination à l'horizon 2030: Une stratégie mondiale pour ne laisser personne de côté (https://www.who.int/fr/publications/m/item/immunization-agenda-2030-a-global-strategy-to-leave-no-one-behind, consulté en septembre 2021).

on ways to extrapolate results to high-income countries (HICs).[1] To respond to the previous IVIR-AC recommendations, the project team presented the current status of work on validation of the first iteration of estimates for HICs and their uncertainty analysis. IVIR-AC was requested to provide feedback on the effectiveness of the proposed uncertainty methodology, its utility with respect to the vaccine impact estimates, and the appropriateness of their planned validation approach.

Summary of IVIR-AC feedback and recommendations

IVIR-AC noted the importance of the team's work and commended their dedication to documenting transparency in estimating future deaths averted due to vaccination.

- IVIR-AC confirmed that using draw-level estimation for constructing uncertainty ranges is appropriate, and clarified that such sampling should draw from:
  - distributions of the "modelled" inputs which include: deaths averted, as estimated by the Vaccine Impact Modelling Consortium (VIMC);[16] global burden of disease mortality estimates; vaccine coverage estimates; sociodemographic index indicators, and healthcare access and quality index indicators, etc.;
  - distributions of vaccine efficacy data (from clinical trial results); and
  - distributions in the coefficients estimated from the regression model. (IVIR-AC further suggested using Latin hypercube sampling for independent inputs.)
- IVIR-AC suggested identifying the main drivers of uncertainty by producing 95% uncertainty ranges, beyond those for the base case, by removing one distribution of inputs at a time, and running multiple univariate sensitivity analyses.
- IVIR-AC suggested making a fully commented version of the code open access to ensure full transparency and replicability.
- IVIR-AC highlighted the need to develop targeted communications for a variety of audiences, and to consult communications guidelines or consider utilizing communications specialists skilled at conveying uncertainty.
- Regarding vaccine impact estimates in HICs, IVIR-AC proposed:
  - engaging with researchers and public health agencies currently producing HIC vaccine impact estimates;
  - translating outcomes in HICs (identified in a literature review) into deaths averted;

[16] See No.17, 2021, pp. 133–144.

revenu élevé.[1] Pour donner suite aux recommandations de l'IVIR-AC, l'équipe chargée du projet a présenté l'état actuel des travaux de validation de la première itération d'estimations pour les pays à revenu élevé et les résultats d'analyse de leur incertitude. L'IVIR-AC a été invité à émettre des commentaires sur l'efficacité de la méthode proposée pour l'analyse de l'incertitude, sur son utilité pour les estimations de l'impact des vaccins et sur la pertinence de l'approche de validation prévue.

Résumé des observations et des recommandations de l'IVIR-AC

L'IVIR-AC a souligné l'importance du travail accompli par l'équipe et salué son engagement à documenter la transparence du processus d'estimation des futurs décès évités grâce à la vaccination.

- L'IVIR-AC a confirmé que l'utilisation d'estimations reposant sur des échantillons tirés pour établir les plages d'incertitude est appropriée, et a précisé que cet échantillonnage devrait être effectué à partir des éléments suivants:
  - distributions des intrants «modélisés», notamment: décès évités, tels qu'estimés par le Consortium de modélisation de l'impact des vaccins (VIMC, Vaccine Impact Modelling Consortium);[16] estimations de la charge de morbidité et de la mortalité à l'échelle mondiale; estimations de la couverture vaccinale; indicateurs sociodémographiques; et indicateurs relatifs à l'accès et à la qualité des soins de santé, etc.;
  - distributions des données d'efficacité vaccinale (provenant des essais cliniques); et
  - distributions des coefficients estimés à partir du modèle de régression. (L'IVIR-AC a en outre proposé d'utiliser l'échantillonnage par hypercube latin pour les intrants indépendants).
- L'IVIR-AC a suggéré d'identifier les principaux facteurs d'incertitude en produisant des plages d'incertitude à 95%, au-delà de celles du scénario de base, en supprimant une distribution d'intrants à la fois et en exécutant des analyses de sensibilité multiples à une variable.
- L'IVIR-AC a proposé qu'une version entièrement commentée du code de modélisation soit disponible en accès libre afin de garantir une transparence et une reproductibilité complètes.
- L'IVIR-AC a souligné la nécessité d'élaborer des matériels de communication ciblés pour divers publics et de consulter les lignes directrices relatives à la communication ou d'envisager de faire appel à des spécialistes de la communication possédant les compétences requises pour transmettre les informations sur l'incertitude.
- S'agissant des estimations de l'impact des vaccins dans les pays à revenu élevé, l'IVIR-AC a émis les propositions suivantes:
  - collaborer avec les chercheurs et les organismes de santé publique qui produisent actuellement des estimations de l'impact des vaccins dans les pays à revenu élevé;
  - traduire les résultats observés dans les pays à revenu élevé (identifiés par une revue de la littérature) en nombre de décès évités;

[16] Voir Nº 17, 2021, pp. 133-144.

  - incorporating findings from the literature review focused on HICs into the estimation procedure;
  - expanding the existing body of HICs literature to include previously published reviews; and,
  - identifying HICs with complete vital registration data of high-quality with attributable deaths and immunization coverage (for certain vaccines), to test model accuracy in replicating those vaccine-preventable deaths observed.
- In addition to total deaths, per vaccine, IVIR-AC recommended producing death rates per person vaccinated and per population and to consider reporting total deaths and death rates, by mortality levels, beyond the World Bank income and WHO regions groupings.
- IVIR-AC suggested compiling a table to document which estimates come from VIMC models and which are derived using additional statistical methods. IVIR-AC advised to elucidate the proportion of estimated deaths averted that is directly represented by the VIMC estimates.
- Given the significant contribution of measles and the likely important decrease in measles vaccine coverage due to COVID-19, IVIR-AC highlighted the critical importance of incorporating measles SIAs into the next modelling iterations.

Vaccine Impact Modelling Consortium

The VIMC[17] is a multinational collaboration of 21 research groups funded by Gavi, the Vaccine Alliance, and the Bill & Melinda Gates Foundation. The Consortium aims to deliver a more sustainable, efficient and transparent approach to generating estimates of disease burden and vaccine impact. This recurring information session at IVIR-AC meetings serves to update IVIR-AC on VIMC's latest models and ongoing workstreams. VIMC presented their latest consortium-wide publication[18] on lives saved with vaccination prior to COVID-19 and 4 ongoing workstreams looking at subnational heterogeneity in vaccine impact, impact post-2021 (with and without COVID-19 disruptions), the effect of clustering in coverage and the indirect benefit, and the impact of demographic uncertainty. IVIR-AC provided their perspective on the work presented.

Summary of IVIR-AC feedback and recommendations

- IVIR-AC commended VIMC for ongoing collaborations with WHO and IVIR-AC and thanked the

[17] The Vaccine Impact Modelling Consortium: https://www.vaccineimpact.org/ (accessed 16 September 2021).

[18] Toor, Jaspreet, et al. Lives saved with vaccination for 10 pathogens across 112 countries in a pre-COVID-19 world. elife. 2021; 10:e67635. https://elifesciences.org/articles/67635.pdf

  - intégrer les résultats de la revue de la littérature portant sur les pays à revenu élevé dans la procédure d'estimation;
  - élargir la base documentaire actuellement utilisée pour les pays à revenu élevé en incluant des revues publiées précédemment; et
  - identifier les pays à revenu élevé disposant de données d'état civil complètes et de qualité, avec des informations sur les causes de décès et sur la couverture vaccinale (pour certains vaccins), afin de vérifier la fiabilité et la capacité du modèle à reproduire le nombre constaté de décès évitables par la vaccination.
- Outre le nombre total de décès, présenté par type de vaccin, l'IVIR-AC a recommandé de produire les taux de mortalité par personne vaccinée et par population et d'envisager de rendre compte du nombre total de décès et des taux de mortalité, par niveau de mortalité, au-delà de la classification par revenu établie par la Banque mondiale et de la classification par Région de l'OMS.
- L'IVIR-AC a suggéré de dresser un tableau indiquant quelles estimations proviennent des modélisations du VIMC et lesquelles ont été obtenues à l'aide de méthodes statistiques supplémentaires. L'IVIR-AC a conseillé de préciser quelle proportion des décès évités estimés est directement représentée par les estimations du VIMC.
- Compte tenu du rôle considérable que joue la rougeole et de la forte baisse escomptée de la couverture vaccinale contre la rougeole en raison de la COVID-19, l'IVIR-AC a souligné qu'il sera indispensable d'intégrer les AVS contre la rougeole dans les prochaines itérations de la modélisation.

Consortium de modélisation de l'impact des vaccins

Le VIMC (Vaccine Impact Modelling Consortium)[17] est une collaboration multinationale comptant 21 groupes de recherche qui est financée par l'Alliance Gavi et la Fondation Bill et Melinda Gates. Ce consortium vise à offrir une approche plus durable, efficace et transparente pour la production des estimations de la charge de morbidité et de l'impact des vaccins. Lors des réunions de l'IVIR-AC, une séance d'information récurrente est organisée pour fournir à l'IVIR-AC des informations actualisées sur les derniers modèles et les travaux en cours du VIMC. Le VIMC a présenté la dernière publication du consortium,[18] portant sur les décès évités grâce à la vaccination avant la COVID-19, et a décrit ses 4 axes de travail actuels, consistant à étudier l'hétérogénéité de l'impact des vaccins au niveau infranational, l'impact à escompter après 2021 (avec et sans perturbations dues à la COVID-19), les effets du regroupement de la couverture et ses avantages indirects, et les effets de l'incertitude démographique. L'IVIR-AC a fait part de ses observations sur les travaux présentés.

Résumé des observations et des recommandations de l'IVIR-AC

- L'IVIR-AC s'est félicité que le VIMC continue de collaborer avec l'OMS et l'IVIR-AC et a remercié le secrétariat du

[17] The Vaccine Impact Modelling Consortium: https://www.vaccineimpact.org/ (consulté le 16 septembre 2021).

[18] Toor, Jaspreet, et al. Lives saved with vaccination for 10 pathogens across 112 countries in a pre-COVID-19 world. elife. 2021; 10:e67635. https://elifesciences.org/articles/67635.pdf

VIMC secretariat for addressing previous IVIR-AC recommendations and requests for clarification[1] in their latest publication.[17]

- IVIR-AC acknowledged VIMC's ongoing workstreams and highlighted the following points:
  - IVIR-AC and VIMC concur on the importance of ensuring transparency of assumptions and uncertainties (e.g. uncertainty in birth rates; mortality from other causes; and assumptions around immigration).
  - Given the possible overlaps of the planned works on clustering in coverage and the indirect benefit and subnational heterogeneity in vaccine impact, the interactions and synergies between the 2 workstreams should be further explored.
  - To capture the broader public health impact of the COVID-19 pandemic, models should incorporate and consider the potential morbidity/mortality impact of public health and social measures, in combination with vaccination. ■

VIMC d'avoir donné suite aux recommandations et demandes de précision de l'IVIR-AC[1] dans sa dernière publication.[17]

- L'IVIR-AC a pris acte des axes de travail actuels du VIMC et a souligné les points suivants:
  - L'IVIR-AC et le VIMC s'accordent sur la nécessité de garantir la transparence des hypothèses et des incertitudes (par exemple, incertitude des taux de natalité, mortalité due à d'autres causes, et hypothèses relatives à l'immigration).
  - Compte tenu des chevauchements possibles entre les axes de travail portant sur le regroupement de la couverture et ses avantages indirects et sur l'hétérogénéité de l'impact des vaccins au niveau infranational, il convient d'étudier de manière plus approfondie les interactions et les synergies entre ces 2 axes de travail.
  - Pour rendre compte de l'impact plus général de la pandémie de COVID-19 sur la santé publique, les modèles devraient examiner et intégrer l'impact potentiel des mesures sociales et de santé publique sur la morbidité/mortalité, en sus de la vaccination. ■

PERFORMANCE OF ACUTE FLACCID PARALYSIS (AFP) SURVEILLANCE AND INCIDENCE OF POLIOMYELITIS (DATA RECEIVED IN WHO HEADQUARTERS AS OF 9 NOVEMBER 2021)

FONCTIONNEMENT DE LA SURVEILLANCE DE LA PARALYSIE FLASQUE AIGUË (PFA) ET INCIDENCE DE LA POLIOMYÉLITE (DONNÉES REÇUES PAR LE SIÈGE DE L'OMS AU 9 NOVEMBRE 2021)

Country/area Pays/territoire	Performance of AFP surveillance, 2021 Fonctionnement de la surveillance de la PFA, 2021			Poliomyelitis cases Cas de poliomyélite			
				2020		2021	
	AFP cases reported Cas de PFA signalés	Annualized non-poliomyelitis AFP rate[1] Taux de PFA non poliomyélitique annuel[1]	AFP cases with adequate specimens[2] Cas de PFA avec échantillons conformes[2]	WPV1 PVS1	cVDPV[3, 4, 5] PVDVc[3, 4, 5]	WPV1 PVS1	cVDPV[3, 4, 5] PVDVc[3, 4, 5]
Regional totals – Totaux régionaux							
AFR	21 835	06.25	76%	0	559	0	360
AMR	1 003	00.48	18%	0	0	0	0
EMR	18 105	09.95	89%	140	547	2	55
EUR	867	00.62	87%	0	1	0	33
SEAR	21 858	04.69	86%	0	0	0	0
WPR	4 586	02.03	82%	0	2	0	0
Global total – Total mondial	**68 254**	**04.11**	**83%**	**140**	**1 112**	**2**	**448**
African Region – Région africaine (AFR)							
Algeria – Algérie	86	00.98	94%	–	–	–	–
Angola[4]	376	04.51	78%	–	3	–	–
Benin[4] – Bénin[4]	220	05.28	73%	–	3	–	3
Botswana	7	01.22	86%	–	–	–	–
Burkina Faso[4]	1121	15.78	77%	–	65	–	2
Burundi	72	01.61	79%	–	–	–	–
Cameroon[4] – Cameroun[4]	603	08.39	62%	–	7	–	2
Cabo Verde – Cap-Vert	2	01.03	50%	–	–	–	–
Central African Republic[4] – République centrafricaine[4]	148	08.02	78%	–	4	–	–
Chad[4] – Tchad[4]	786	14.97	90%	–	101	–	–
Comoros – Comores	4	01.19	100%	–	–	–	–
Congo[4]	133	08.53	69%	–	2	–	2
Côte d'Ivoire[4]	572	07.80	87%	–	63	–	–

Country/area Pays/territoire	Performance of AFP surveillance, 2021 Fonctionnement de la surveillance de la PFA, 2021			Poliomyelitis cases Cas de poliomyélite			
				2020		2021	
	AFP cases reported Cas de PFA signalés	Annualized non-poliomyelitis AFP rate[1] Taux de PFA non poliomyélitique annuel[1]	AFP cases with adequate specimens[2] Cas de PFA avec échantillons conformes[2]	WPV1 PVS1	cVDPV[3, 4, 5] PVDVc[3, 4, 5]	WPV1 PVS1	cVDPV[3, 4, 5] PVDVc[3, 4, 5]
Democratic Republic of the Congo[4] – République démocratique du Congo[4]	2675	07.98	73%	–	81	–	11
Equatorial Guinea – Guinée équatoriale	15	06.81	87%	–	–	–	–
Eritrea – Érythrée	93	04.09	91%	–	–	–	–
Eswatini	9	02.40	67%	–	–	–	–
Ethiopia[4] – Éthiopie[4]	1 255	03.47	66%	–	36	–	9
Gabon	38	09.24	55%	–	–	–	–
Gambia	25	03.64	76%	–	–	–	–
Ghana[4]	670	08.08	64%	–	12	–	–
Guinea[4] – Guinée[4]	295	07.02	84%	–	44	–	6
Guinea-Bissau[4] – Guinée-Bissau[4]	14	01.23	50%	–	–	–	3
Kenya	435	02.56	86%	–	–	–	–
Lesotho	5	00.73	60%	–	–	–	–
Liberia[4] – Libéria[4]	120	05.75	94%	–	–	–	3
Madagascar[5]	523	06.08	52%	–	2	–	10
Malawi	108	01.64	86%	–	–	–	–
Mali[4]	337	05.36	70%	–	52	–	–
Mauritania – Mauritanie	62	05.16	69%	–	–	–	–
Mauritius – Maurice	5	02.07	100%	–	–	–	–
Mozambique	369	03.95	62%	–	–	–	–
Namibia – Namibie	23	03.50	78%	–	–	–	–
Niger[4]	423	05.48	62%	–	10	–	5
Nigeria[4] – Nigéria[4]	6 241	09.53	82%	–	8	–	274
Reunion – Réunion	–	00.00	0%	–	–	–	–
Rwanda	85	01.85	100%	–	–	–	–
Saint Helena – Saint-Hélène	–	00.00	0%	–	–	–	–
Sao Tome and Principe – Sao Tomé-et-Principe	–	00.00	0%	–	–	–	–
Senegal[4] – Sénégal[4]	273	05.10	56%	–	–	–	16
Seychelles	–	00.00	0%	–	–	–	–
Sierra Leone[4]	144	05.41	92%	–	10	–	5
South Africa – Afrique du Sud	287	02.19	60%	–	–	–	–
South Sudan[4] – Soudan du Sud[4]	445	09.55	73%	–	50	–	9
Togo[4]	235	08.44	84%	–	9	–	–
Uganda – Ouganda	1 598	09.63	68%	–	–	–	–
United Republic of Tanzania – République-Unie de Tanzanie	627	03.45	98%	–	–	–	–
Zambia – Zambie	165	03.18	65%	–	–	–	–
Zimbabwe	106	02.40	62%	–	–	–	–
Region of the Americas – Région des Amériques (AMR)							
Argentina – Argentine	3	00.03	33%	–	–	–	–
Bolivia (Plurinational State of) – Bolivie (État plurinational de)	14	00.49	86%	–	–	–	–
Brazil – Brésil	184	00.52	55%	–	–	–	–
Canada	2	00.04	0%	–	–	–	–
CAREC – Centre d'épidémiologie des Caraïbes*	2	00.14	33%	–	–	–	–
Chile – Chili	20	00.67	80%	–	–	–	–
Colombia – Colombie	103	01.13	89%	–	–	–	–
Costa Rica	7	00.81	71%	–	–	–	–
Cuba	–	00.00	0%	–	–	–	–
Dominican Republic – République dominicaine	2	00.08	0%	–	–	–	–
Ecuador – Équateur	12	00.30	50%	–	–	–	–
El Salvador	22	01.57	91%	–	–	–	–
Guatemala	32	00.65	56%	–	–	–	–
Haiti – Haïti	8	00.26	63%	–	–	–	–
Honduras	37	01.50	89%	–	–	–	–

Country/area Pays/territoire	Performance of AFP surveillance, 2021 Fonctionnement de la surveillance de la PFA, 2021			Poliomyelitis cases Cas de poliomyélite			
				2020		2021	
	AFP cases reported Cas de PFA signalés	Annualized non-poliomyelitis AFP rate[1] Taux de PFA non poliomyélitique annuel[1]	AFP cases with adequate specimens[2] Cas de PFA avec échantillons conformes[2]	WPV1 PVS1	cVDPV[3, 4, 5] PVDVc[3, 4, 5]	WPV1 PVS1	cVDPV[3, 4, 5] PVDVc[3, 4, 5]
Mexico – Mexique	440	01.63	79%	–	–	–	–
Nicaragua	10	00.63	100%	–	–	–	–
Panama	5	00.53	80%	–	–	–	–
Paraguay	22	01.31	83%	–	–	–	–
Peru – Pérou	22	00.33	32%	–	–	–	–
United States of America – États-Unis d'Amérique	NA	00.00	0%	–	–	–	–
Uruguay	–	00.00	0%	–	–	–	–
Venezuela (Bolivarian Republic of) – Venezuela (République bolivarienne du)	56	00.90	48%	–	–	–	–
* These countries have been grouped together for reporting purposes. – Ces pays ont été regroupés dans le but de déclarer des cas.							
Eastern Mediterranean Region – Région de la Méditerranée orientale (EMR)							
Afghanistan[4]	3353	23.57	94%	56	308	1	43
Bahrain – Bahreïn	5	03.04	100%	–	–	–	–
Djibouti	4	01.45	75%	–	–	–	–
Egypt – Égypte	1 018	04.44	89%	–	–	–	–
Iran (Islamic republic of) – Iran (République islamique d')	532	03.01	96%	–	–	–	–
Iraq	568	05.13	91%	–	–	–	–
Jordan – Jordanie	30	01.56	100%	–	–	–	–
Kuwait – Koweït	39	05.94	87%	–	–	–	–
Lebanon – Liban	34	03.61	85%	–	–	–	–
Libya (State of) – Libye (État de)	64	03.53	100%	–	–	–	–
Morocco – Maroc	56	00.70	55%	–	–	–	–
Oman	8	01.06	75%	–	–	–	–
Pakistan[4]	10 380	19.54	87%	84	135	1	8
Qatar	9	04.65	89%	–	–	–	–
Saudi Arabia – Arabie saoudite	164	02.11	93%	–	–	–	–
Somalia[4] – Somalie[4]	302	07.45	96%	–	14	–	1
Sudan[4] – Soudan[4]	465	03.23	94%	–	59	–	–
Syrian Arab Republic – République arabe syrienne	370	05.50	91%	–	–	–	–
Tunisia – Tunisie	17	00.78	71%	–	–	–	–
United Arab Emirates – Émirats arabes unis	13	01.45	100%	–	–	–	–
West Bank and Gaza Strip – Cisjordanie et bande de Gaza	11	00.79	100%	–	–	–	–
Yemen[5] – Yémen[5]	663	06.35	90%	–	31	–	3
European Region – Région européenne (EUR)							
Albania – Albanie	1	00.25	100%	–	–	–	–
Andorra – Andorre	–	00.00	0%	–	–	–	–
Armenia – Arménie	6	00.00	100%	–	–	–	–
Austria – Autriche	1	00.00	0%	–	–	–	–
Azerbaijan – Azerbaïdjan	9	00.10	100%	–	–	–	–
Belarus – Bélarus	43	02.37	79%	–	–	–	–
Belgium – Belgique	NA	00.00	0%	–	–	–	–
Bosnia and Herzegovina – Bosnie-Herzégovine	–	00.00	0%	–	–	–	–
Bulgaria – Bulgarie	–	00.00	0%	–	–	–	–
Croatia – Croatie	–	00.00	0%	–	–	–	–
Cyprus – Chypre	–	00.00	0%	–	–	–	–
Czechia – Tchéquie	–	00.00	0%	–	–	–	–
Denmark – Danemark	NA	00.00	0%	–	–	–	–
Estonia – Estonie	–	00.00	0%	–	–	–	–
Finland – Finlande	NA	00.00	0%	–	–	–	–
France	NA	00.00	0%	–	–	–	–
Georgia – Géorgie	7	00.45	100%	–	–	–	–

Country/area Pays/territoire	Performance of AFP surveillance, 2021 Fonctionnement de la surveillance de la PFA, 2021			Poliomyelitis cases Cas de poliomyélite			
				2020		2021	
	AFP cases reported Cas de PFA signalés	Annualized non-poliomyelitis AFP rate[1] Taux de PFA non poliomyélitique annuel[1]	AFP cases with adequate specimens[2] Cas de PFA avec échantillons conformes[2]	WPV1 PVS1	cVDPV[3, 4, 5] PVDVc[3, 4, 5]	WPV1 PVS1	cVDPV[3, 4, 5] PVDVc[3, 4, 5]
Germany – Allemagne	NA	00.00	0%	–	–	–	–
Greece – Grèce	3	00.09	67%	–	–	–	–
Hungary – Hongrie	4	00.17	75%	–	–	–	–
Iceland – Islande	NA	00.00	0%	–	–	–	–
Ireland – Irlande	NA	00.00	0%	–	–	–	–
Israel – Israël	17	00.35	29%	–	–	–	–
Italy – Italie	16	00.00	63%	–	–	–	–
Kazakhstan	37	00.72	97%	–	–	–	–
Kyrgyzstan – Kirghizistan	31	00.28	81%	–	–	–	–
Latvia – Lettonie	1	00.37	0%	–	–	–	–
Lithuania – Lituanie	–	00.00	0%	–	–	–	–
Luxembourg	NA	00.00	0%	–	–	–	–
Malta – Malte	–	00.00	0%	–	–	–	–
Moldova (Republic of) – Moldavie (République de)	2	00.00	100%	–	–	–	–
Monaco	NA	00.00	0%	–	–	–	–
Montenegro – Monténégro	–	00.00	0%	–	–	–	–
Netherlands – Pays-Bas	NA	00.00	0%	–	–	–	–
North Macedonia – Macédoine du Nord	1	00.35	100%	–	–	–	–
Norway – Norvège	–	00.00	0%	–	–	–	–
Poland – Pologne	8	00.17	0%	–	–	–	–
Portugal	–	00.00	0%	–	–	–	–
Romania – Roumanie	–	00.00	0%	–	–	–	–
Russian Federation – Fédération de Russie	229	00.60	93%	–	–	–	–
San Marino – Saint Marin	NA	00.00	0%	–	–	–	–
Serbia – Serbie	4	00.18	75%	–	–	–	–
Slovakia – Slovaquie	1	00.00	100%	–	–	–	–
Slovenia – Slovénie	–	00.00	0%	–	–	–	–
Spain – Espagne	17	00.25	47%	–	–	–	–
Sweden – Suède	NA	00.00	0%	–	–	–	–
Switzerland – Suisse	4	00.37	0%	–	–	–	–
Tajikistan[4] – Tadjikistan[4]	158	03.79	95%	–	1	–	32
Turkey – Turquie	116	00.59	79%	–	–	–	–
Turkmenistan – Turkménistan	21	00.00	100%	–	–	–	–
Ukraine[4]	66	00.89	100%	–	–	–	1
United Kingdom – Royaume-Uni	NA	00.00	0%	–	–	–	–
Uzbekistan – Ouzbékistan	64	00.64	100%	–	–	–	–
South-East Asia Region – Asie du Sud-Est (SEAR)							
Bangladesh	1 034	02.13	99%	–	–	–	–
Bhutan – Bhoutan	2	01.26	50%	–	–	–	–
Democratic People's Republic of Korea – République populaire démocratique de Corée	109	02.69	100%	–	–	–	–
India – Inde	19 856	06.14	86%	–	–	–	–
Indonesia – Indonésie	509	00.94	75%	–	–	–	–
Maldives	2	02.26	50%	–	–	–	–
Myanmar	23	00.22	87%	–	–	–	–
Nepal – Népal	219	02.26	98%	–	–	–	–
Sri Lanka	43	01.16	84%	–	–	–	–
Thailand – Thaïlande	61	00.53	69%	–	–	–	–
Timor Leste	–	00.00	0%	–	–	–	–
Western Pacific Region – Pacifique occidental (WPR)							
Australia – Australie	50	02.68	64%	–	–	–	–
Brunei Darussalam – Brunéi Darussalam	1	01.97	100%	–	–	–	–
Cambodia – Cambodge	5	00.11	100%	–	–	–	–
China – Chine	3502	02.18	85%	–	–	–	–

Country/area Pays/territoire	Performance of AFP surveillance, 2021 Fonctionnement de la surveillance de la PFA, 2021			Poliomyelitis cases Cas de poliomyélite			
				2020		2021	
	AFP cases reported Cas de PFA signalés	Annualized non-poliomyelitis AFP rate[1] Taux de PFA non poliomyélitique annuel[1]	AFP cases with adequate specimens[2] Cas de PFA avec échantillons conformes[2]	WPV1 PVS1	cVDPV[3, 4, 5] PVDVc[3, 4, 5]	WPV1 PVS1	cVDPV[3, 4, 5] PVDVc[3, 4, 5]
China, Hong Kong SAR – Chine, Hong Kong RAS	6	00.00	100%	–	–	–	–
China, Macao SAR – Chine, Macao RAS	1	00.00	100%	–	–	–	–
Japan – Japon	–	00.00	0%	–	–	–	–
Lao People's Democratic Republic – République démocratique populaire lao	15	00.79	73%	–	–	–	–
Malaysia[5] – Malaisie[5]	85	02.28	76%	–	1	–	–
Mongolia – Mongolie	1	00.33	100%	–	–	–	–
New Zealand – Nouvelle-Zélande	7	01.74	43%	–	–	–	–
Pacific Island countries and areas – Pays et territoires insulaires du Pacifique*	11	02.38	55%	–	–	–	–
Papua New Guinea – Papouasie-Nouvelle-Guinée	26	02.03	50%	–	–	–	–
Philippines[4]	744	03.46	76%	–	1	–	–
Republic of Korea – République de Corée	28	00.89	79%	–	–	–	–
Singapore – Singapour	3	01.13	100%	–	–	–	–
Viet Nam	101	00.57	95%	–	–	–	–

*These countries have been grouped together for reporting purposes. – Ces pays ont été regroupés dans le but de déclarer des cas.

CAREC: Caribbean Epidemiology Centre; VDPV: vaccine-derived poliovirus; cVDPV1: circulating vaccine-derived poliovirus type-1; cVDPV2: circulating vaccine-derived poliovirus type-2; cVDPV3: circulating vaccine-derived poliovirus type-3. – Caribbean Epidemiology Centre, connu sous le nom de CAREC; PVDV: poliovirus dérivé d'une souche vaccinale; PVDV1c: poliovirus circulant dérivé d'une souche vaccinale de type 1; PVDV2c: poliovirus circulant dérivé d'une souche vaccinale de type 2; PVDV3c: poliovirus circulant dérivé d'une souche vaccinale de type 3.

Endemic countries are shaded. – Les pays d'endémie sont grisés.

[1] Annualized non-poliomyelitis AFP rate for 100 000 population aged <15 years. UNPD population data is used to calculate the non-polio AFP rate. – Taux annualisé de PFA non poliomyélitique pour 100 000 personnes âgées de <15 ans. Les données sur la population collectées par le Programme des Nations Unies pour le développement (PNUD) sont utilisées pour calculer le taux de PFA non poliomyélitique.

[2] Defined as 2 stool specimens collected within 14 days of onset of paralysis, 24–48 hours apart, except for the Region of the Americas, where only 1 specimen is collected. – Défini comme 2 échantillons de selles recueillis à 24-48 heures d'intervalle dans les 14 jours suivant l'apparition de la paralysie, à l'exception de la Région des Amériques, où 1 seul échantillon est recueilli.

[3] For cVDPV definition see document «Reporting and classification of vaccine-derived polioviruses» at http://polioeradication.org/wp-content/uploads/2016/09/Reporting-and-Classification-of-VDPVs_Aug2016_EN.pdf. Implementation as of 15 August 2015. Figures exclude cVDPV from non-AFP sources. – La définition d'un PVDVc est disponible (uniquement en langue anglaise) dans le document «Reporting and classification of vaccine-derived polioviruses», à l'adresse http://polioeradication.org/wp-content/uploads/2016/09/Reporting-and-Classification-of-VDPVs_Aug2016_EN.pdf. Mise en œuvre au 15 août 2015. Sont exclus de ces chiffres les PVDVc de source non-PFA.

[4] cVDPV2 reported in Afghanistan, Angola, Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Ethiopia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Niger, Nigeria, Pakistan, Philippines, Senegal, Sierra Leone, Somalia, South Sudan, Sudan, Tajikistan, Togo and Ukraine. – Des cas de PVDV2c ont été signalés en Afghanistan, en Angola, au Bénin, au Burkina Faso, au Cameroun, au Congo, en Côte d'Ivoire, en Éthiopie, au Ghana, en Guinée, en Guinée-Bissau, au Libéria, au Mali, au Niger, au Nigéria, au Pakistan, aux Philippines, en République centrafricaine, en République démocratique du Congo, au Sénégal, en Sierra Leone, en Somalie, au Soudan du Sud, au Soudan, au Tadjikistan, au Tchad, au Togo et en Ukraine.

[5] cVDPV1 reported in Madagascar, Malaysia and Yemen. – Des cas de PVDV1c ont été signalés à Madagascar, en Malaisie et au Yémen.

ND – Country not reporting AFP data or country conducting supplementary poliovirus surveillance through other means (e.g. environmental, enterovirus or both). – Pays ne rapportant pas de données sur la PFA ou pays menant une politique de surveillance de la polio supplémentaire par le biais d'autres moyens (par exemple, surveillance environnementale ou des entérovirus, ou les deux).

The most recent AFP and wild poliovirus data can be found on the WHO web site (https://extranet.who.int/polis/public/CaseCount.aspx) which is updated weekly. – Les données les plus récentes concernant les cas de PFA et les poliovirus sauvages peuvent être consultées sur le site OMS suivant: https://extranet.who.int/polis/public/CaseCount.aspx, où elles sont mises à jour une fois par semaine.

CORRIGENDUM TO No. 37, 2021

Published on 17 September 2021, vol. 96, 37 (pp. 445–460)

Cholera, 2020

Page 449, Table 1, Asia section

Please read as follows (changes shown in **red**).

RECTIFICATIF AU Nº 37, 2021

Publié le 17 septembre 2021, vol. 96, 37 (pp. 445-460)

Choléra, 2020

Page 449, Tableau 1, section sur l'Asie

Prière de lire comme suit (changements indiqués en **rouge**).

Table 1 **Number of cholera cases and deaths reported to WHO in 2020**
Tableau 1 **Nombre de cas de choléra et de décès signalés à l'OMS en 2020**

Region – Région	Country – Pays	Total no. of cases, including imported cases/deaths – Nombre total de cas (incluant cas importés et décès)	Imported cases – Cas importés	Deaths – Décès	Case- fatality rate (%) – Taux de létalité (%)
	Bangladesh	212	NR	NR	NR
	Cambodia – Cambodge	48	0	0	0
	China – Chine	11	0	0	0
	Inde – Inde	**70**	**NR**	**NR**	**NR**
	Iran (Islamic Republic of) – Iran (République islamique d'Iran)	**1**	**0**	**0**	**0**
	Iraq – Irak	**9**	**0**	**0**	**0**
Asia – Asie	Japan – Japon	**1**	**0**	**0**	**0**
	Pakistan	**21**	**NR**	**NR**	**NR**
	Philippines	**3**	**0**	**0**	**0**
	Taiwan, China – Taïwan, Chine	**1**	**0**	**0**	**0**
	Thailand – Thaïlande	7	0	1	14.3
	United Arab Emirates – Émirats arabes unis	13	13	0	0
	Yemen – Yémen	275 712	0	115	0.04

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@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?

1) Par le serveur Web de l'OMS: A l'aide de votre logiciel de navigation WWW, connectez-vous à la page d'accueil du REH à l'adresse suivante: **http://www.who.int/wer/**

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@listserv.who.int** en laissant vide le champ du sujet. Le texte lui même ne devra contenir que la phrase suivante: subscribe wer-reh. Une demande de confirmation vous sera envoyée en retour.

www.who.int/wer
Email • send message **subscribe wer-reh** to **listserv@listserv.who.int**
Content management & production • wantzc@who.int or werreh@who.int

www.who.int/wer
Email • envoyer message **subscribe wer-reh à listserv@listserv.who.int**
Gestion du contenu & production • wantzc@who.int or werreh@who.int

WHO web sites on infectious diseases – Sites internet de l'OMS sur les maladies infectieuses

Adolescent health	**https://www.who.int/health-topics/adolescent-health#tab=tab_1**	Santé des adolescents
Avian influenza	**https://www.who.int/health-topics/influenza-avian-and-other-zoonotic#tab=tab_1**	Grippe aviaire
Buruli ulcer	**https://www.who.int/health-topics/buruli-ulcer#tab=tab_1**	Ulcère de Buruli
Child health	**https://www.who.int/health-topics/child-health#tab=tab_1**	Santé des enfants
Cholera	**https://www.who.int/health-topics/cholera#tab=tab_1**	Choléra
COVID-19	**https://www.who.int/health-topics/coronavirus#tab=tab_1**	Maladie à coronavirus 2019 (COVID-19)
Dengue	**https://www.who.int/health-topics/dengue-and-severe-dengue#tab=tab_1**	Dengue
Ebola virus disease	**https://www.who.int/health-topics/ebola#tab=tab_1**	Maladie à virus Ebola
Emergencies	**https://www.who.int/emergencies/situations**	Situations d'urgence sanitaire
Emergencies dashboard	**https://extranet.who.int/publicemergency**	Tableau de bord des urgences sanitaires
Foodborne diseases	**https://www.who.int/health-topics/foodborne-diseases#tab=tab_1**	Maladies d'origine alimentaire
Global Health Observatory (GHO) data	**https://www.who.int/data/gho**	Données de l'Observatoire de la santé mondiale
Global Influenza Surveillance and Response System (GISRS)	**https://www.who.int/initiatives/global-influenza-surveillance-and-response-system**	Système mondial de surveillance et d'intervention
Global Outbreak Alert and Response Network (GOARN)	**https://extranet.who.int/goarn/**	Réseau mondial d'alerte et d'action en cas d'épidémie (GOARN)
Health topics	**https://www.who.int/health-topics/**	La santé de A à Z
Human African trypanosomiasis	**https://www.who.int/health-topics/human-african-trypanosomiasis#tab=tab_1**	Trypanosomiase humaine africaine
Immunization, Vaccines and Biologicals	**https://www.who.int/health-topics/vaccines-and-immunization#tab=tab_1**	Vaccination, Vaccins et Biologiques
Influenza	**https://www.who.int/health-topics/influenza-seasonal#tab=tab_1**	Grippe
International Health Regulations	**https://www.who.int/health-topics/international-health-regulations#tab=tab_1**	Règlement sanitaire international
International travel and health	**https://www.who.int/health-topics/travel-and-health#tab=tab_1**	Voyages internationaux et santé
Leishmaniasis	**https://www.who.int/health-topics/leishmaniasis#tab=tab_1**	Leishmaniose
Leprosy	**https://www.who.int/health-topics/leprosy#tab=tab_1**	Lèpre
Lymphatic filariasis	**https://www.who.int/health-topics/lymphatic-filariasis#tab=tab_1**	Filiariose lymphatique
Malaria	**https://www.who.int/health-topics/malaria#tab=tab_1**	Paludisme
Middle East respiratory syndrome coronavirus (MERS-CoV)	**https://www.who.int/health-topics/middle-east-respiratory-syndrome-coronavirus-mers#tab=tab_1**	Coronavirus du syndrome respiratoire du Moyen-Orient (MERS-CoV)
Neglected tropical diseases	**https://www.who.int/health-topics/neglected-tropical-diseases#tab=tab_1**	Maladies tropicales négligées
Onchocerciasis	**https://www.who.int/health-topics/onchocerciasis#tab=tab_1**	Onchocercose
OpenWHO	**https://openwho.org/**	OpenWHO
Outbreak news	**https://www.who.int/emergencies/disease-outbreak-news**	Flambées d'épidémies
Poliomyelitis	**https://www.who.int/health-topics/poliomyelitis#tab=tab_1**	Poliomyélite
Rabies	**https://www.who.int/health-topics/rabies#tab=tab_1**	Rage
Schistosomiasis	**https://www.who.int/health-topics/schistosomiasis#tab=tab_1**	Schistosomiase
Smallpox	**https://www.who.int/health-topics/smallpox#tab=tab_1**	Variole
Soil-transmitted helminthiases	**https://www.who.int/health-topics/soil-transmitted-helminthiases#tab=tab_1**	Géohelminthiases
Trachoma	**https://www.who.int/health-topics/trachoma#tab=tab_1**	Trachome
Tropical disease research	**https://tdr.who.int/**	Recherche sur les maladies tropicales
Tuberculosis	**https://www.who.int/health-topics/tuberculosis#tab=tab_1**	Tuberculose
Weekly Epidemiological Record	**http://www.who.int/wer**	Relevé épidémiologique hebdomadaire
WHO Lyon Office for National Epidemic Preparedness and Response	**https://www.who.int/about/structure/lyon-office**	Bureau OMS de Lyon pour la préparation et la réponse des pays aux épidémies
Yellow fever	**https://www.who.int/health-topics/yellow-fever#tab=tab_1**	Fièvre jaune
Zika virus disease	**https://www.who.int/health-topics/zika-virus-disease#tab=tab_1**	Maladie à virus Zika

World Health Organization

Background information to the sessions

World Health Organization

Session 1

Measles Case Fatality Ratio estimation

Measles Case Fatality Ratios

Background

Patrick O’Connor, MD, MPH

IVIR-AC meeting, (Remotely)

7 March 2022

Measles CFR: Background

- Robust, transparent, and dynamic age- and country-specific measles case fatality ratios (CFRs) are critical for updating WHO's measles mortality estimates – *limitations in data availability* were noted in recent reviews – literature search and predictive model to estimate measles CFR.
- 2021: IVIR-AC recommended continued updates of measles CFR estimates with increased transparency and systematic covariate selection.

Measles CFR: Background

Ongoing CFR work

- Use primary data – grey literature review – to estimate measles CFR estimates using unpublished primary data.
  - Support from WHO Regional and Country Offices
- Develop a study protocol and data collection tool to estimate age stratified measles CFR and contributory risks for deaths in outbreaks and high endemic settings.
  - Collect primary data for measles CFR – age/sex stratified risk factors.

Measles CFR: Background

- 2022: IVIR-AC to provide advise on the conceptual framework, preliminary modelling results, ongoing primary data needs, and best practices on promoting the longevity and utility of dynamic measles CFR estimates moving forward.
- *Measles CFR Working Group* to provide an update on methods, data and estimates.

Measles Case Fatality Ratio Estimation: Update on methods, data and estimates available

7 March 2022

Alyssa Sbarra[1,2], Allison Portnoy[3], Jon Mosser[2,4], Mark Jit[1], on behalf of Measles CFR Working Group

[1]Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine
[2]Institute for Health Metrics and Evaluation, University of Washington
[3]Center for Health Decision Science, Harvard T.H. Chan School of Public Health
[4]Department of Health Metrics Sciences, University of Washington

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Acknowledgements

- IVIR-AC members
- Measles CFR Working Group
  - Natasha Crowcroft (WHO)
  - Felicity Cutts (LSHTM)
  - Emily Dansereau (BMGF)
  - Matthew Ferrari (Penn State)
  - Deepa Gamage (WHO)
  - Katy Gaythorpe (VIMC)
  - Kendall Krause (BMGF)
  - Katrina Kretsinger (WHO / CDC)
  - Kevin McCarthy (IDM / BMGF)
  - Mark Papania (CDC)
  - Niket Thakkar (IDM / BMGF)

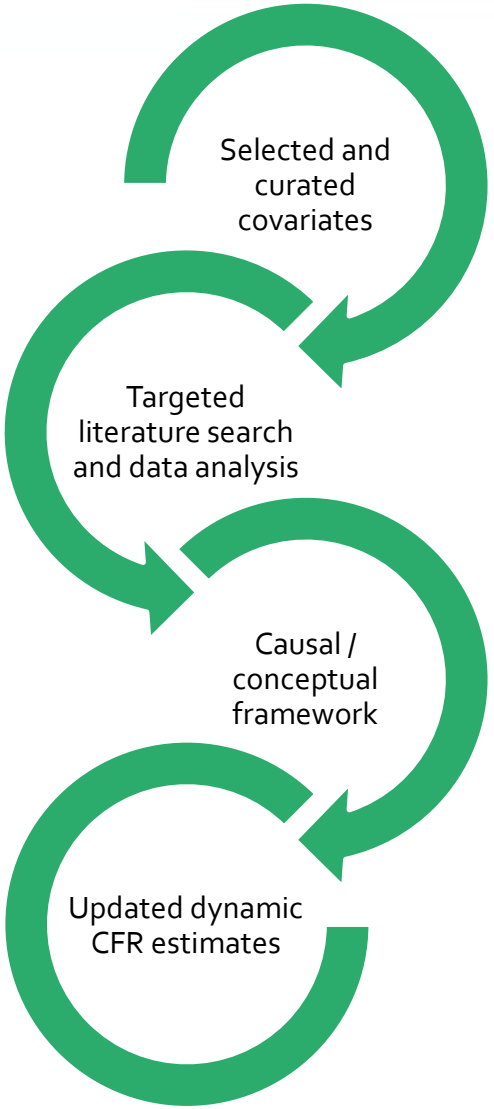
Outline

- Motivation
- Conceptual framework of indicators
    - Measles CFR Working Group
- Updates to CFR data and modeling

Motivation

Following the March 2021 meeting, IVIR-AC:

- recommended continued updates of dynamic measles CFR estimates;
- noted that time-varying CFRs will be sensitive to covariate selection and parameter estimates, which may present future methodological challenges;
- supported a clear rationale for covariates that have an explicit link to CFRs and that represent poverty and socioeconomic inequalities;
- supported possible use of 1) a theoretical model of causal factors that influence disease incidence and progression, and 2) geographical and other markers which represent the most vulnerable populations;
- supported possible inclusion of covariates on the short versus long-term impact of COVID-19 on healthcare capacity and the impact on vaccination coverage;
- encouraged acknowledgement of the importance of vitamin A therapy on CFRs; and
- recommended transparency and clear documentation.



WHO. Weekly epidemiological record. 30 April 2021. 96(17): 133 – 144.

Goal

Produce national-level age-specific estimates of measles CFR, by:

- Using national predictive modeling framework
- Accounting for incidence
- Extrapolating from heterogeneous within-country primary data

These estimates will:

- Be used for country-level modeling of measles mortality and vaccine impact
- Capture underlying dynamics of measles CFR

Outline

- Motivation
- Conceptual framework of covariates
    - Measles CFR Working Group
- Updates to CFR data and modeling

Conceptual framework of indicators

With the guidance and feedback from a working group of experts, we

- Identified all possible indicators and mechanistic groups as related to measles CFR
- Created a conceptual framework relating mechanistic groups to CFR
- Conducted a systematic literature review to assess strength evidence of relationships between indicators and CFR
- Searched databases for available covariate sets representing indicators and proxys
- Conducted data analysis to remove highly correlated and uninformative covariate sets
- Generated final covariate list

Mechanistic groups related to measles CFR

Health system access and care seeking behaviors

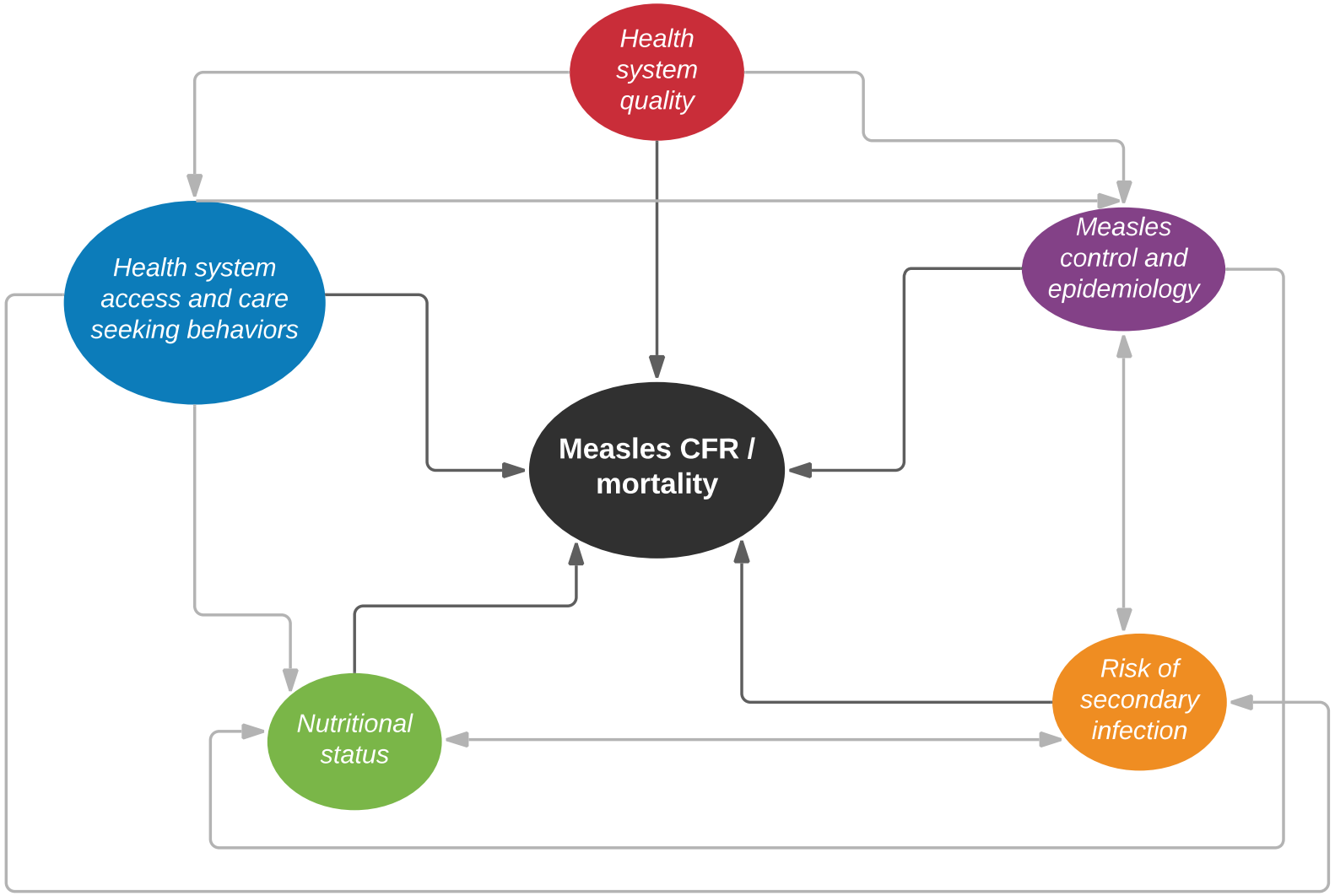
Health system quality

Nutritional status

Risk of secondary infection

Measles control and epidemiology

Conceptual framework



All possible indicators related to measles CFR

- Access to ICU
- Age
- Ambient air pollution
- Antibiotic use for measles-related pneumonia
- Asthma prevalence
- Autoimmune condition prevalence
- Average household size
- BCG vaccination coverage
- Breastfeeding prevalence
- Cancer prevalence
- De-worming frequency
- Diarrheal disease prevalence
- DTP vaccination coverage
- Health expenditure per capita
- Hib vaccination coverage,
- HIV prevalence,
- HIV treatment / ART prevalence,
- Household air pollution,
- Level of healthcare available,
- Lower respiratory infection prevalence
- Malaria prevalence
- Maternal (measles) vaccination coverage
- Maternal smoking prevalence
- Measles attack rate
- Measles incidence
- MCV1 coverage
- MCV2 coverage
- MenA vaccination coverage
- ORT/S for measles-related diarrhea
- Outbreak susceptibility
- Overweight prevalence
- PCV coverage
- Polio vaccination coverage
- Preterm birth prevalence
- Proxy for maternal antibody dynamics
- Proxy for vaccination coverage equity
- Rotavirus vaccine coverage
- Rubella vaccine coverage
- Sanitation quality
- Sex
- Stunting prevalence
- Surrounding conflict
- TB prevalence
- Time
- Time to care seeking
- Total fertility rate
- Travel time to major city or settlement
- Travel time to nearest health facility
- Under-5 mortality
- Underweight prevalence
- Vaccination efficacy
- Vaccination schedule
- Vitamin A deficiency prevalence
- Vitamin A supplementation prevalence
- Vitamin A treatment prevalence
- Wasting prevalence
- Water quality
- Yellow fever vaccination coverage

Pruned set of indicators – per mechanistic group

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Health system access & seeking

- Educational attainment
- Percent living in urban setting
- Surrounding conflict
- Travel time to nearest health facility
- Time to care seeking
- Travel time to major city or settlement

Nutritional status

- Stunting prevalence
- Underweight prevalence
- Vitamin A supplementation
- Vitamin A deficiency prevalence
- Wasting prevalence

Health system quality

- Access to ICU
- Health expenditure per capita
- Level of health care available
- Under-5 mortality

Risk of secondary infection

- Ambient air pollution
- Antibiotic use for measles-related pneumonia
- Average household size
- De-worming frequency
- Diarrheal disease prevalence
- HIV prevalence
- HIV treatment / ART prevalence
- Malaria (PF + PV) prevalence
- LRI prevalence
- ORT/S for measles-related diarrhea
- PCV vaccine coverage
- Population density
- Preterm birth prevalence
- TFR / average children per woman

Measles control & epidemiology

- Maternal (measles) vaccination coverage
- MCV1 coverage
- MCV2 coverage
- Measles attack rate
- Measles incidence
- Proxy for maternal antibody dynamics
- Proxy for vaccine coverage equity
- Vaccine efficacy (per schedule)
- Vaccine schedule
- Vitamin A treatment

Systematic literature review

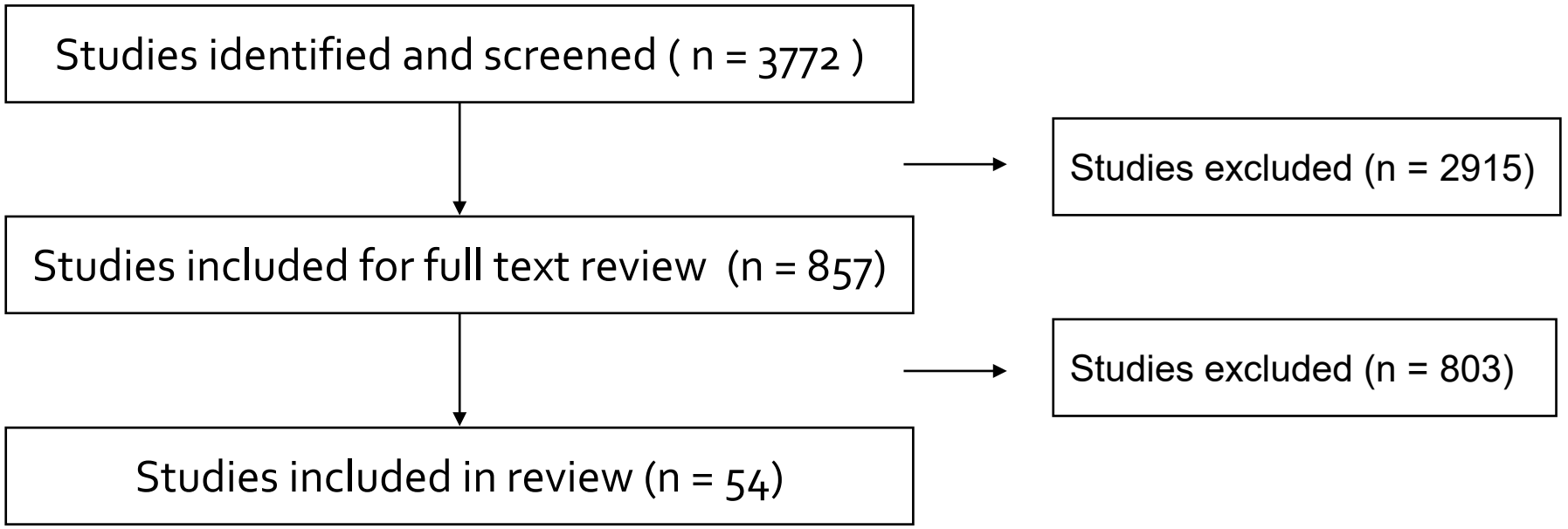
- Searched Pubmed from dates 1 Jan 1980 – 31 oct 2021
  - Only human studies

- (indicator specific search terms)

  AND “measles”

  AND (“case fatality” OR “CFR” OR “fatality” OR “mortality” OR “morbid*” OR “comorbid*” OR “sever*” OR “complicat*” OR “risk” OR “secondary outcome” OR “death”)

Systematic literature review flow diagram



Available evidence per indicator

Including, or stratified by:

- Age
- Measles incidence / attack rate

Published literature supports causal relationship

- Vitamin A treatment

Published literature supports observation-level relationship

- Educational attainment
- Distance to health care facility
- Surrounding conflict
- Vitamin A deficiency
- Vitamin A supplementation
- Under-5 mortality
- Average household size
- HIV prevalence
- MCV1 vaccination
- MCV2 vaccination
- Stunting
- Wasting
- Underweight

Published literature with supporting qualitative evidence

- Level of health care available

No evidence found

- Percent living in urban setting
- Proximity to major city / settlement
- Time to care seeking
- Access to ICU
- Ambient air pollution
- Antibiotic use
- De-worming frequency
- HIV treatment / ART prevalence
- Malaria prevalence
- ORT/S for measles-related diarrhea
- PCV coverage
- Population density
- TFR/average children per woman
- Lower respiratory infection prevalence
- Diarrheal disease prevalence

Database search

- World Health Organization
- World Bank
- United Nations
- Global Burden of Diseases, Risk Factors, Injuries Study

Available covariate sets per indicator

- **Available covariate set for indicator:** educational attainment, vitamin A deficiency, under-5 mortality, HIV prevalence, MCV1 coverage, MCV2 coverage, stunting, wasting
- **Available proxy to represent indicator:**
    - travel time to nearest healthcare facility (proxy of proportion living in urban setting, population density)
    - surrounding conflict (various proxy metrics, including mortality rate due to war and terrorism)
    - average household size (proxy of total fertility rate)
    - equity (various proxy metrics including GDP per capita)
    - level of healthcare available (various proxy metrics including under-5 mortality, health expenditure per capita)
- **No covariate or proxy available:** vitamin A treatment

Data analysis

Step 1: Covariate correlation coefficients, per mechanistic group

Step 2: Regression with CFR data, per mechanistic group

Example – Risk of secondary infection

Step 1:

	HIV prevalence	Population density	TFR
HIV prevalence	1.0	-0.0653	0.2279
Population density		1.0	-0.1534
TFR			1.0

Step 2:

	Estimate	P-value
Intercept	-1.540e-02	0.1686
HIV prevalence	2.675e-01	0.2462
Population density	8.466e-05	0.0198
TFR	8.409e-03	0.0003

Covariate list

Including, or stratified by:

- Age
- Measles incidence / attack rate

Health system access & seeking

- Maternal education
- Mortality rate due to war and terrorism
- Percent living in urban setting

Health system quality

- GDP per capita
- Under-5 mortality

Nutritional status

- Vitamin A deficiency prevalence
- Wasting prevalence

Risk of secondary infection

- HIV prevalence
- Total fertility rate

Measles control & epidemiology

- MCV1 coverage

Outline

- Motivation
- Conceptual framework of covariates
    - Measles CFR Working Group
- Updates to CFR data and modeling

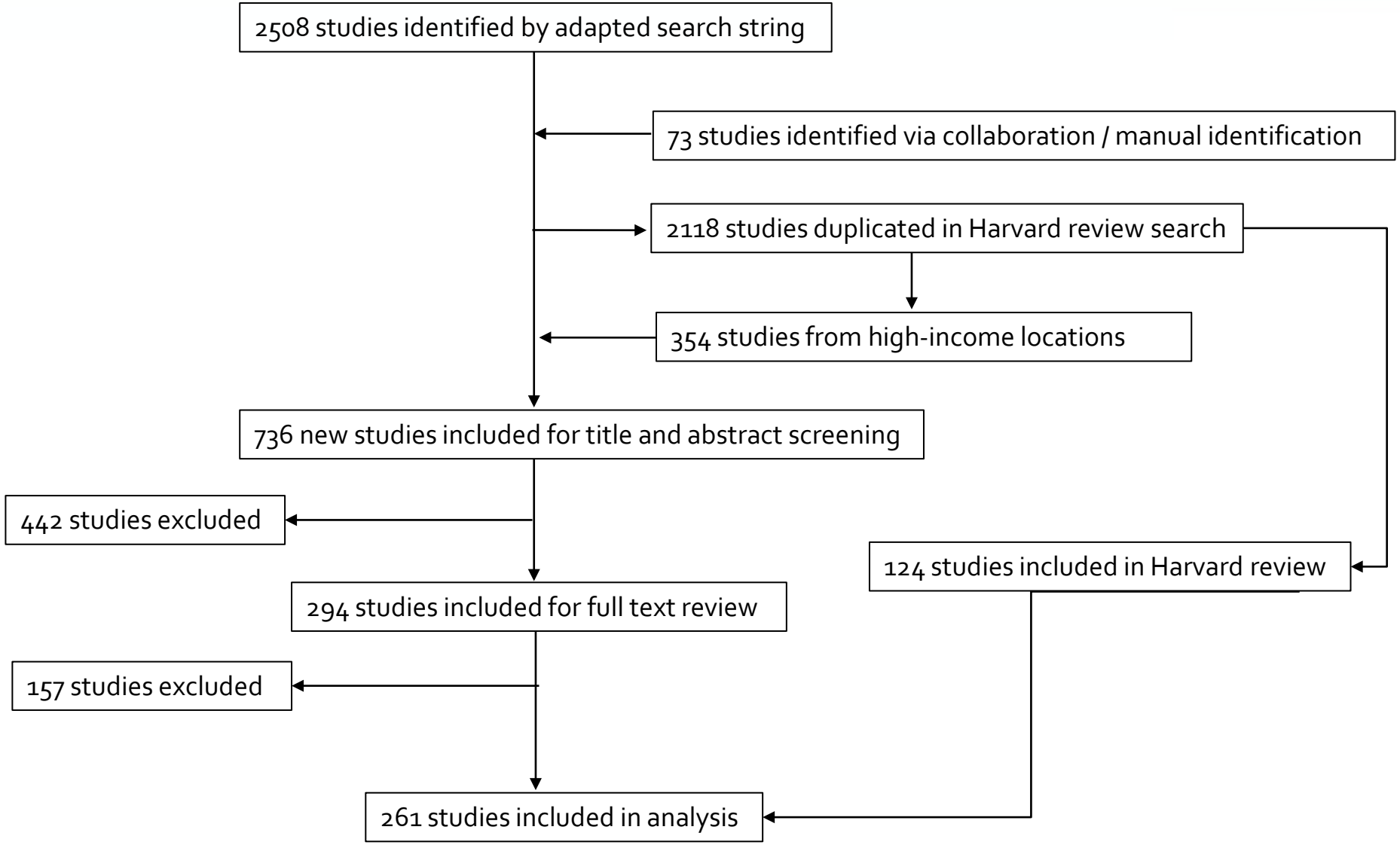
Data updates

- Low- and middle-income countries:
  - 1980 – 2016: Data from former Harvard review
  - 2017 – present: updated literature review

- High-income countries:
  - 1980 – present: updated literature review

- Other: non-English studies

Data update flow diagram



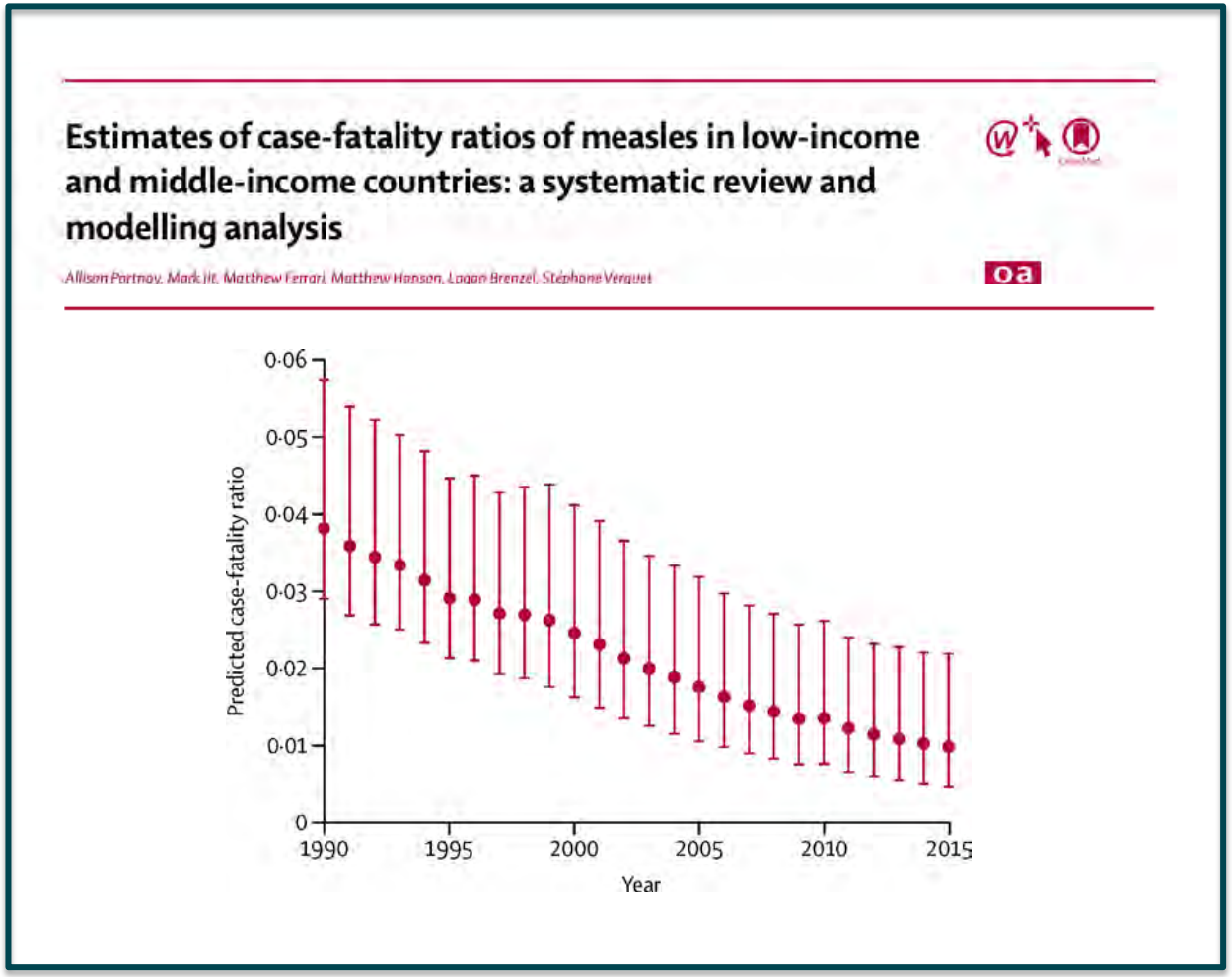
Modelling agenda

- Develop transparent framework to provide dynamic estimates of measles CFR
- Bayesian meta-regression platform with publicly available code and online repository
- Step-wise, decomposition analysis
    1. Using former data and covariates, incorporate updated modelling framework
    2. Using former data, incorporate new modelling framework and updated covariates
    3. Incorporate new modelling framework with updated data and covariates

Results – illustrative example

Results, to be:

- Age-specific
- Location-specific
- Year-specific
- With uncertainty intervals



Planned ongoing work

- Finalization of national modelling framework
- Spatial CFR disaggregation
- Finalization of updated national, age-specific CFR estimates (August 2022)
- Use of updated model framework to examine short- and long-term impact of COVID-19 pandemic on measles mortality burden
- Development of user-friendly R package with clear documentation for both WHO and community use

Questions

Has the updated effort, which reflects the available evidence of factors related to CFR, sufficiently responded to the recommendations from IVIR-AC?

Are there additional methodological considerations that need to be taken into account for the proposed CFR modelling study?

How can the transparency and sustainability of this work be promoted in this update with an eye to continuing this work in future iterations?

Activities of the Measles CFR Working Group

Per IVIR-AC recommendation, the Measles CFR Conceptual Framework Project intends to develop a conceptual framework for factors related to measles CFR that can be used with the purpose for informing updates of covariates and statistical models to predict measles CFR, as well as provide direction for future studies related to measles CFR work. This work was led by Alyssa Sbarra (LSHTM / University of Washington) and Allison Portnoy (Harvard), with supervision from Mark Jit (LSHTM) and Jon Mosser (University of Washington) and guidance from the Measles CFR Working Group (WG). End results of this project include theoretical (given ideal covariate availability) and realistic (with available covariates) frameworks for CFR model implementation.

The Working Group was established with the intent to gain feedback throughout the development of a conceptual framework as related to measles CFR. Members of the Working Group included:

- Natasha Crowcroft (WHO)
- Felicity Cutts (LSHTM)
- Emily Dansereau (BMGF)
- Matthew Ferrari (Penn State)
- Deepa Gamage (WHO)
- Katy Gaythorpe (VIMC)
- Kendall Krause (BMGF)
- Katrina Kretsinger (WHO / CDC)
- Kevin McCarthy (IDM / BMGF)
- Mark Papania (CDC)
- Niket Thakkar (IDM / BMGF)

The overall objectives for convening this Working Group were as follows:

1. Determine all possible indicators (and proxy metrics, as needed) as related to measles CFR
2. Determine relative order and group of available indicator importance
3. Provide guidance and recommendation on targeted literature reviews
4. Approve final covariate list and conceptual framework
5. Review materials to be presented during Spring 2022 IVIR-AC meeting

To date, the Working Group has met for five sessions; objectives, and activities for each Session are outlined below.

Session 1 (13 September 2021)

Objectives

1. *Discuss a full list of possible covariates to explore, including proxys*
2. *Determine overall importance of each covariate candidate*

Working Group members brainstormed a comprehensive, full list of population-level possible indicators related to measles CFR. These were not to include those describing special populations, such as internally displaced persons and refugees, as the underlying available CFR data does not include adequate information on these groups.

The full list of indicators generated by the Working Group were as follows:

- access to ICU
- age
- ambient air pollution
- antibiotic use for measles-related pneumonia
- asthma prevalence
- autoimmune condition prevalence
- average household size
- BCG vaccination coverage
- breastfeeding prevalence
- cancer prevalence
- de-worming frequency
- diarrheal disease prevalence
- DTP vaccination coverage
- health expenditure per capita

- Hib vaccination coverage
- HIV prevalence
- HIV treatment / ART prevalence
- household air pollution
- level of healthcare available
- lower respiratory infection prevalence
- malaria prevalence
- maternal (measles) vaccination coverage
- maternal smoking prevalence
- measles attack rate / incidence
- MCV1 coverage
- MCV2 coverage
- MenA vaccination coverage
- ORT/S for measles-related diarrhea
- outbreak susceptibility
- overweight prevalence
- PCV coverage
- polio vaccination coverage
- preterm birth prevalence
- proxy for maternal antibody dynamics
- proxy for vaccination coverage equity
- rotavirus vaccine coverage
- rubella vaccine coverage
- sanitation quality
- sex
- stunting prevalence
- surrounding conflict
- TB prevalence
- time
- care-seeking
- total fertility rate
- travel time to major city or settlement
- travel time to nearest health facility
- under-5 mortality
- underweight prevalence
- vaccination efficacy
- vaccination schedule
- vitamin A deficiency prevalence
- vitamin A supplementation prevalence
- vitamin A treatment prevalence
- wasting prevalence
- water quality
- yellow fever vaccination coverage

Working Group members voted for each indicator that they thought had an important relationship with measles CFR; members could “up-vote” or “down-vote” for each. Indicators with no more than 2 down-votes were considered for further inclusion. This list was as follows:

- age
- access to ICU
- ambient air pollution
- antibiotic use for measles-related pneumonia
- average household size
- de-worming frequency
- diarrheal disease prevalence
- educational attainment
- health expenditure per capita
- HIV prevalence
- HIV treatment / ART prevalence
- level of healthcare available
- lower respiratory infection prevalence
- malaria prevalence
- maternal (measles) vaccination coverage
- MCV1 coverage
- MCV2 coverage
- measles attack rate /incidence
- ORT/S for measles-related diarrhea
- outbreak setting indicator
- PCV coverage
- percent living in urban setting
- population density
- preterm birth prevalence
- proxy for maternal antibody dynamics
- proxy for vaccine coverage equity
- sanitation quality
- stunting prevalence
- surrounding conflict
- care-seeking
- total fertility rate
- travel time to nearest health facility
- travel time to major city or settlement
- under-5 mortality
- underweight prevalence
- vaccine efficacy
- vaccination schedule
- vitamin A deficiency prevalence
- vitamin A supplementation prevalence
- vitamin A treatment
- wasting prevalence

Session 2 (12 October 2021)

Objectives:

1. *Anonymously rank indicators to determine relative importance*
2. *Determine indicator candidates further worth investigation*

Working Group members ranked indicators in order of importance to consider relative to one another. Each ranked position from 1 to 42 was assigned each corresponding weight. Age was removed from this process. Overall indicator rank was determined by average weight across responses, shown below:

1. Age (1.86)
2. MCV1 coverage (8.43)
3. Underweight prevalence (9.71)
4. Wasting prevalence (9.71)
5. Vitamin A treatment (13.29)
6. Travel time to nearest health facility (13.86)
7. MCV2 coverage (14.00)
8. Level of health care available (14.57)
9. ORT/S for measles-related diarrhea (14.86)
10. Antibiotic use for measles-related pneumonia (15.14)
11. Time to care seeking (15.71)
12. Vitamin A deficiency prevalence (15.71)
13. Stunting prevalence (18.00)
14. Measles incidence (19.57)
15. Surrounding conflict (20.00)
16. Health expenditure per capita (20.14)
17. Access to ICU (20.29)
18. Measles attack rate (20.43)
19. Under-5 mortality (20.71)
20. LRI prevalence (21.00)
21. Diarrheal disease prevalence (21.29)
22. Average household size (21.71)
23. Outbreak setting indicator (23.00)
24. Vitamin A supplementation (23.29)
25. HIV prevalence (23.71)
26. Travel time to nearest city or settlement (23.71)
27. Population density (25.43)
28. Sanitation quality (25.43)
29. HIV treatment prevalence / ART prevalence (25.86)
30. Maternal (measles) vaccination coverage (26.00)
31. Preterm birth prevalence (26.00)
32. TFR / average children per woman (26.86)
33. Percent living in urban setting (27.00)
34. Proxy for maternal antibody dynamics (27.71)
35. Proxy for vaccine coverage equity (28.71)
36. PCV vaccine coverage (30.29)
37. Educational attainment (30.71)
38. Vaccination efficacy (32.14)
39. Ambient air pollution (32.71)
40. Malaria prevalence (33.71)
41. De-worming frequency (34.43)
42. Vaccination schedule (36.71)

Members asserted, with at least one verbal yes, their desire for the inclusion of all indicators for further analysis. Members suggested considering mechanisms that might impact measles mortality or case fatality so it could be ensured that remaining indicators adequately captured the underlying components of these possible mechanisms.

Session 3 (1 November 2021)

Objectives

1. *Review mechanistic groups and indicators per group*
2. *Review protocol for literature review and dataset investigation*

Members reviewed the following mechanistic groups and indicators corresponding with each group. The groups and related covariates are as follows:

Group	Indicators
Health system access and care seeking	• educational attainment

	• percent living in urban setting • surrounding conflict • time to care seeking • travel time to nearest health facility • travel time to major city or settlement
Health system quality	• access to ICU • health expenditure per capita • level of healthcare available • under-5 mortality
Nutritional status	• stunting prevalence, • underweight prevalence, • vitamin A deficiency, • vitamin A supplementation, wasting prevalence
Risk of secondary infection	• age • ambient air pollution • antibiotic use for measles-related pneumonia • average household size • de-worming frequency • diarrheal disease prevalence • HIV prevalence • HIV treatment / ART prevalence • malaria prevalence • lower respiratory infection prevalence • ORT/S for measles-related diarrhea • PCV coverage • population density • preterm birth prevalence • sanitation quality • total fertility rate
Measles control and epidemiology	• maternal (measles) vaccination coverage • MCV1 coverage • MCV2 coverage • measles attack rate • measles incidence • outbreak setting indicator • proxy for maternal antibody dynamics • proxy for vaccine coverage equity • vaccination efficacy • vaccination schedule • vitamin A treatment

Members confirmed the inclusion of all indicators other than sanitation quality and the following protocol for literature review and data analysis:

1. Search for and review any available literature (systematic literature review)
2. Search for and review any available population level data (database search)
3. Categorize into following groups:

a. Published literature supporting causal relationship and population-level data
b. Published literature supporting observational relationship and population-level data
c. Published literature with supporting qualitative evidence and population-level data
d. No literature published, but population-level data available
e. No literature published and population-level data is untrustworthy, contains missingness, or is otherwise unsuitable

4. Follow-up with Working Group to share covariate categories
5. Data analysis and framework development

Session 4 (20 January 2022)

Objectives

1. *Provide feedback on proposed conceptual framework of mechanistic groups*
2. *Review results from literature review and dataset investigation*
3. *Provide specific recommendation for areas in literature with ambiguous results*

From a systematic review of the literature, each covariate was classified as one of the following:

Published literature supports causal relationship	Published literature supports observational relationship	Published literature with supporting qualitative evidence	No evidence found
• vitamin A treatment	• educational attainment, equity (at large, not vaccine coverage specific) • distance to nearest healthcare facility • household size • HIV status • receipt of MCV1 • receipt of MCV2 • stunting • surrounding conflict • under-5 mortality • underweight • vitamin A deficiency • wasting	• level of healthcare available	• access to ICU • ambient air pollution • antibiotic use for measles-related pneumonia • diarrheal disease prevalence • de-worming frequency • HIV treatment / ART prevalence • lower respiratory infection prevalence • malaria prevalence • ORT/S for measles-relate diarrhea • PCV coverage • percent living in urban setting • population density • time to care seeking • total fertility rate • travel time to major city or settlement

From a search of databases across sources such as the United Nations, World Bank, World Health Organization, and the Global Burden of Diseases, Injuries and Risk Factors Study, indicators with a published relationship with measles case fatality were classified as follows:

Available covariate set for indicator	Available proxy to represent indicator	No covariate or proxy available
• educational attainment • vitamin A deficiency • under-5 mortality • HIV prevalence • MCV1 coverage • MCV2 coverage • stunting • wasting	• travel time to nearest healthcare facility (proxy of population density) • surrounding conflict (various proxy metrics, including mortality rate due to war and terror) • average household size (proxy of total fertility rate) • equity (various proxy metrics including GDP per capita) • level of healthcare available (various proxy metrics including under-5 mortality, health expenditure per capita)	• vitamin A treatment

Members provided feedback on and a discussion of these results of indicator systematic literature review and database search via a discussion corresponding classification for each indicator. Members also provided feedback and suggestion on draft conceptual framework of mechanistic groups.

Session 5 (14 February 2022)

Objectives

1. *Review revised conceptual framework and results from data analysis*
2. *Approve covariate list*

Members discussed data analysis methods and results, as well as that covariate set recommended for further inclusion. These covariates include:

- Maternal education
- Mortality rate due to war and terrorism
- Percent living in urban setting
- GDP per capita
- Under-5 mortality
- Vitamin A deficiency prevalence
- Wasting prevalence
- HIV prevalence
- Total fertility rate
- MCV1 coverage

Members also provided feedback and suggestion on overall approach to presentation during upcoming IVIR-AC session.

List of acronyms / abbreviations

ART – Antiretroviral therapy
BCG - Bacille Calmette-Guérin
BMGF – Bill & Melinda Gates Foundation
CFR – Case fatality ratio
CDC – Centers for Disease Control and Prevention
DTP – Diphtheria- tetanus- pertussis
GDP per capita – Gross Domestic Product per capita
Hib – *Haemophilus influenzae* type B
HIV – Human immunodeficiency virus

IDM – Institute for Disease Modeling
ICU – Intensive care unit
LSHTM – London School of Hygiene and Tropical Medicine
MCV1 – First dose of measles-containing vaccine
MCV2 – Second dose of measles-containing vaccine
MenA – Meningococcal serogroup A
ORT/S – Oral rehydration therapy / treatment / salt / solution
PCV – Pneumococcal conjugate vaccine
TB – Tuberculosis
VIMC – Vaccine Impact Modelling Consortium
WHO – World Health Organization

World Health Organization

Session 2

Behavioural and social drivers of vaccination

Behavioural and social drivers (BeSD):

How to harmonize local and global data?

8 March 2022

Presentation to IVIR-AC

Professor Julie Leask (University of Sydney); Lisa Menning WHO/IVB

Agenda

Topic	Time	Presenter
• Background and questions to IVIR-AC	5 mins.	Professor Julie Leask
• Update on plans to support gathering and use of data on behavioural and social drivers • Outline of proposed processes for data harmonization and sharing	15 mins.	Lisa Menning
• Q&A and discussion	30 mins.	Facilitated by IVIR-AC focal points

Questions for IVIR-AC to consider:

- What feedback is there on the proposed next steps to produce comparable datasets?
- How to encourage and support standardized use of tools and methods (to benefit countries)?

The need

- **IA2030 highlights demand and people-centred approaches**
- **COVID-19 has led to a major shift for immunization:**
  - Increased awareness of vaccination
  - Engagement of new prioritised populations
  - More attention on equity within and between countries
  - Global interest in hesitancy and trends in uptake

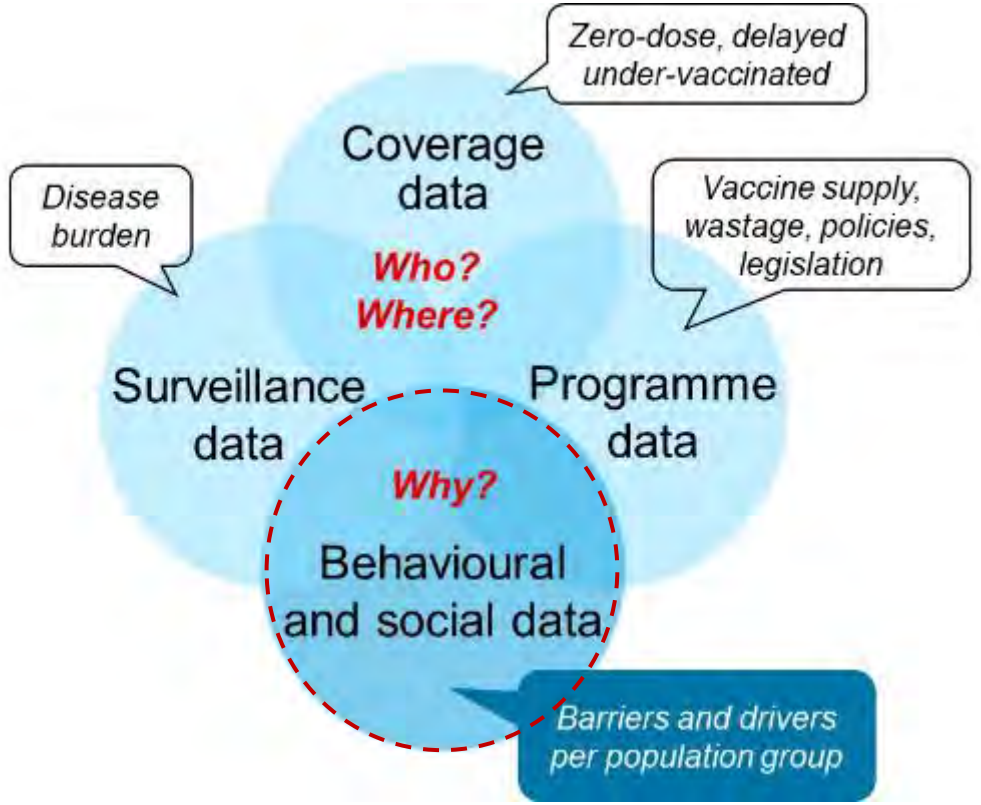
  … and threatened many gains in routine immunization
- However, the **causes of low uptake are poorly measured**
- **Our understanding of the reasons for low uptake has evolved** in recent years, including contribution of hesitancy

IMMUNIZATION AGENDA 2030

How to assess and address drivers of uptake?

Our objectives:

- **Boost the quality, availability and use** of data on behavioural and social drivers with validated, standardized and user-friendly tools
- **Integrate tools** into existing mechanisms for data collection and use, or as separate
- **Monitor and evaluate** interventions and track comparable trends at all levels
- **Support reporting** for IA2030 and Gavi 5.0 global indicators



What tools and guidance are available?

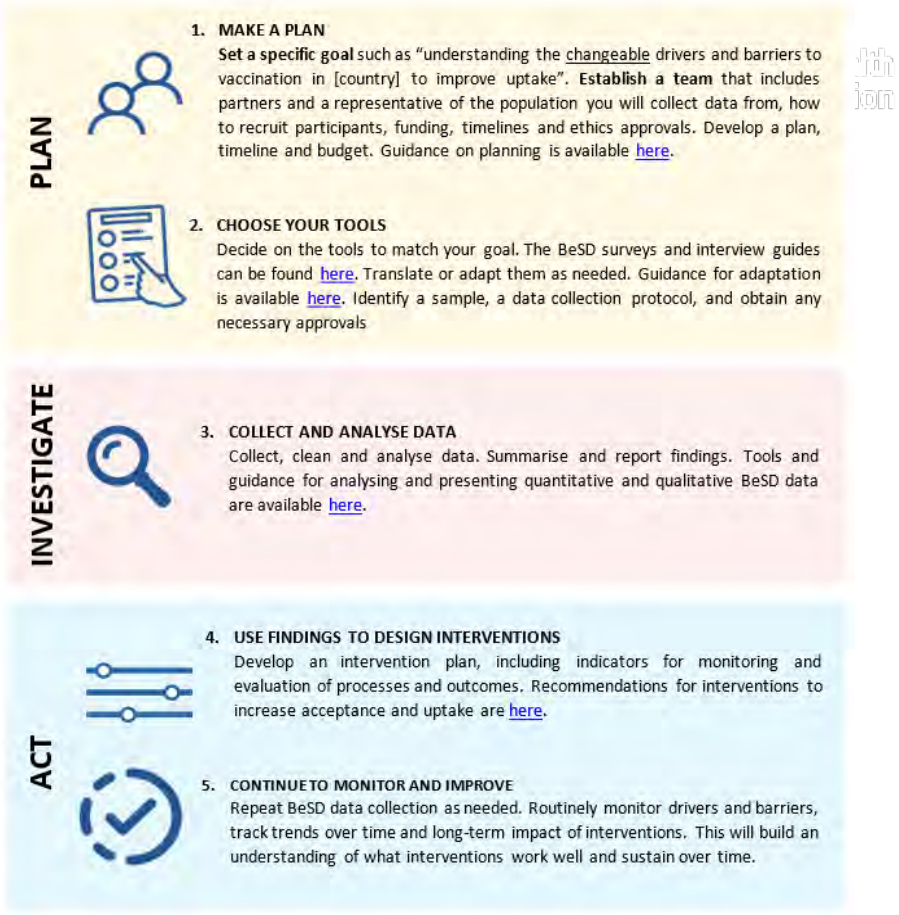
Childhood vaccination tools

- **Survey:** for parents of children under 5 years
- **Qualitative tools:**
  1) caregivers, 2) providers, 3) community stakeholders, and 4) authorities

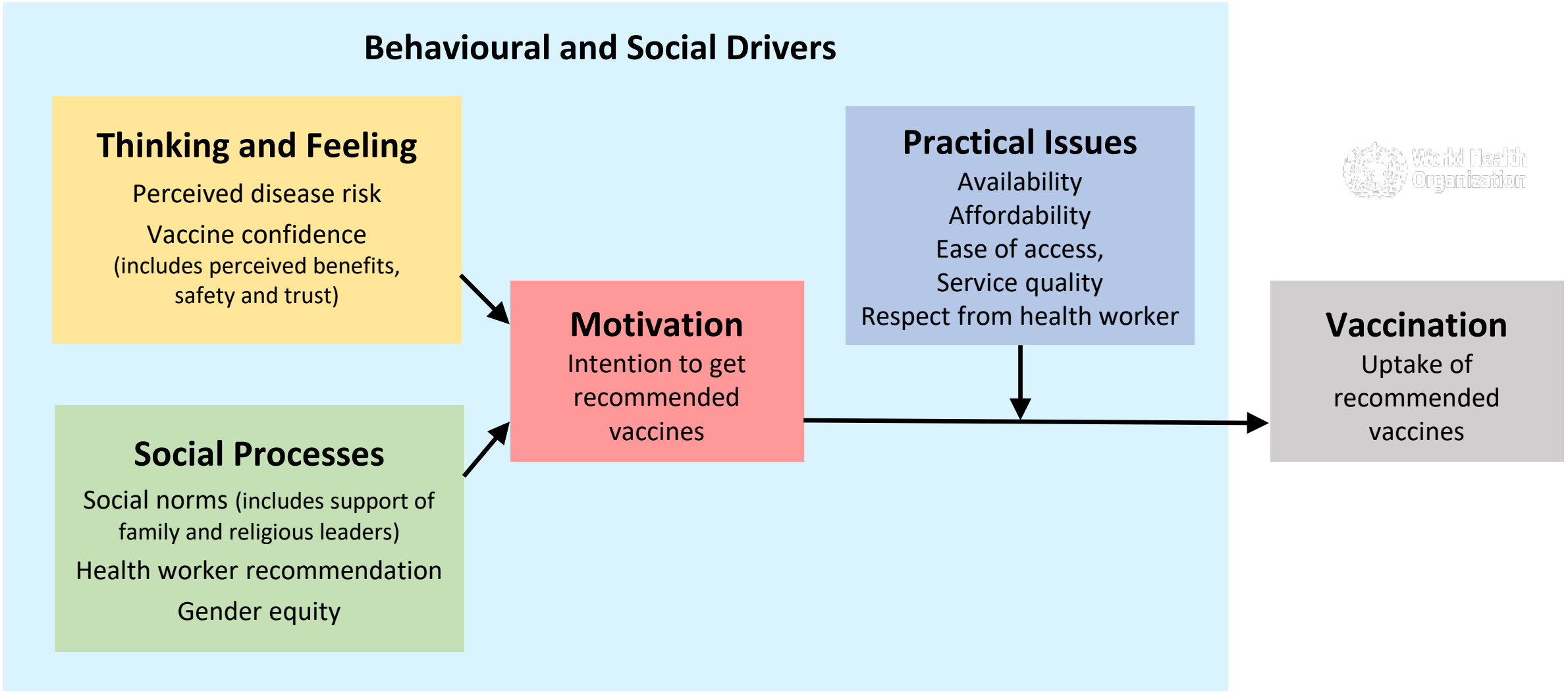
COVID-19 vaccination tools

- **Surveys:** for 1) adults, 2) health workers
- **Qualitative tools**

Practical implementation guidance



What are we measuring?



The Behavioural and Social Drivers (BeSD) Framework. Source: The WHO BeSD working group. Based on Increasing Vaccination Model (Brewer et al., 2017)

Priority indicators for regular M&E

World Health Organization

DOMAIN/ construct	Childhood vaccination survey		COVID-19 vaccination survey	
	Question	***Indicator***	**Question**	***Indicator***
THINKING AND FEELING Confidence in vaccine benefits	How important do you think vaccines are for your child's health? Would you say… ☐ Not at all important ☐ A little important ☐ Moderately important, *or* ☐ Very important?	*% of parents/caregivers who think that vaccines are "moderately" or "very" important for their child's health*	How important do you think getting a COVID-19 vaccine will be for your health? Would you say… ☐ Not at all important ☐ A little important ☐ Moderately important, *or* ☐ Very important?	*% of adults/health workers who think a COVID-19 vaccine is "moderately" or "very" important for their health*
SOCIAL PROCESSES Family norms	Do you think most of your close family and friends want you to get your child vaccinated? ☐ NO ☐ YES	*% of parents/caregivers who think most of their close family and friends want their child to be vaccinated*	Do you think most of your close family and friends would want you to get a COVID-19 vaccine? ☐ NO ☐ YES	*% of adults/health workers who think most of their close family and friends would want them to get a COVID-19 vaccine*
MOTIVATION Intention to get vaccine	[COUNTRY NAME] has a schedule of recommended vaccines for children. Do you want your child to get none of these vaccines, some of these vaccines or all of these vaccines? ☐ NONE ☐ SOME ☐ ALL	*% of parents/caregivers who want their child to get "all" of the recommended vaccines*	Do you want to get a COVID-19 vaccine? Would you say… ☐ No, you do not want to, ☐ Yes, you do want to, *or are you* ☐ Not sure?	*% of adults/health workers who want to get a COVID-19 vaccine*
PRACTICAL ISSUES Know where to get vaccination	Do you know where to go to get your child vaccinated? ☐ NO ☐ YES	*% of parents/caregivers who know where to get their child vaccinated*	Do you know where to go to get a COVID-19 vaccine for yourself? ☐ NO ☐ YES	*% of adults/health workers who know where to get a COVID-19 vaccine for themselves*
PRACTICAL ISSUES Affordability	How easy is it to pay for vaccination? When you think about the cost, please consider any payments to the clinic, the cost of getting there, plus the cost of taking time away from work. Would you say… ☐ Not at all easy ☐ A little easy ☐ Moderately easy, or ☐ Very easy?	*% of parents/caregivers who say vaccination is "moderately" or "very" easy to pay for*	How easy is it to pay for vaccination? When you think about the cost, please consider any payments to the clinic, the cost of getting there, plus the cost of taking time away from work. Would you say… ☐ Not at all easy ☐ A little easy ☐ Moderately easy, *or* ☐ Very easy?	*% of adults/health workers who say vaccination is "moderately" or "very" easy to pay*

Summary of the development process

(2019-2021)

Testing sites:
Indonesia, Sierra Leone, Guatemala, Australia

Validation sites:
Angola, Ethiopia, DRC, India, Nigeria, Pakistan

	PHASE	KEY ACTIVITIES	END-USER INPUTS
1	**Tool development**	☑ Literature review ☑ Identification of constructs ☑ Qualitative interview questions ☑ Survey items and iterative reduction ☑ Demographic items and survey instructions	☑ Key informant interviews ☑ IVIR-AC consultations (two)
2	**Field testing**	☑ Languages and countries selected ☑ Study protocol and scripts ☑ Translation of all materials (& translator feedback) **Surveys:** ☑ Cognitive interviewing ☑ Analysis spreadsheet: item, results, revisions **Qualitative tools:** ☑ Draft qualitative guides ☑ Interviewer debrief form and analysis framework	☑ Regional and Country Offices feedback ☑ EPI programme and implementer feedback
3	**Psychometric validation and indicator selection**	☑ Validation study protocol ☑ Translations and data-gathering ☑ Data analysis ☑ Working group review and indicator selection	☑ Implementing end-user feedback on guidebook
4	**Finalisation of all tools and guidance**	☑ Tools for childhood vaccination ☑ Tools for COVID-19 vaccination ☑ Data for Action Guidebook	☑ Continue to gather end-user feedback
5	SAGE recommendations on systematic gathering and use of data on BeSD, October 2021 (WER report)		

How can BeSD data be used?

COUNTRY AND REGIONAL-LEVEL:

Integrated into relevant existing activities or for priority populations…

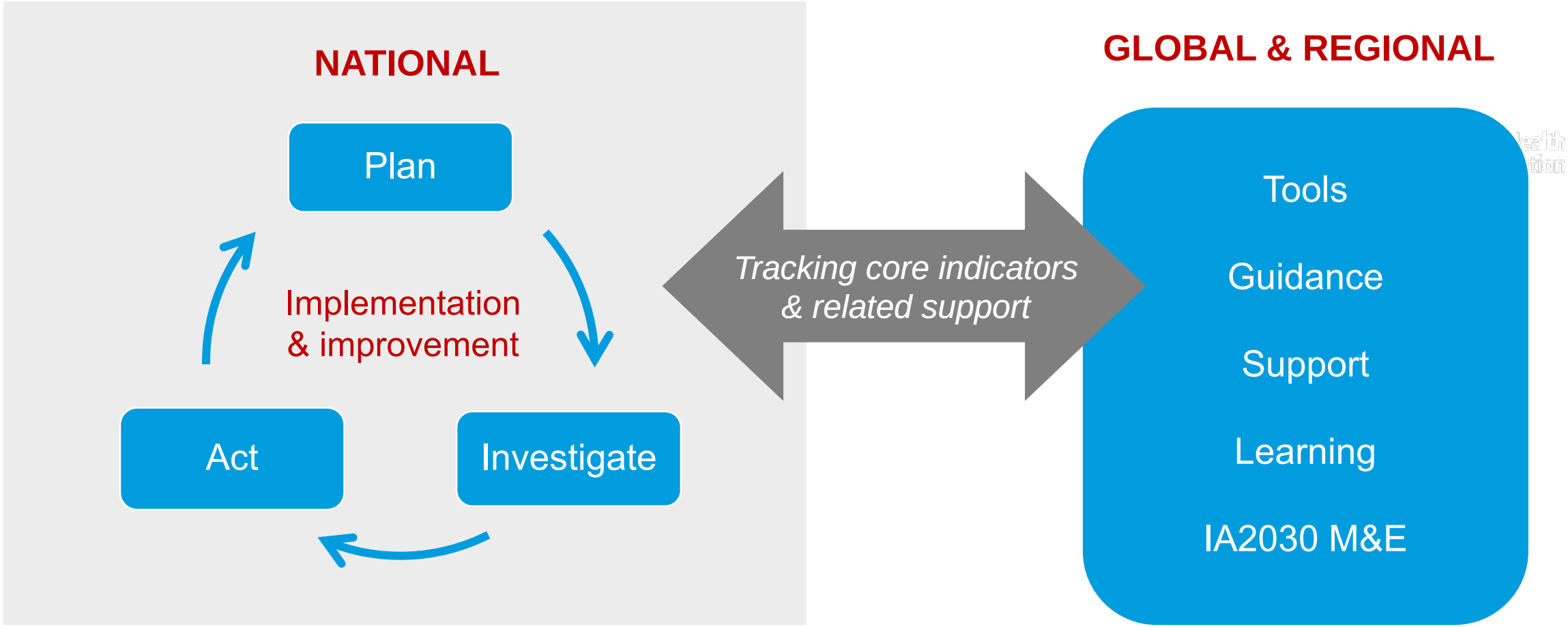
- National and sub-national planning
- Triangulation with other programme data
- Focus on priority groups, e.g., inequities, zero dose, gender-related barriers
- Guide local tailoring of interventions
- Inform monitoring and evaluation
- Engage stakeholders and advocates

GLOBAL LEVEL:

- Understand main reasons for low uptake
- Contribute to knowledge on trends, measures and interventions
- Guide policy-making, planning and support
- Better allocate resources
- Enhance transparency and ownership
- Support training programmes
- Contribute to global reporting, e.g., IA2030

IA2030 Monitoring and Evaluation Framework: http://www.immunizationagenda2030.org/images/documents/IA2030_FrameworkForActionv04.pdf

Connecting national to global

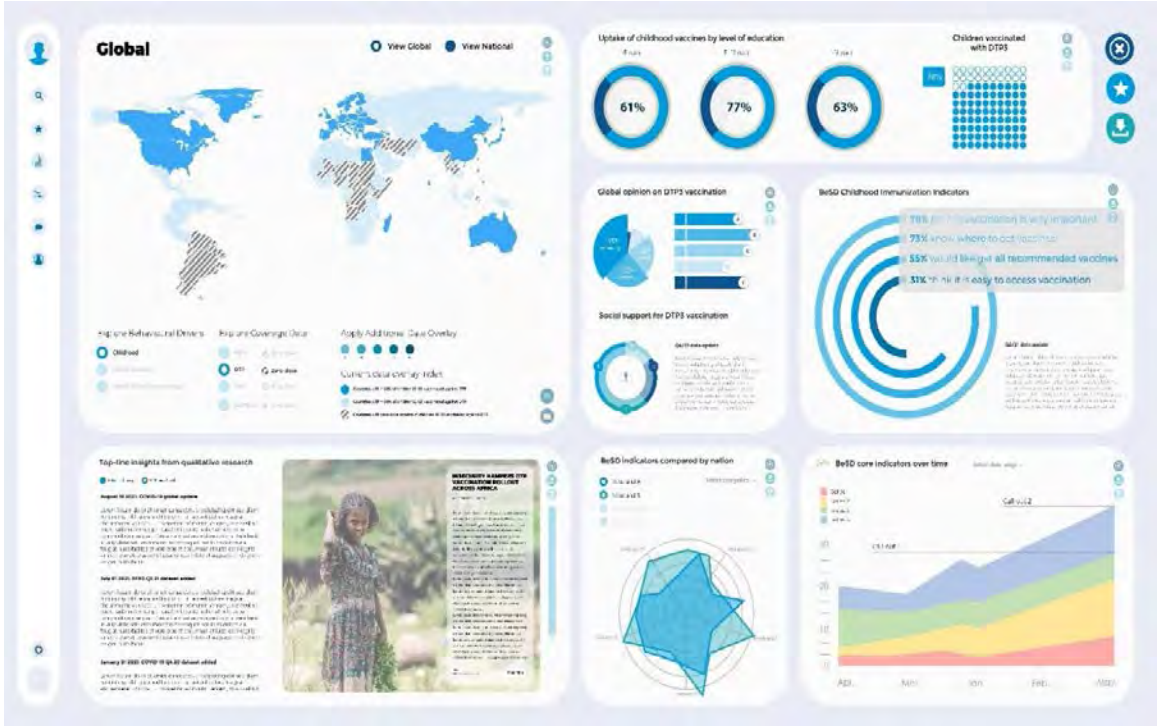


Features of a global interactive BeSD dashboard

To understand reasons for low uptake, track trends, guide planning and implementation

- Based on globally validated tools and indicators endorsed by SAGE
- Combines data from multiple sources and time-points
- Integrated with WHO immunization information management systems
- Offers analysis of BeSD indicators by vaccine, geography (country, region, global), gender, coverage rate, country income classification
- Includes summary qualitative findings
- Includes links to BeSD tools and methods for data harmonization

Illustrative example:



What's next?

Supporting programmes and partners to gather and use data

Collaboration with partners, NITAGs, CSOs, experts, researchers

- **Integrate tools and indicators** into existing processes
- **Launch and promote tools,** trainings, report templates, end-user network
- **Coordinate with partners** for use of tools and data, and track learning
- **Map full range of data sources,** gather and consolidate data as available
- **Establish processes to track use**, gather feedback, document lessons
- **Continue to develop data management plans and tools**, e.g. automated reports, global database, digital tools (ODK)
- **Relaunch working group** for overall monitoring and future updates

Building a global BeSD data ecosystem

World Health Organization

COUNTRY

Pipelines

GLOBAL
Storage and dissemination

Multiple data sources:

- Routine facility-based or community-based
- Ad-hoc: coverage survey, DHIS, MICS, online or mobile-app surveys, etc.
- Qualitative data

Rapid reports for planning

Process:

- Mapping sources
- Cleaning
- Harmonization
- Automated reports
- Qualitative analysis

Global dashboard

How to produce compatible and comparable datasets?

Data harmonization considerations

Objectives:

- To produce **compatible** and **comparable** data from multiple national and sub-national sources
- To facilitate interoperable systems and enable wide and timely use of data at all levels

Main considerations:

- Different data collection methods, samples, questions, response options
- Need to allow some flexibility for local contextualisation and ownership in the process

Proposed process for harmonization:

- Define data formats and frameworks in advance: **enable harmonization before data collection**
- Develop decision tree for matching and adjusting data to make compatible where possible
- Widely communicate the method and incentives for countries, e.g., rapid reports for planning

NB. Where a relevant precedent exists, e.g., WUENIC estimates, will follow similar principles and processes

Examples of considerations

Variable	"Standard requirement"	Alternative 1	Alternative 2
Method	Nationally representative (telephone survey or face-to-face) ✓	Not nationally representative, but very large sample (mobile app-based) ?	Very large sample, only 50% of districts ?
Response options (priority indicator)	Do you think most of your close family and friends want you to get your child vaccinated? ☐ No ☐ Yes ✓	Do you think most of your close family and friends want you to get your child vaccinated? ☐ No ☐ Yes ☐ Maybe X	Missing data ?
Response options (priority indicator)	How important do you think vaccines are for your child's health? Would you say… ☐ Not at all important ☐ A little important ☐ Moderately important, *or* ☐ Very important? ✓	How important do you think vaccines are for your child's health? Would you say… ☐ Not at all important ☐ Moderately important, *or* ☐ Very important? X	Do you agree or disagree that vaccines are important for your child's health? Would you say… ☐ Strongly agree ☐ Somewhat agree ☐ Neither / don't know ☐ Somewhat disagree ☐ Strongly disagree X

LEGEND:
✓ = Include
? = Request/revise
X = Discard

Two main streams of work

1.
NATIONAL tools and monitoring forms
(unique per country)

ACTION: Recommend and support standardized use of BeSD questions corresponding to priority indicators

Promote the added value to countries:

- Facilitate local harmonization of multiple data sources
- Enable rapid reporting for local use of data and M&E
- Enhance data quality for implementation and tracking of trends

2.
GLOBAL assessments with standardized tools and methods, e.g., DHIS, MICS, coverage surveys, and BeSD ODK tools

Partner-supported data collection, using various methods, from nationally representative to mobile app-based

ACTION: Coordinate closely with colleagues, partners and donors to integrate BeSD questions into existing tools and planned data-collection activities (Work is underway, e.g., for MICS, DHIS2)

Proposed next steps for harmonization

STEP 1: Coordinate with colleagues and partners to integrate tools into existing tools and planned activities, using standardized methods

STEP 2: Map alternatives to design a process of matching heterogenous sources with inclusion/exclusion criteria per option

STEP 3: Facilitate consultation with colleagues and partners on the matching process and related benefits at all levels

STEP 4: Communicate the final approach, coordinate with colleagues and partners, and assist with local integration of BeSD indicators

Taking into account the importance of local contextualisation and ownership, ***what level of stringency is acceptable?***

- For the data collection methods?
- For questions and response options?

Discussion

Questions for IVIR-AC to consider:

- What feedback is there on the proposed next steps to produce comparable datasets?
- How to encourage and support standardized use of tools and methods (to benefit countries)?

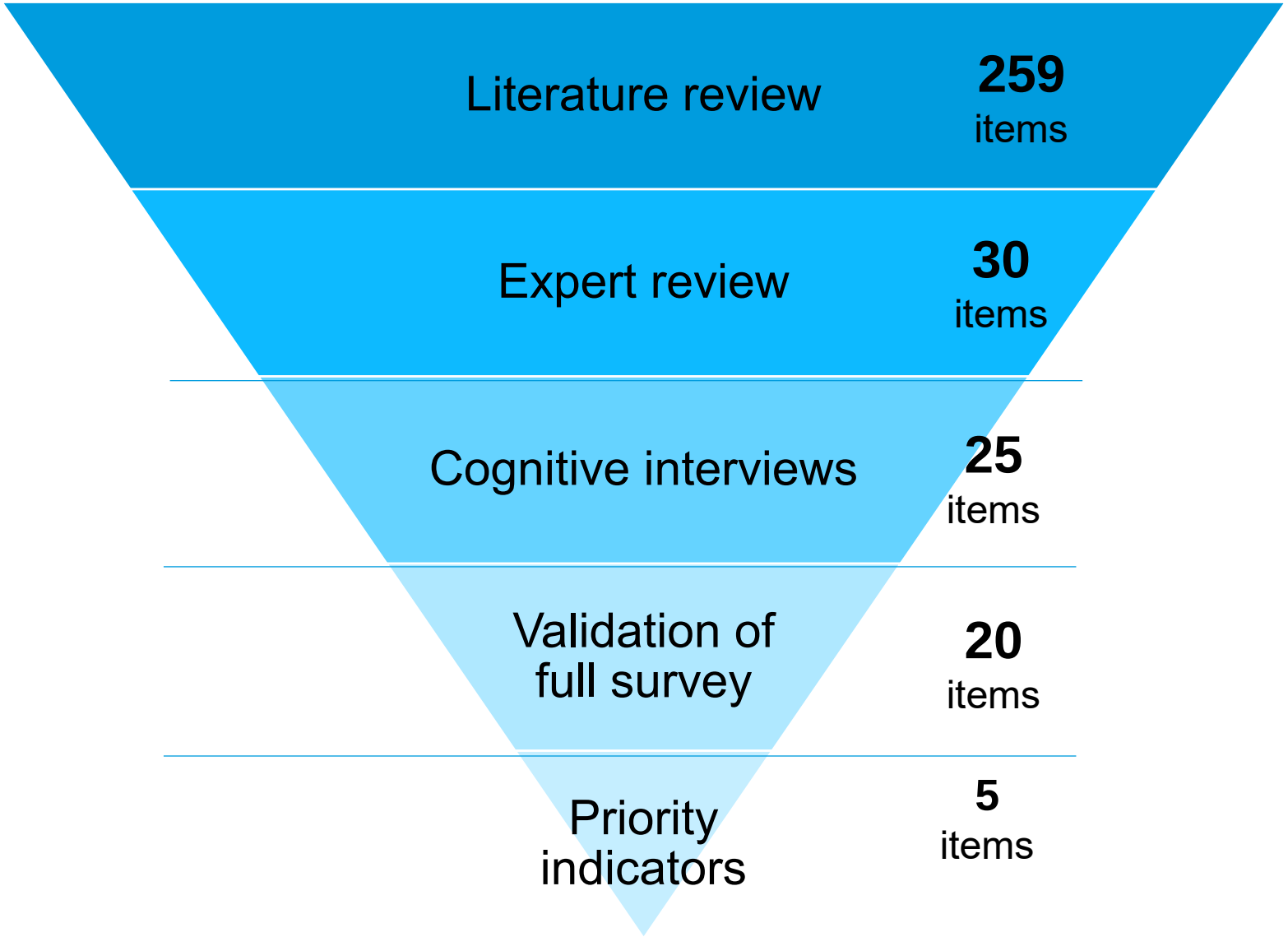

Thank you

Back-up slides:

Further information on the tool development process and brief examples of data

Summary of tool development:

Evolution of survey questions per step



We focused on proximal influences that are:

- **Measurable in individuals**
- **Specific to vaccination**
- **Potentially changeable by immunization programmes**

Distal influences (e.g., literacy, education, politics, rurality) are covered via in-depth interview guides and demographics items.

How were the full surveys and priority indicators validated?

Data collected in 6 countries: Angola, DRC, Ethiopia, India, Nigeria, Pakistan (*n*=1,819)

Analysis focused on:

1. ***Overlap and information.*** Conducted exploratory factor analysis, and examined information curves for the scales to select most informative items

2. ***Stability.*** Examined item stability across country, education, and respondent gender (differential item functioning and differential predictive validity)

3. ***Predictive of vaccination.*** Examined which items were most predictive of uptake all recommended vaccines

>> Findings informed final selection of questions and priority indicators

Summary of all topics measured:
Childhood vaccination survey

Thinking and feeling	Motivation	Social processes	Practical issues
✪ Confidence in vaccine benefits	✪ Intention to get child vaccinated	✪ Family norms	✪ Know where to get vaccination
● Confidence in vaccine safety		● Health worker recommendation	✪ Affordability
○ Confidence in health workers		● Peer norms	● Took child for vaccination
		● Community leader norms	● Received recall
		○ Religious leader norms	● Ease of access
		○ Mother's travel autonomy	● Reasons for low ease of access
			● Vaccination availability
			● Service satisfaction
			● Service quality

Demographics
Age
Gender
Number of children
Age of child
Gender of child
Vaccination status

● Main survey question.
✪ Priority question in main survey.
○ Optional question.

Summary of all topics measured:
COVID-19 vaccination survey

Thinking and feeling	Motivation	Social processes	Practical issues
✪ Confidence in COVID-19 vaccine benefits	✪ Intention to get vaccinated	✪ Family norms	✪ Know where to get vaccination
● Confidence in COVID-19 vaccine safety	● Vaccine confidence – brand	● Peer norms	✪ Affordability
● COVID-19 vaccine –see friends and family	● Willingness to recommend vaccine to others	● Religious leader norms	● Received recall
○ Perceived risk – self		● Community leader norms	● Ease of access
○ Confidence in health workers		● Health worker recommendation	● Reasons for low ease of access
		○ Workplace norms	● Service satisfaction
		○ Gender equity – travel autonomy	● Service quality
			○ On-site vaccination

Demographics
Age
Gender
Occupation
*Health worker role
COVID-19 risk
COVID-19 diagnosis

● Main survey question.
✪ Priority question in main survey.
○ Optional question.

CASE EXAMPLE

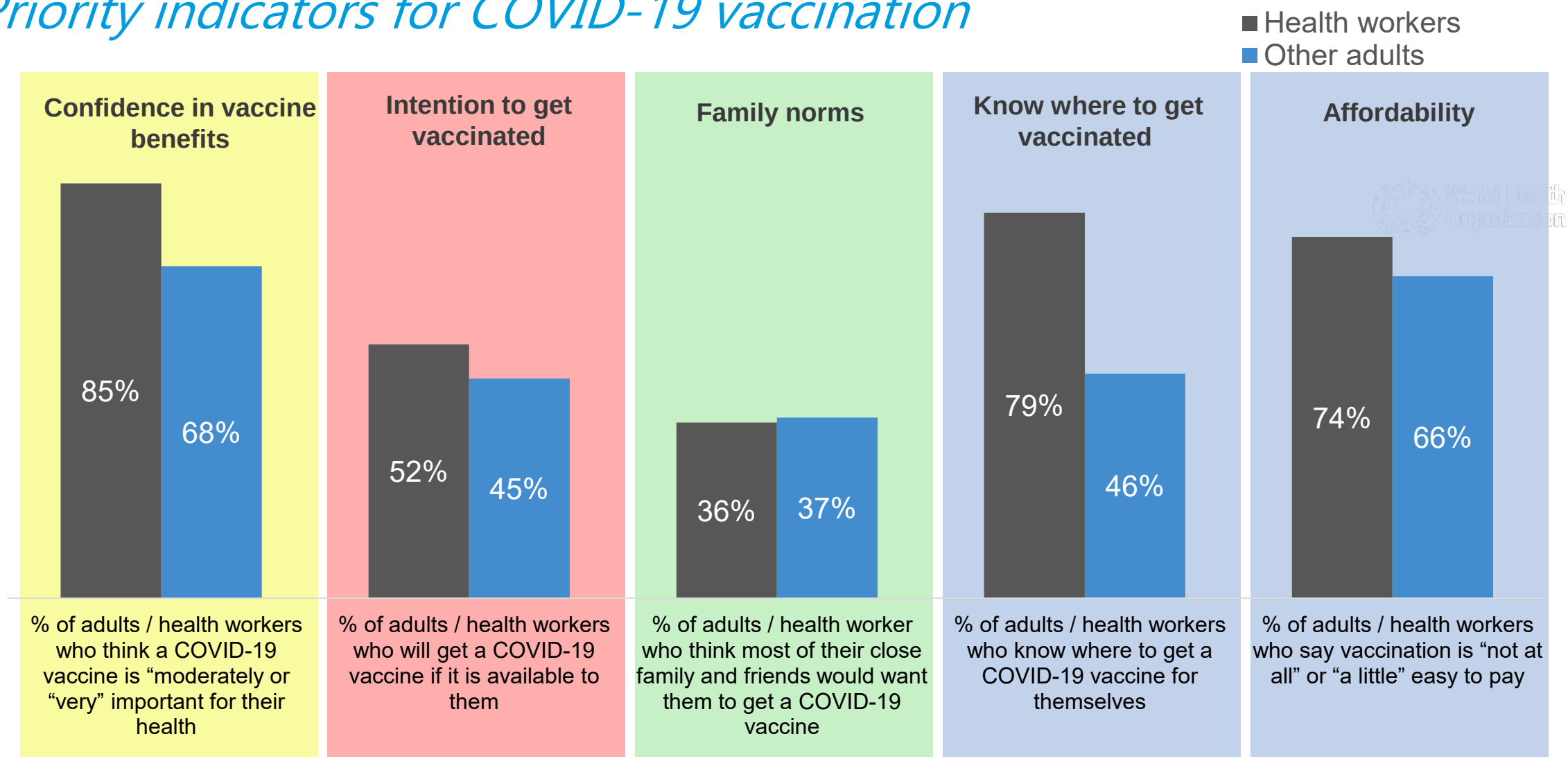
South Africa: From data to action for COVID-19 vaccines

	KEY FINDINGS	ACTIONS TAKEN
Practical Issues	• **Only 19%** think vaccine will be **very easy to access**	• Expanded sites • Disseminated list of vaccination sites • Explainer videos (steps for registration; steps on site)
Thinking and Feeling	• **80%** feel **vaccine is important** for their health *BUT* • **32%** will **trust the vaccine "very much"** • **31%** noted concerns about **efficacy** • **26%** concerns on **safety** • **14% trust in authorities** being main reasons for not wanting the vaccine	• Live TV broadcast of HWs, President and Minister of Health getting vaccinated, then union leaders • Health Minister webinars – national and provincial • Carried out daily press conferences • Intensified social listening • Launched website, disseminated social media GIFs • Targeted communications in specific sites • Videos of health workers supporting vaccination
Social Processes	• **50%** think adults in **communities and co-workers will vaccinate** • **74%** would **recommend vaccine to others**	• Targeted community engagement in specific areas • 'Vaxscenes' - video stories of people targeted in each phase talking about their experience getting vaccinated
Motivation	• **70%** said they **will take the vaccine**	• Planning behavioural interventions

CASE EXAMPLE

A snapshot of findings from DRC

Priority indicators for COVID-19 vaccination



Total sample (n=618); health worker (n=303), other adults (n=315). Data gathered August 2021

Insights from use of tools to date

World Health Organization

Selected examples:

- COVID-19 vaccine surveys in Vietnam, East and Southern Africa, Pacific Islands by UNICEF
- COVID-19 vaccine surveys of health workers in 14 Caribbean countries by WHO/AMRO
- Qualitative tools for childhood vaccination in Mozambique via Village Reach
- Selected items used in mobile app data collection through Premise/Gavi partnership
- Use of BeSD framework in CDC Field Guide
- Use of BeSD framework by BMGF to inform appropriate investments

Insights gained:

- Tools easily integrate into existing surveys and platforms
- BeSD framework intuitive and enables cross-checking to avoid gaps
- Practical factors items may risk being omitted in some settings
- Updated guidebook addresses user needs:
  - How to add context-specific questions
  - New interactive '*Quick Start Guide*'
- More needed on local use of data and M&E

Behavioural and social drivers of vaccine uptake:
How to harmonize local and global data?

Background brief for IVIR-AC
21 February 2022

This background brief is to support information sharing in advance of a session with the Implementation and Vaccines-related Implementation Research Advisory Committee (IVIR-AC) on 8 March 2022. Together with this document are two added pre-reads: 1) A guidance document *Behavioural and social drivers: tools and practical guidance for achieving high uptake*, expected to be published in early March, and, 2) A Power point titled *Behavioural and social drivers: how to harmonize local and global data?*

Purpose of the session

This session on '*Behavioural and social drivers (BeSD) of vaccine uptake'* will build on the most recent discussions with IVIR-AC and SAGE on the same topic. It will share updates with IVIR-AC on recent developments in this field of work and consult with IVIR-AC on key questions related to global harmonization of data on BeSD.

Session agenda

Topic	Time	Presenter
- Background and questions to IVIR-AC	5 minutes	Professor Julie Leask
- Updated on plans to support gathering and use of data on behavioural and social drivers - Outline of proposed processes for data harmonization and sharing	15 minutes	Lisa Menning
- Q&A and discussion	30 minutes	Facilitated by IVIR-AC focal points

It is proposed that the session will consult with IVIR-AC on two main questions:
- What feedback is there on the proposed next steps to produce comparable datasets?
- How to encourage and support standardized use of tools and methods (to benefit countries)?

Background

To better support measurement of the BeSD of vaccination, WHO established a global working group called 'Measuring Behavioural and Social Drivers of Vaccination' (BeSD) in October 2018. This group contributed to the development of tools and practical guidance to assess the BeSD of vaccine uptake for childhood vaccination and COVID-19 vaccination, enabling programmes to address under-vaccination through an enhanced understanding of the causes. The work culminated in a session at the October 2021 meeting of the WHO Strategic Advisory Group of Experts on immunization (SAGE). SAGE reviewed the findings of the tool testing and validation process, as well as draft guidance for local use of tools and data and put forward recommendations to Member States on standardized data collection and use.

Evidence presented at the October 2021 SAGE meeting are available here and the resulting conclusions and recommendations from the session were published in the Weekly Epidemiological Report vol 96, 50.

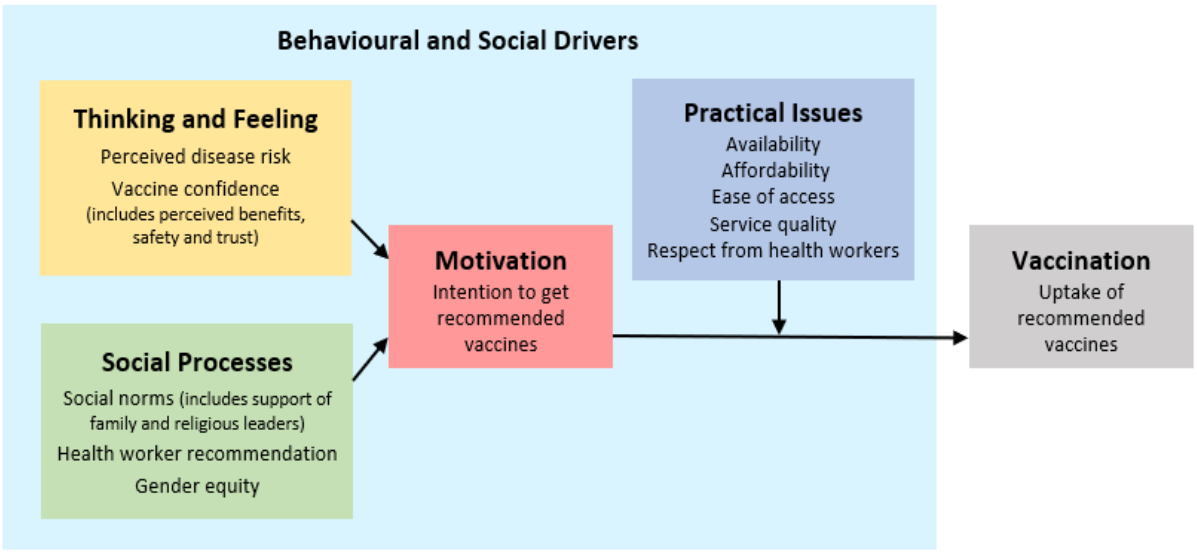
The first position paper on behavioural and social drivers (BeSD) of vaccine uptake is expected to be published in May 2022, summarizing the development process of the tools and indicators, preliminary work to identify interventions to improve vaccine uptake, and finally, priorities for gathering and use of BeSD data and future research directions.

This work puts forward new evidence, tools, and guidance to support programmes to assess and address reasons for non- or under-vaccination. BeSD Tools include surveys and in-depth interview guides for both childhood and COVID-19 vaccinations, and a guidebook to support the gathering and use of data. The importance of measuring practical issues, motivations, thinking and feeling, and social processes is highlighted, and priority indicators for standardized evaluation are provided. The BeSD Tools are field-tested, validated, user-friendly, and can provide standardized data on the reasons for low uptake; guide planning of vaccine programmes at sub-national, national, regional, and global levels; and inform continuous learning and improvement.

The tools are structured according to the BeSD framework (Figure 1) consisting of four domains: 1) *thinking and feeling*, which includes peoples' cognitive and emotional responses to vaccine-preventable diseases and vaccines; 2) *social processes*, which includes social norms about vaccination and receiving recommendations to be vaccinated; 3) *motivation*, which includes peoples' intention, willingness, and hesitancy to get vaccinated (but not their "reasons"); and 4) *practical issues*, which includes the experiences people have when trying to get vaccinated, including any barriers they face. The framework includes influences that are measurable, potentially changeable, and specific to vaccination. It does not include broader influences such as literacy, political views, and socio-economic status, all of which can be explored through use of the BeSD qualitative tools.

The development, testing and validation process contributed data to guide the finalization of the tools and selection of priority indicators (Table 1) for routine tracking both locally and globally.

Figure 1. *The behavioural and social drivers of vaccination framework*



Source: The BeSD expert working group. Based on: Brewer NT, Chapman GB, Rothman AJ, Leask J, and Kempe A (2017). Increasing vaccination: Putting psychological science into action. *Psychological Science for the Public Interest.* 18: 149-207.

Table 1. *Behavioural and social drivers domains, constructs, and priority indicators*

Domain	Construct	Priority indicator for childhood vaccination	Priority indicator for COVID-19 vaccination
Thinking and feeling	Confidence in vaccine benefits	% of parents who say vaccines are "moderately" or "very" important for their child's health	% of adults / health workers who say a COVID-19 vaccine is "moderately or "very" important for their health
Social processes	Family norms	% of parents who say most of their close family and friends want their child to be vaccinated	% of adults / health worker who say most of their close family and friends would want them to get a COVID-19 vaccine
Motivation	Intention to get vaccinated	% of parents who say they want their child to get "all" of the recommended vaccines	% of adults/health workers who say they want to get a COVID-19 vaccine
Practical issues	Know where to get vaccination	% of parents who say they know where to get their child vaccinated	% of adults / health workers who say they know where to get a COVID-19 vaccine for themselves
Practical issues	Affordability	% of parents who say vaccination is "moderately" or "very" easy to pay for	% of adults / health workers who say vaccination is "not at all" or "a little" easy to pay for

Support for implementation of BeSD Tools

In consultation with partners, WHO is preparing for a range of activities to support the implementation of the BeSD tools and guidance. These will focus on enhancing capacity, providing technical assistance, global dissemination of findings and trends, and documentation of case examples to illustrate the tools in practice. Where possible, these tools and indicators are being integrated into existing global surveys and platforms, e.g., IA2030, use as a Gavi 5.0 Strategy Indicator, DHIS, MICS, coverage survey tools, the WHO immunization information management systems. Integrated analysis will also be encouraged to support use of BeSD data alongside other programme indicators, such as coverage, surveillance, and vaccine supply.

The tools have been designed to be easily integrated into existing programme data-collection and planning processes to minimize the need for added resources. However, some additional national investments will be required to implement these tools (e.g., for translation, local adaption, training) on a periodic basis, or to support supplementary data collection activities for priority populations. These added requirements will need to be included in national plans (including activities, budgets, roles, and responsibilities), and updated on an annual basis as the context and needs evolve. Above all, linkages to IA2030 (specifically strategic priority 2 on commitment and demand) and other regional or national strategies should provide a reference to guide prioritization and investment in activities. Importantly these tools offer new potential for monitoring and evaluation of interventions, offering all stakeholders essential insights to guide future investments.

Questions for IVIR-AC on data harmonization

Programmes gather data through a variety of routine and ad-hoc streams. To enable the full use of BeSD data for planning and monitoring, and comparisons across time and location, rapid processing, analysis and reporting will be required. Despite availability of priority indicators and recommendations for standardized use, consolidation of this data into national-level or global-level reports will require steps

to harmonize datasets that are not immediately compatible and comparable. For example, datasets may contain variables that measure the same construct differently.

To generate comparable datasets, a range of steps are now being taken to identify the variable features across datasets: the construct measured, question asked, response options, and the data structure. Options and pathways for completely matching, partially matching, and completely un-matching variables across datasets are being determined, i.e., variables that are completely unmatching will not be harmonized into a single variable. An initial approach to harmonization will be discussed with IVIR-AC, with a goal of generating comparable datasets for consolidation into national or global databases. Establishing such a process – preferably for harmonization before data collection occurs – will permit programmes to answer critical questions about reasons for low uptake in a timely and efficient manner (and potentially provide an opportunity to increase study power and the utility of existing data).

The considerations for establishing processes for data collection need to consider local contextualization and ownership of data. Further details are provided in the Powerpoint file supporting this session. Guidance from IVIR-AC is invited on how to balance these considerations for local contextualization with potential benefits to rapid reporting and data quality. This will enable a harmonization process to be developed and shared with programmes and partners for consultation and finalization.

Behavioural and social drivers of vaccination

Tools and practical guidance for achieving high uptake

February 2022

World Health Organization

Foreword

The tools in this guide were developed, tested and validated through a rigorous, evidence-based process with support from a global working group. The outputs of this effort were presented to the WHO Strategic Advisory Group of Experts on immunization (SAGE) at its meeting in October 2021. In a subsequent report SAGE recognized the importance of measuring factors that contribute to low uptake and took note of the evidence-informed framework with four domains for measuring behavioural and social drivers (BeSD). SAGE recommended the systematic gathering and use of data on BeSD to assess the reasons for low uptake, for routine tracking of trends, and for monitoring and evaluation of interventions.

The full SAGE recommendations appeared in the *Weekly epidemiological record*, 17 December 2021, https://apps.who.int/iris/handle/10665/350649.

Purpose of the document

This guidebook supports the use of the BeSD of vaccination tools to understand what drives uptake of vaccines. It is intended for immunization programme managers, research advisors and others who are collecting, analysing and using data for immunization programme planning and evaluation. Routine tracking of BeSD data will offer insights into how to continually improve programme implementation.

Using the validated tools presented here will equip programmes and partners to understand the reasons for low vaccine uptake, track trends over time and reduce coverage inequities by gathering and using data to systematically design, implement and evaluate tailored interventions.

To enable the World Health Organization (WHO) and partners to gather feedback and any lessons on the use of these tools, any comments or queries can be shared through this contact form.

Recommended citation

World Health Organization. Behavioural and social drivers of vaccination: tools and practical guidance for achieving high uptake. Geneva: World Health Organization; 2022.

Contents

Acknowledgements

Special thanks are due to all members of the WHO working group on measuring behavioural and social drivers of vaccination (BeSD) who guided the development of this document and all BeSD tools. The BeSD working group was active from November 2018 to January 2022, chaired by Julie Leask (University of Sydney, Australia) with deputy chair, Noel Brewer (University of North Carolina, United States). Members providing research support include Gilla Shapiro (University of Toronto, Canada), Kerrie Wiley (University of Sydney, Australia) and Nisha Gottfredson (University of North Carolina, United States).

Other BeSD working group members include Neetu Abad (Centers for Disease Control and Prevention, United States [US CDC]); Sohail Agha (the Bill & Melinda Gates Foundation [BMGF], United States); Helena Ballester Bon (United Nations Children's Fund [UNICEF]); Cornelia Betsch (University of Erfurt, Germany); Vinod Bura (WHO, Indonesia); Ève Dubé (Laval University, Canada); Michelle Dynes (UNICEF); Melissa Gilkey (University of North Carolina, United States); Monica Jain (International Initiative for Impact Evaluation, India); Abdul Momin Kazi (Aga Khan University, Pakistan); Saad Omer (Yale University, United States); Anna Lisa Ong-Lim (University of the Philippines, Philippines); Deepa Risal Pokharel (UNICEF); Dimitri Prybylski (US CDC); Jennifer Requejo (UNICEF); Aaron Scherer (University of Iowa, United States); Holly Seale (University of New South Wales, Australia); Nick Sevdalis (King's College London, United Kingdom); Smita Singh (Gavi, the Vaccine Alliance, Switzerland [Gavi]); Riswana Soundardjee (Gavi); Gillian SteelFisher (Harvard University, United States); and Charles Shey Wiysonge (South African Medical Research Council, South Africa).

Historical BeSD working group members who contributed to the development of the tools include Gustavo Correa (Gavi), Wenfeng Gong (BMGF), Benjamin Hickler (UNICEF) and Mohamed Jalloh (US CDC). Additionally, Aybüke Koyuncu and Shibani Kulkarni (US CDC) contributed significantly to the development of this guidebook and refinement of the tools.

All inputs are acknowledged with sincere gratitude.

This document was developed by the Demand and Behavioural Sciences team of the Department of Immunization, Vaccines and Biologicals, World Health Organization.

Conflicts of interest

For the development of this document, a global and multidisciplinary group was established by WHO consisting of individuals with expertise across multiple areas of specialization and regional representation (see above list of names and affiliations). Declarations of interest have been collected from all external contributors and assessed for any conflicts of interest. Potential conflicts of interest have been managed according to WHO's policies and procedures.

Terms of reference for the group described the required set of duties and contributions of the members, in addition to scope, objectives and expected outputs. All procedures were followed in accordance with ethical standards. The document was developed via an iterative, open and transparent process of development and review, with the full working group being offered the opportunity to comment at the end of each round of revisions.

All working group members contributed in their individual capacity, and no one member was ever given added preference. At each stage of content development, inputs were collectively reviewed by the working group or a subgroup of the broader group. It was expected that group members acted honestly

and fairly in the interests of WHO, as was the case. Discussions were managed by the working group chair in a manner to ensure that scientific integrity, process and reputation were sustained.

These actions together helped to ensure that working group members brought their best experience, expertise and commitment to the discussions.

Abbreviations

BeSD	behavioural and social drivers of vaccination
BMGF	Bill & Melinda Gates Foundation
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease
DHS	Demographic and Health Surveys
DTP1	first dose of diphtheria toxoid, tetanus toxoid and pertussis vaccine
EPI	Expanded Programme on Immunization
Gavi	Gavi, the Vaccine Alliance
GIS	geographical information systems
GPS	Global Positioning System
IHR	International Health Regulations
MICS	Multiple Indicator Cluster Surveys
NGO	nongovernmental organization
NITAGs	National Immunization Technical Advisory Groups
ODK	Open Data Kit
OR	odds ratio
UNICEF	United Nations Children's Fund
VPD	vaccine-preventable disease
WHO	World Health Organization
SAGE	Strategic Advisory Group of Experts on Immunization

Glossary

Behavioural and social drivers: Vaccination-specific beliefs and experiences that programmes may be able to modify to boost vaccine uptake.

Confidence: Belief that vaccines work, are safe and are part of a trustworthy medical system, including perceived importance and effectiveness of vaccines and concerns about vaccines being unsafe.

Hesitancy: Motivational state of being conflicted about, or opposed to, getting vaccinated; includes intentions and willingness.

BeSD framework domains:

Thinking and feeling: Cognitive and emotional responses to vaccine-preventable diseases (VPDs) and vaccines.

Social processes: Social experiences related to vaccines, including social norms about vaccination and receiving recommendations to be vaccinated.

Motivation: Readiness to vaccinate, including vaccination intentions, willingness and hesitancy, but not reasons for vaccination.

Practical issues: Experiences people have when trying to get vaccinated, including access barriers.

1. Introduction

This guidebook supports the use of the behavioural and social drivers of vaccination (BeSD) tools to understand what drives uptake of vaccines. It is intended for immunization programme managers and others collecting, analysing and using data for vaccine programme planning and evaluation. Routine tracking of BeSD data will offer insights into how to continually improve programme implementation.

The guide follows a three-step process (**plan**, i**nvestigate** and **act**) and includes:

- a **quick start guide** – an overview on how to gather, analyse and use BeSD data;
- an **explanation of each step** and best-practice recommendations; and
- **tools** to measure the drivers of vaccine uptake:
    - **childhood vaccination** surveys and interview guides (**Annex 1**); and
    - **adult COVID-19 vaccination** surveys and interview guides (**Annex 2**).

Behavioural and social drivers are people's beliefs, experiences and their circumstances that affect whether they get vaccinated or not. The behavioural and social drivers of vaccination can be grouped and **measured in four domains** (Fig. 1) *(1-5)*:

1) **thinking and feeling** about vaccines
2) **social processes** that drive or inhibit vaccination
3) **motivation** (or hesitancy) to seek vaccination
4) **practical issues** involved in seeking and receiving vaccination.

While many factors affect uptake, the BeSD tools focus primarily on proximal factors that are measurable in individuals, specific to vaccination and potentially changeable by programmes. Behavioural and social drivers do not directly include broader influences such as literacy, political views and socioeconomic status. Broader influences can be explored using the BeSD qualitative tools and demographic questions.

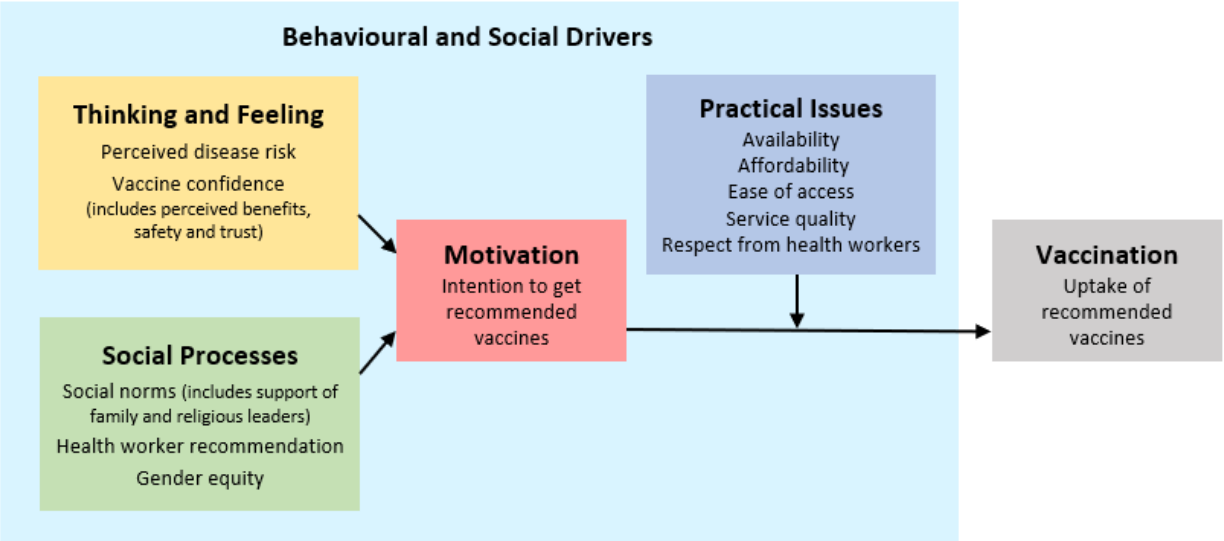


Fig. 1. Behavioural and social drivers of vaccination (BeSD) framework. *Source: WHO BeSD working group; based on (6)*

A quick-start guide: assessing reasons for low uptake

This summary shows the process of using the BeSD tools to assess and address behavioural and social drivers.

PLAN

MAKE A PLAN

Set a specific goal such as "understanding the drivers and barriers to vaccination in [country] to improve uptake". Establish a team that includes key stakeholders and representatives of the participating population. Consider the research methods, any funding needs, timelines and ethics requirements. Develop a plan, timeline and budget. See section 3.1 Key steps in planning for more guidance.

CHOOSE YOUR TOOLS

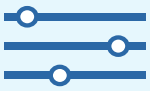
Decide on the tools to match your goal. See section 3.3 Select data collection tools for an overview of the BeSD tools. Translate or adapt them as needed. Always include BeSD priority questions, and do not change the wording of those questions. Guidance for integration with other assessments and adaptation is available in section 3.4 and section 3.5. Identify sample and data collection protocols and obtain any necessary approvals.

INVESTIGATE

COLLECT AND ANALYSE DATA

Collect, clean and analyse data. Report findings, including data resulting from at least the five BeSD priority questions. Tools and guidance for analysing and presenting quantitative and qualitative BeSD data are available in section 4. Investigate the drivers.

ACT



USE FINDINGS TO DESIGN INTERVENTIONS

Develop an intervention plan, including indicators for monitoring and evaluating processes and outcomes. Recommendations for interventions to increase acceptance and uptake are available in section 5.2 Planning interventions.

CONTINUE TO MONITOR AND IMPROVE

Repeat BeSD data collection as needed. Routinely monitor drivers and barriers, and track trends and the long-term impact of interventions, using at least the five BeSD priority questions. This will build an understanding of which interventions work well and can be sustained over time.

2. What is measured?

2.1 Priority questions and indicators

The BeSD surveys include priority questions that programmes can use to calculate priority indicators. Together, the questions and indicators support regular collection of standardized, quality data for monitoring trends over time. Table 1 shows the minimum requirement for use. All countries should integrate the BeSD priority questions into the appropriate routine or ad hoc data collection processes. This can include, for example, coverage surveys, Expanded Programme on Immunization (EPI) reviews, Multiple Indicator Cluster Surveys (MICS), Demographic and Health Surveys (DHS) and other nationally representative surveys. **To preserve their meaning and the comparability of resulting indicator data between settings and time periods, the priority questions and response options should not be changed**.

Table 1. BeSD priority questions and indicators

Domain/ construct	**Childhood vaccination survey**		**COVID-19 vaccination survey**	
	Priority question	**Priority indicator**	**Priority question**	**Priority indicator**
Thinking and feeling Confidence in vaccine benefits	How important do you think vaccines are for your child's health? Would you say… ☐ Not at all important ☐ A little important ☐ Moderately important, *or* ☐ Very important?	% of parents/caregivers who say that vaccines are "moderately" or "very" important for their child's health	How important do you think getting a COVID-19 vaccine will be for your health? Would you say… ☐ Not at all important ☐ A little important ☐ Moderately important, *or* ☐ Very important?	% of adults/health workers who say a COVID-19 vaccine is "moderately" or "very" important for their health
Social processes Family norms	Do you think most of your close family and friends want you to get your child vaccinated? ☐ NO ☐ YES	% of parents/caregivers who say most of their close family and friends want their child to be vaccinated	Do you think most of your close family and friends want you to get a COVID-19 vaccine? ☐ NO ☐ YES	% of adults/health workers who say most of their close family and friends want them to get a COVID-19 vaccine
Motivation Intention to get vaccine	[COUNTRY NAME] has a schedule of recommended vaccines for children. Do you want your child to get none of these vaccines, some of these vaccines or all of these vaccines?	% of parents/caregivers who say they want their child to get "all" of the recommended vaccines	Do you want to get a COVID-19 vaccine? Would you say… ☐ No, you do not want to, ☐ Yes, you do want to, *or are you* ☐ Not sure?	% of adults/health workers who say they want to get a COVID-19 vaccine

Domain/ construct	**Childhood vaccination survey**		**COVID-19 vaccination survey**	
	Priority question	**Priority indicator**	**Priority question**	**Priority indicator**
	☐ NONE ☐ SOME ☐ ALL			
Practical issues Know where to get vaccination	Do you know where to go to get your child vaccinated? ☐ NO ☐ YES	% of parents/caregivers who say they know where to get their child vaccinated	Do you know where to go to get a COVID-19 vaccine for yourself? ☐ NO ☐ YES	% of adults/health workers who say they know where to get a COVID-19 vaccine for themselves
Practical issues Affordability	How easy is it to pay for vaccination? When you think about the cost, please consider any payments to the clinic, the cost of getting there, plus the cost of taking time away from work. Would you say… ☐ Not at all easy ☐ A little easy ☐ Moderately easy, or ☐ Very easy?	% of parents/caregivers who say vaccination is "moderately" or "very" easy to pay for	How easy is it to pay for vaccination? When you think about the cost, please consider any payments to the clinic, the cost of getting there, plus the cost of taking time away from work. Would you say… ☐ Not at all easy ☐ A little easy ☐ Moderately easy, *or* ☐ Very easy?	% of adults/health workers who say vaccination is "moderately" or "very" easy to pay

2.2 Summary of constructs measured in BeSD surveys

The full BeSD surveys measure the constructs (themes) shown in Tables 2 and 3. Constructs are categorized as priority, main or are optional, based on the outcomes of the validation process. The priority questions (corresponding to priority indicators) were the best performing questions across the domains and most strongly associated with vaccine uptake.

Table 2. Childhood vaccination survey

Thinking and feeling	Motivation	Social processes	Practical issues
✪ Confidence in vaccine benefits	✪ Intention to get child vaccinated	✪ Family norms	✪ Know where to get vaccination
● Confidence in vaccine safety		● Health worker recommendation	✪ Affordability
○ Confidence in health workers		● Peer norms	● Took child for vaccination
		● Community leader norms	● Received recall
		○ Religious leader norms	● Ease of access
		○ Mother's travel autonomy	● Reasons for low ease of access
			● Vaccination availability
			● Service satisfaction
			● Service quality

Table 3. COVID-19 vaccination survey for adults and health workers

Thinking and feeling	Motivation	Social processes	Practical issues
✪ Confidence in COVID-19 vaccine benefits	✪ Intention to get vaccinated	✪ Family norms	✪ Know where to get vaccination
● Confidence in COVID-19 vaccine safety	● Vaccine confidence – brand	● Peer norms	✪ Affordability
● COVID-19 vaccine – see friends and family	● Willingness to recommend vaccine to others	● Religious leader norms	● Received recall
○ Perceived risk – self		● Community leader norms	● Ease of access
○ Confidence in health workers		● Health worker recommendation	● Reasons for low ease of access
		○ Workplace norms	● Service satisfaction
		○ Gender equity – travel autonomy	● Service quality
			○ On-site vaccination

● Main survey question.
✪ Priority question in main survey.
○ Optional question.

3. Plan to use the tools

Why assess the behavioural and social drivers of vaccination?

To increase vaccination coverage, it is vital to know *why* uptake is low. Immunization programmes should collect data on what people are thinking and feeling, their motivation, and the social processes and practical issues that drive or hinder vaccination to develop evidence-informed strategies that increase uptake. This process enables programmes to design, target and evaluate interventions to achieve greater impact with more efficiency, and to examine and understand trends over time.

3.1 Key steps in planning

Before starting to use the tools, immunization programmes should:

- ✓ Establish a small stakeholder team of immunization staff, partners and expert advisors with research expertise. Involve this team and local community representatives throughout the process, being sure to include persons with disadvantage or disability.
    - Involvement of stakeholders from the outset is key, and will facilitate access to the target population, local permissions and ethics approvals.
    - If a dedicated research group will conduct the data collection and analysis, the small stakeholder team will still carry out planning and coordination among the researchers and other stakeholders.
- ✓ Develop a research question.
- ✓ Select data collection tools (see section 2.2 for details).
- ✓ Develop a data collection and analysis plan.
- ✓ Establish realistic timelines for each phase of work, factoring in additional time needed for possible delays. Phases may include protocol development and ethics review, data collection and analysis, recommendations and dissemination.

Immunization programmes should also consider policies on data ownership and sharing. Obtain the required permits and ethical approvals prior to data collection, anonymize all data and respect local principles of data privacy and protection. Refer to the ethical principles of the Helsinki Declaration for medical research involving humans, and consider the guidance on respect for research participants; protection of health, rights and dignity; the right to self-determination; and the privacy and confidentiality of personal information collected. Follow the local and international ethical, legal and regulatory norms and standards.

3.2 Develop a research question

It is important to develop a research question to focus the investigation. The following are examples of research questions related to vaccination:

- *Which social and behavioural drivers predict vaccine uptake among X population?*
- *What are the barriers to and enablers of vaccine uptake among X population?*
- *How are vaccination services experienced among X population?*

In some cases, it may be useful to develop up to three or four research questions. Research questions help guide how data are collected (e.g., population, methods, sample size). For example, questions with the words “predict” or “associated” are often best answered by quantitative methods with larger sample sizes that represent the population. Questions with words such as “describe” and “experience” are often

best answered by qualitative methods, or a combination of quantitative and qualitative methods that employ smaller sample sizes.

Resources that may assist in **developing a research question**:

- Mitchell RD, O'Reilly GM, Phillips GA, Sale T, Roy N. Developing a research question: a research primer for low-and middle-income countries. Afr J Emerg Med. 2020;10:S109–14.
- Wyatt J, Guly H. Identifying the research question and planning the project. Emerg Med J. 2002:19(4):318–21.

3.3 Select the data collection tools

BeSD tools are available to understand the drivers of uptake for childhood vaccines and adult COVID-19 vaccines. The BeSD surveys and in-depth interview guides can be implemented as stand-alone assessments or integrated into other data collection activities (see Table 4 and section 3.4). Priority indicators for tracking can be found in the annexes above the relevant survey.

BeSD tools for childhood vaccination – Annex 1

- Childhood vaccination priority indicators
- Childhood vaccination survey for caregivers
- Childhood vaccination in-depth interview guide for caregivers
- Childhood vaccination in-depth interview guide for health workers
- Childhood vaccination in-depth interview guide for community influencers
- Childhood vaccination in-depth interview guide for programme managers

BeSD tools for adult COVID-19 vaccination – Annex 2

- COVID-19 vaccination survey priority indicators
- COVID-19 vaccination survey for adults and health workers
- COVID-19 vaccination in-depth interview guide for adults and health workers

Table 4. Main differences between the surveys and interview guides

Surveys	Qualitative interview guides
• **Fixed questions** quantify topics related to pre-identified drivers and barriers. • **Large and representative sample** are surveyed at one point in time or over time. • Yield **categorical** summaries with numerical frequencies and associations.	• **Flexible and open-ended questions** guide an interview that explores the participant's own accounts of the drivers and barriers. • **Small number of participants (10-30)** are interviewed at one point in time or over time. • Yield **narrative** summaries with key themes and indicative quotes.

The BeSD surveys are formatted for verbal administration. They can be adapted to various interview modes, including online, mailed and in-person.

The in-depth interview guides can be used in a stand-alone assessment with individuals.

The surveys and interview guides can be used independently or together for a thorough assessment of the behavioural and social drivers of vaccination. The interview guides can be used before or after a survey to gather in-depth information about a particular population group or survey finding of interest.

3.4 Integrate the BeSD tools into other data collection processes

The BeSD surveys can be integrated as supplementary modules into other data collection activities, such as an EPI review, coverage survey, MICS or DHS. Integration into these large national surveys requires good coordination, expert input and strong partner engagement. It is also possible to integrate the BeSD tools into local data-gathering activities, regional assessments and academic research studies.

When integrating, include at least the five BeSD priority indicators, in addition to other BeSD survey questions that are relevant to the country or research objective. Ensure the chosen questions align with the target audience of the broader activity (e.g., caregivers, health-care workers), remove duplicate questions (if any) and order questions to create a logical flow.

3.5 Adapt and test the tools to match local needs and context

A global group of experts and partners carried out a rigorous process to develop, test and validate the tools.[*] Changing questions or response options removes their validity and comparability. Therefore, to maintain accuracy, standards for tracking trends and comparability across countries, **BeSD questions and response options should not be revised**. Additional questions can be included to accommodate specific contexts. To assist with local translation, all BeSD tools include details on the rationale for each question and related descriptions. Complete the translations and then check the quality of translations through cognitive interviews.

Adapting the BeSD tools requires three steps:

1) **Translating each survey** into local language(s) with review by stakeholders to ensure the original intended meaning of concepts is retained. If resources allow, parallel translation may offer added rigour, in which two experts independently translate the survey and then meet to discuss and align the translations.
2) **Conducting cognitive interviews** of each survey to check that each question and its response options convey the intended meaning in the local language and cultural context. See Annex 3 for more details. Also use cognitive interviewing to test the visual representation of the four-point scale (Annex 1.3).
3) **Piloting** (or pre-testing) to ensure that the surveys and interview guides work in the field and yield usable data.
    - Test the **qualitative interview guides** with at least 2–3 people from the target population to check that questions are appropriate to the local context and flow well.
    - Test the **surveys** with a sample of 5–10 people to check for flow, skip logic and response options and to ensure that the survey process yields complete, high-quality data.
    - Test the **mode of data collection** (e.g., door-to-door, online surveys) to guide refinements to tools and processes.

[*] The BeSD tool development process is described in the *Weekly epidemiological record*, 17 December 2021, https://apps.who.int/iris/handle/10665/350649.

In addition, adapt any written materials for persons with disadvantage or disability to enable basic accessibility. This could include, for example, use of plain language, large fonts, clearly readable questions and response options, images and audio for the visually impaired.

Country example: Adapting the BeSD surveys in Guatemala

Spanish and Mayan translations of the BeSD surveys were done through a consensus exercise involving linguists, anthropologists and experienced qualitative interviewers. This process was critical for refining translations and ensuring the interviewers were comfortable with the survey concepts before conducting cognitive interviews.

Cognitive interviews quickly revealed that the translated script had to be flexible enough to accommodate gendered words and inflections in language that mark respect to elders. A different visual representation of the four-point response scale was also needed in Guatemala. Instead, interviewers took with them grains or dried beans and four buckets to represent the response-scale options: one empty, one with a little grain, one with a moderate amount of grain and one very full. Before the interview, some time was spent describing these amounts to ensure participants understood the options on the scale.

Box 1. Recommendations for enhancing data quality

When adapting the BeSD surveys for local needs, remember:

- ✓ **Adapt demographic questions to the local setting** (e.g., update response options for ethnicity, education, religion). Ask the minimum necessary demographic questions to support subgroup analyses stated in the analysis plan.
- ✓ **Follow this topic order for survey question flow**: 1) infectious disease, 2) vaccination status, 3) motivation, 4) thinking and feeling, 5) social processes, 6) practical issues.
- ✓ **Do not add or remove options** from the four-point response scale. If needed, use a visual scale to help improve understanding of the response options (Annex 1).
- ✓ **Use consistent response-scale direction**, from negative (lowest) to positive (highest).
- ✓ If adding new questions, consider how they fit within the BeSD domains (Fig. 1). Align response options to match the BeSD response options. Box 2 offers more tips on adding new questions.

The BeSD surveys have been validated according to the above principles. Following these will allow data to be comparable across countries.

The BeSD surveys are designed to be read aloud to respondents. The surveys can be easily adapted for self-completion; this is when the respondent reads and answers the questions for themselves on paper or online. When **adapting the BeSD surveys for online data collection**:

- ✓ Remove interviewer instructions. See examples in Table 5.
- ✓ Include simple instructions to help respondents answer the questions and know what to expect.
- ✓ Avoid changing question wording and do not remove or add response options or change scales.
- ✓ Where possible, evaluate any changes to the wording of specific questions. Assess understanding of the question and how the changes may affect respondents' answers.

The qualitative interview guides mirror the four BeSD domains in the survey (Fig. 1). However, if a topic needs deeper exploration, it can be expanded in the interview. For further information on adapting the qualitative interview guides in response to a local context, see Annex 3.

Box 2. Adding new questions for specific contexts

Countries can add questions to BeSD tools to understand context-specific issues. Be sure to:

- ✓ use available evidence about the priority group, or in-depth interviews with them, to determine which questions to add;
- ✓ include demographic questions to facilitate subgroup analysis; and
- ✓ follow the quality guidance in Box 1.

Examples of additional questions for gender and religious considerations:

Mother's decision-making autonomy:

"In your household, who made the decision about vaccinating your child? Would you say… the **mother** of the child, the **father** of the child, **both parents** of the child or **someone else**?"

Compatibility with religious beliefs:

"Do your religious or spiritual beliefs **encourage** vaccinating your child, **discourage** vaccinating your child, or would you say this **doesn't apply** to you?"

Table 5. Adapting survey questions for verbal vs self-administration

Construct	Verbal administration (interviewer to read aloud)	Self-administration (read by respondent)
Gender	This may seem obvious, but I have to ask the question. What is your gender? Would you say… ☐ Woman, ☐ Man, ☐ Nonbinary, *or would you* ☐ Prefer not to say?	What is your gender? ☐ Woman ☐ Man ☐ Nonbinary ☐ Prefer not to say
Service quality	What is not satisfactory about the vaccination services? Would you say… [READ ALOUD ALL RESPONSE OPTIONS, PAUSING TO ALLOW RESPONDENT TO ANSWER "YES" OR "NO" AFTER EACH RESPONSE OPTION. RESPONDENTS MAY SELECT MULTIPLE RESPONSE OPTIONS.] ☐ Nothing, you are satisfied, [IF NOTHING, SKIP REST OF RESPONSES] ☐ Vaccine is not always available, ☐ The clinic does not open on time, ☐ Waiting times are long, ☐ The clinic is not clean, ☐ Staff are poorly trained, ☐ Staff are not respectful,	What is not satisfactory about the vaccination services? Select all that apply. ☐ Nothing, you are satisfied [IF THIS RESPONSE IS SELECTED, DO NOT ALLOW OTHER RESPONSES] ☐ Vaccine is not always available ☐ The clinic does not open on time ☐ Waiting times are long ☐ The clinic is not clean ☐ Staff are poorly trained ☐ Staff are not respectful ☐ Staff do not spend enough time with people ☐ Something else, please specify: _____

Construct	Verbal administration (interviewer to read aloud)	Self-administration (read by respondent)
	☐ Staff do not spend enough time with people, *or is there* ☐ Something else? [RECORD ANSWER: _____]	
Affordability	How easy is it to pay for vaccination? When you think about the cost, please consider any payments to the clinic, the cost of getting there, plus the cost of taking time away from work. Would you say… ☐ Not at all easy, ☐ A little easy, ☐ Moderately easy, *or* ☐ Very easy?	How easy is it to pay for vaccination? When you think about the cost, please consider any payments to the clinic, the cost of getting there, plus the cost of taking time away from work. ☐ Not at all easy ☐ A little easy ☐ Moderately easy ☐ Very easy
Know where to go to get vaccination	Do you know where to go to get your child vaccinated? ☐ NO ☐ YES	Do you know where to go to get your child vaccinated? ☐ No ☐ Yes

Box 3. Assessments for zero-dose children and missed communities

Assessing behavioural and social drivers of vaccination (BeSD) can be useful for understanding why children are unvaccinated. **Zero-dose children** are those who have not received any routine vaccines. **Missed communities** face poor access to primary health-care and social services, limited economic and educational opportunities, and lack of political representation.

The BeSD process (Plan, Investigate, Act) is compatible with the Gavi Alliance IRMMA Framework (Identify, Reach, Measure, Monitor and Advocate) as part of a strategy to reduce zero-dose children. For more information visit:

- Gavi Zero-Dose Funding Guidelines
- Gavi Zero-Dose Brief (slide deck)
- Gavi Zero-Dose Analysis Cards

How do I identify zero-dose children?

Identifying who, where and how many zero-dose children exist and why they have been missed requires analysing multiple sources of existing data, including the behavioural and social drivers of under-vaccination. A useful proxy (substitute) measure for the number of zero-dose children is missing DTP1 (first dose of diphtheria toxoid, tetanus toxoid and pertussis vaccine); this can be calculated using data from the immunization programme, other health programmes (e.g., maternal, neonatal and child health) and sectors (e.g., education, social services). Analysing demographic data of zero-dose or missed communities can help characterize the types of inequities they face (e.g., gender, ethnicity/culture, religion, socioeconomic, or disability status).

Which of the BeSD tools should I use?

To gain a deeper understanding of *why* these children are not vaccinated, use the BeSD qualitative interview guides (Annex 1.4). As a minimum, aim to interview caregivers and community influencers using the relevant interview guides.

If inadequate data are available to identify zero-dose children, it may be necessary to implement the full BeSD Childhood Vaccination Survey (Annex 1.2). If the full survey cannot be implemented, a shorter version can be used, including the five priority BeSD childhood vaccination indicator questions (Annex 1.1), and the following questions from the full survey:

- *Social process questions*: mother's travel autonomy, religious leader support;
- *Practical issue questions*: service satisfaction, service quality, reasons for low ease of access; and
- *Socio-demographic questions*: add questions as needed to understand *who* zero-dose children are.

How should I adapt the BeSD tools for zero dose?

Adapt the BeSD tools using the principles highlighted in section 3.5. Add probes to the interview guides to address context-specific issues (e.g., natural disasters, conflict). It may also be important to assess whether primary care services or public service platforms exist to reach the target population.

4. Investigate the drivers: data collection, analysis and reporting

This section outlines steps to support collection of quality data using BeSD surveys and qualitative interview guides and offers frameworks to facilitate data analysis. To ensure the best data collection approaches are used for the setting and goals, the study programme should develop a research protocol. The research protocol should clearly describe:

- ✓ what the research question is;
- ✓ who the target population is;
- ✓ how members of the target population will be identified;
- ✓ how data will be collected from the target population;
- ✓ how the sample size and response rate will be calculated;
- ✓ how sampling bias will be minimized to ensure the sample closely reflects the target population;
- ✓ how and by whom members of the target population will be invited to participate;
- ✓ how informed and voluntary consent will be obtained;
- ✓ how data will be stored and the anonymity of participants protected; and
- ✓ how data will be analysed and reported.

Safeguard completed questionnaires in locked cabinets/offices (paper based) or on password-protected computers/encrypted devices (electronic) to protect private and personally identifiable information.

4.1 Choosing a data collection mode

For both tools, data collection can be done using verbal administration, pen and paper or digital tools, for example using the Open Data Kit (ODK) application. Table 6 summarizes the strengths and limitations of a range of data collection modes available for implementing the BeSD tools.

Table 6. Strengths and limitation of different data collection modes

Data collection mode	Strengths	Limitations
Face-to-face	Allows for longer interviews; the presence of an interviewer can increase response rates and motivate respondents to complete the interview. An interviewer can also explain difficult concepts or questions. Involvement of key local stakeholders may facilitate access to specific population groups and contribute as advocates in later activities.	Time and resource intensive due to the logistics involved (e.g., training of interviewers, interviewer time, transport, materials for data collection). The presence of an interviewer or other official may lead to socially desirable responses for sensitive questions.
Telephone	Less costly than face-to-face interviewing; has the advantage of the presence of an interviewer, yet lower	Limited to populations with telephones. Can result in biased samples in some settings (e.g., in some countries men,

Data collection mode	Strengths	Limitations
	levels of socially desirable responses than face-to-face.	urban younger and better-educated respondents are overrepresented). Interviews need to be shorter than for face-to-face (up to approx. 25 minutes). Relies on trained interviewers to implement.
Online (including app-based data collection*)	A cost-effective approach, as it does not require interviewers and thus training. Lessens socially desirable responses due to lack of interviewer presence. Online methods offer greater speed and efficiency. Data are entered automatically, which avoids manual transfer that can be impacted by human error. *Data can be collected offline or when participants are "on the go".	Limited to populations with online access, which may be less than half the population, depending on the country. Response rates are usually lower than face-to-face or telephone methods. Can result in more biased samples in some settings (e.g., over-representation of men, urban younger and better-educated respondents). Time taken to complete survey needs to be limited to about 15 minutes or less; otherwise the number of non-completions increases substantially. *App-based approaches rely on populations with access to smartphones or computers, further limiting and biasing the sample. Questions need to be very simple to be accurately interpreted on a screen and understood, as no interviewer is present to clarify questions. *On the smaller mobile phone screen, questions and their response options must be short and clear to be well understood.

*Content pertains to app-based data collection methodologies only.

4.2 Develop a sampling plan

Sampling refers to identifying and selecting people who will participate in the study. The sampling approach will depend on the study goals, setting, and human and financial resources. To develop a sampling plan identify a priority population such as caregivers to children under 5 years old or health workers. Then, develop a sampling plan (Table 7). **The sample should be representative of the priority**

population according to its main socio-demographic characteristics (e.g., age, education, region). Consult with a sampling expert to help develop the sampling plan.

There are two broad approaches to sampling:

1) **Probability sampling** provides data that can closely represent the characteristics of the target population. This approach is based on the principle of random or chance selection of persons in the target population to participate in the study.
    - **Advantages:** Study results can usually be generalized to a wider population.
    - **Disadvantages:** It is usually more time-consuming and costly, and data analysis can be more complicated. Consider working with existing population-based surveys using probability sampling in your area to integrate the BeSD survey questions.
    - **Types:** Simple[*], Systematic[†], Stratified, Cluster.
2) **Non-probability sampling** provides data that can reflect individual/small group experiences and perspectives but that is not representative of the population. It does not give each person in the target population an equal chance of being selected to participate in the study**.**
    - **Advantages:** It can be used when probability sampling is too expensive or logistically difficult or when information rich cases are needed, for example, in a qualitative study.
    - **Disadvantages:** It limits the ability to generalize the study findings to the population. To reduce bias, include varying days, times and targeted locations for recruitment in your sampling plan.
    - **Types:** Convenience[‡], Purposive[§], Quota, Snowball, Self-selection.

Qualitative interviews mostly involve non-probability sampling of people who can provide the richest insights into the study topic. The term purposeful sampling is used for qualitative methods and there are several types of purposeful sampling. For example, maximum variation sampling aims to include a wide range of perspectives (e.g., parents from different age groups) and criterion sampling aims to include people who meet a specific criterion (e.g., caregivers of children with zero doses).

For **surveys**, you can use either probability or non-probability sampling. The approach and sample size will depend on the resources available and study objectives. Your sample size should also take the expected response rate into consideration (e.g., What percentage of potential participants will agree to participate?). **Cluster sampling is when a population is divided into smaller groups** (known as clusters) for the purposes of sample selection and data collection.

For further guidance see:

- *World Health Organization vaccination coverage cluster surveys: reference manual*. Geneva: World Health Organization; 2018 (https://apps.who.int/iris/handle/10665/272820).

[*] **Simple random sampling** is when people are randomly selected from the target population. For example, if you have a list of all nurses registered in the country, you could select participants at random from the list; each nurse would have an equal chance of being selected.

[†] **Systematic random sampling** is when people from the target population are selected according to a random starting point, and then at a predetermined interval thereafter.

[‡] **Purposive sampling** is when the study team chooses the people to recruit for the study based on preselected experiences or characteristics that are valuable to the objectives of the study.

[§] **Convenience sampling** is when people are recruited where they are easy to find (e.g., interviewing people as they exit a health clinic).

Table 7. Target population and sampling examples

Example target population	Example sampling methods
Parents and caregivers of children under age 5	• Integrate BeSD questions into an existing population-based survey (e.g., DHS, EPI coverage surveys, MICS household surveys) (probability) • Post flyers in nurseries, at schools and with women's groups. (non-probability) • Recruit people leaving a health clinic. (non-probability)
Adults over age 65	• Integrate BeSD questions into an existing population-based representative survey. (probability) • Recruit older adults from a retirement community. (non-probability)
Health workers	• Examine archival data from a national registry of all nurses; randomly select a subset. (probability) • Post flyers at health clinics. (non-probability) • Advertise in professional associations or societies. (non-probability) • Recruit health workers who leave a selected health clinic during a pre-determined time frame. (non-probability)
Individuals with underlying health conditions	• Use a national chronic disease registry. (probability) • Recruit people attending an outpatient clinic related to the health conditions of interest. (non-probability)
Persons with disadvantage and disabilities	• From the national census, randomly select a subset. (probability) • Contact organizations of persons with disabilities to seek recommendations for recruitment. (non-probability) • Plan a referral mechanism to survey persons with disadvantage or disability who may require reasonable accommodation (like local sign language translation). (non-probability)

Resources that may assist in **developing a sampling plan**:

- Ayton D, Pritchard E. Qualitative research methods for public health. Melbourne: Monash University; 2017.
- Lavrakas PJ. Encyclopedia of survey research methods. Thousand Oaks (CA): Sage; 2008 . doi: 10.4135/9781412963947.

4.3 Demographic and immunization coverage measures

Collecting demographic information as part of the survey is vital. Use demographic data to:

- Identify differences in demographic characteristics (e.g., education, gender) between the target population and the sample participants.

    - Understanding these differences will help support data weighting, a method used in data analysis to rebalance the sample data so the information better reflects the target population.
- Identify differences in perceptions (e.g., willingness to be vaccinated), behaviours (e.g., vaccine acceptance) and health outcomes (e.g., VPD) among sample participants by demographic characteristics.
    - Understanding these differences will help you design programmes to improve vaccination among specific subpopulations at risk (e.g., low socioeconomic status, location).

Collect Global Positioning System (GPS) data for surveyed clusters or sampling area provided by MICS and other standard surveys such as DHS, if this information is not already available elsewhere. The substantial benefits of GPS data collection include making it possible to link the BeSD tools with other data sets containing similar geographic information, such as MICS or DHS (see Annex 4).

In addition to the BeSD survey questions, and the minimum socio-demographic questions recommended for each survey, plan to collect immunization status (vaccine uptake) from participants, particularly for childhood immunization. WHO has published guidelines for collecting, processing, analysing and reporting coverage indicators. For practical information on coverage measures and indicators for vaccination delivered through routine immunization services, see Annex 5.

4.4 Survey data analysis and reporting

It is common for data errors to be introduced during data collection and entry. As such, all data sets need to be "cleaned" before data analysis. Data cleaning involves identifying and dealing with responses that are missing or incomplete, out of range of what is expected (e.g., age 125), inconsistent/contradictory as well as responses that don't follow skip patterns.

For more information on data cleaning, weighting and analysis, use the BeSD contact form or consult with a statistician.

4.4.1 Analysis of survey data

General descriptions of broad analytical approaches are summarized below, but consider consulting with a statistician or other researcher for help in developing a data analysis plan *before* interviewing participants. This will help to ensure that data are collected and analysed appropriately and can save time and resources in the long term.

Descriptive statistics provide information about characteristics in the population or variables studied. Examples of descriptive statistics include percentages, ranges and means (averages).

Inferential analyses identify associations (relationships) between variables, including examining demographic differences and identifying variables that correlate with key outcomes (e.g., vaccine uptake).

Inferential analyses can include the following:

Bivariate analyses provide information about relationships between two variables. For example, include **chi-square analysis** allow for compare receipt of a health worker recommendation in urban vs

rural areas or **correlations** to examine the relationship between age of caregivers and perceptions of vaccine safety.

Multivariable analyses determine the relationship between two or more variables and control for other variables that may confound the relationship. For example, to determine whether income is associated with vaccination uptake, consider using **logistic regression,** controlling for gender and education.

4.4.2 Reporting survey findings

Report findings concisely, using clearly presented data that answer the research question. Report data as percentages in most instances with raw numbers in brackets (e.g., 58% [*n* = 203]). In instances where the sample size is small, it is acceptable to use just the raw numbers (e.g., *n* = 5). Annex 6 contains examples of data reporting and presentation.

Report survey data in a manner that can be easily understood and is useful for the target audience. The following steps serve as a guide for reporting quantitative survey findings.

- ✓ **Identify the main audience:**
  - Consider which people have an interest in these data.
  - Decide the best way to present the data based on how the audience will likely use it.
- ✓ **Decide on a structure:**
  - Tell the story of the research to the audience. One option is to explain the key findings and how they answer or relate to the research question.
- ✓ **Describe the methods, including**:
  - the overall research design and sampling approach, including justification and recruitment methods;
  - how survey data were collected (e.g., in person, household surveys);
  - how data were handled, including how missing or incomplete data were dealt with;
  - which statistical analyses were done and why; and
  - any ethical considerations relevant to the investigation and data collection.
- ✓ **Describe the results of the study, including:**
  - the response rate of the survey;
  - characteristics of the sample (e.g., age, gender, geographic location);
  - the percentage of respondents who report uptake or intention to accept vaccines;
  - frequencies for the BeSD priority indicators; and
  - association of vaccine uptake with priority indicators (and other BeSD survey indicators, if measured) and demographics.

Further analyses may include assessing variation in the uptake or intention to accept vaccines by BeSD indicators and demographic variables. For example, are women more likely than men to accept all vaccines? Are those who think vaccines are not important less likely to accept vaccines?

Some suggestions for reporting:

- **Report what is most important in answering the research question**. Use the main report to provide the major findings and appendices for detailed tables.

- **Present data visually** when possible to make the results easier to understand (e.g., use tables, graphs, images or icons if possible, such as showing percentages of a sample who know where to get their child vaccinated).
- **Interpret the data** to show or explain why the result is important – do not simply provide the frequencies or percentages.
- When comparing results in multiple figures, make sure the y-axis uses the same range (e.g., from 1 to 100) so that results are easy to compare.
- Results that are not statistically significant may be important because they sometimes challenge assumptions. Report these results, especially if you have analysed the relationships between variables to address a research question.
- Where possible, use qualitative findings to explain or support quantitative survey data and their interpretation.

Resources that may assist in reporting **survey** findings:

- Eysenbach G. Improving the quality of web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). J Med Internet Res. 2004;6:e34.
- Boynton PM. Administering, analysing and reporting your questionnaire [published correction appears in BMJ. 2004 Aug 7;329(7461):323]. BMJ. 2004;328(7452):1372–5. doi:10.1136/bmj.328.7452.1372.

4.5 Qualitative analysis and reporting of data from interview guides

4.5.1 Qualitative analysis of BeSD data

There are many approaches to qualitative data collection and analysis. A **framework analysis** is recommended for the qualitative data; templates are **available in Annex 1 (childhood) and Annex 2 (COVID).** The framework analysis approach is a structured method for qualitative analysis well suited to a team with varied levels of qualitative research experience. At least one team member should have strong expertise in qualitative methods.

For more information on the framework methodology, including an illustrative example, refer to:

- Gale NK, Health G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol. 2013;13:117.
- Furber C. Framework analysis: a method for analysing qualitative data. Afr J Midwifery Womens Health. 2013;4(2):97–100.

For a general overview of how qualitative approaches differ from epidemiologic approaches, see:

- Carter SM, Ritchie JE, Sainsbury P. Doing good qualitative research in public health: not as easy as it looks. N S W Public Health Bull. 2009;20(7–8):105–11 (https://pubmed.ncbi.nlm.nih.gov/19735621/).

Data collection: Carry out interviews as planned, collecting data in the form of detailed interview notes, audio recordings and any materials gathered during the interviews (e.g., self-completed socio-demographic forms).

Data analysis: The main stages in the framework analysis process are as follows:

Stage 1: Transcribe and familiarize. Convert interviews into a format for analysis using verbatim notes from transcribed recordings or detailed interviewer notes taken during interviews, usually by a second person. Immersion in the data will build familiarity. This occurs through reading and rereading, reflection and taking notes about the data.

Stage 2: Develop codes. Use codes to formally organize concepts in the data. Codes are simply a label given to data units. For example, if someone mentions their concern about vaccine reactions, the relevant line of text in the interview transcript could be labelled "safety concerns", and all lines in the remaining interviews that describe similar concerns expressed by other participants would also be coded as "safety concerns". This approach allows systematic comparison of codes across all of the interviews and can be done using comments or annotation functions in an MS Word document, or using specialized software such as Dedoose, QSR NVivo, ATLAS.ti or MAXQDA. After a few interviews, the analyst usually observes patterns where the same codes appear in several interviews. Ideally, for rigour, several members of the team should independently code the first few interviews to enable comparisons and agreement on what codes will be applied to the whole data set.

Stage 3: Develop and apply an analytical framework. After identifying reoccurring codes, group similar or related codes into defined subcodes (or categories). Building on the example above, the "safety concerns" code might include more granular categories, such as "side effects," "testing", "newness" and "vaccine components". Doing so creates a framework you can use for subsequent interviews and revise to cover concepts arising from the interviews. To help with interpretation, develop a summary spreadsheet with an interview per row, and data charted across codes and categories per column (see templates in the Annexes 1.5 and 2.5 for examples).

Stage 4: Interpret the data. Generate themes from the data by viewing the codes in the summary spreadsheet and drawing connections across participants and categories. Themes can be the relationships between codes or patterns that emerge from the coded data. Interpret the data to develop themes, which may offer explanations for what has emerged in the interviews. For example, create typologies (or classifications) and map relationships between themes. Also, interpret data considering intersectionality among different socio-demographic elements, vulnerability factors and conditions. That could mean analysing data according to gender, age, disability, migrant status, etc.

Researchers involved in interviewing and data analysis should keep a **researcher diary**. The diary is a place for each researcher to record their impressions from the interviews and analysis and document their thinking and ideas as they occur. Doing so increases researchers' awareness of how their own perspectives affect their interpretation of the data – a process known as reflexivity. In performing and writing the qualitative analysis, a reflexive researcher is better able to disentangle the findings from their own unique world view, reducing bias in the interpretation of the data.

4.5.2 Reporting qualitative findings

Reporting qualitative research findings involves constructing a representation of social occurrences and experiences based on accounts of the people who were interviewed. Writing up findings also forms part of the qualitative analytical process, which starts with the researcher diary (see section 4.5.1). There are

a number of ways to report qualitative data, and many good references are available *(7, 8)*. The COREQ checklist is also helpful (https://cdn.elsevier.com/promis_misc/ISSM_COREQ_Checklist.pdf) *(9)*. The following set of general steps will guide reporting of qualitative data.

- ✓ **Identify the main audience:**
  - Consider which people have an interest in these data.
  - Decide the best way to present these data to the audience based on how they are likely to use the data.
- ✓ **Decide on a structure:**
  - Decide the best way to tell the story of this research to the audience. One option is to explain the key findings and how they answer or relate to the research question.
- ✓ **Describe the methods:**
  - It is important to clearly state the methods used in data collection and analysis, including:
    - overall research design, and sampling approach including justification
    - recruitment methods
    - how the interviews were conducted and recorded
    - analytical approach
    - ethical considerations and approval.
- ✓ **Describe the results of the study:**
  - Start by describing how many interviews were undertaken and over what time period.
  - Tell the story of the results, and how they relate to the research questions.
  - Focus on the concepts and themes, and how they relate to the research questions.
  - Give example quotes to illustrate the concept or theme.
  - If links between the themes and concepts were identified, describe these links also, but take care to justify how and why these links were made, using the data as evidence.

Some suggestions for reporting:

- **Avoid using numerical statements.** Avoid sentences that describe how many participants had a certain trait or described a certain attitude. Qualitative data are not about prevalence, but about understanding *why* or *how* something is happening. The purposive method of sampling and the smaller sample sizes mean that statements such as "25% said they were worried about vaccine safety" may be misleading. When reporting qualitative results, it is best to focus on the concept rather than how many people said it. For example, the previous statement could be better phrased as "some of the participants were concerned about the safety of the vaccine".
- **Use quotes to illustrate the concept or theme being reported.** De-identify quotes and keep them short and to the point.
- **Where possible, illustrate the range or diversity in the findings.** When discussing concepts, be sure to discuss any findings that appear to contradict emerging codes and patterns. Include illustrative quotes where appropriate.
- If available, use **qualitative data to help explain unclear or counterintuitive quantitative data** (e.g., why respondents in rural areas were more likely to believe that vaccination services are easy to get to than respondents in urban areas). In addition, qualitative data allow exploring and reporting how minorities and disadvantaged population groups may experience a certain phenomenon (like specific barriers to accessing vaccination and how such groups are treated by a service).

4.6 Sharing plans, data and reports

The findings of the report are more likely to have an impact if the research team involve key stakeholders in plans for data collection, hypothesis generation and drafting reports. This approach often elevates the profile of the work and brings to the surface other relevant studies, allowing cross-comparison of findings. Consult with experienced researchers for in-depth or more complex analyses. Where resources for data collection are limited, sharing anonymized data between programmes and researchers can be an efficient way of maximizing the use of limited resources and the impact of data.

Consider sharing plans and materials, and initiating discussion with the following groups:

- **Other stakeholders** can offer broad expertise, contextualization and resource mobilization.
- **Experienced researchers** can support informal peer review of the data and suggest connections with other data sets or established knowledge, often resulting in deeper analysis and new findings.
- **Target population** input can also help improve the quality of analysis and is a well-established method for validating analysis and interpretation of results.

For further reference, Annex 7 provides the WHO policy on data sharing.

5. Act: using BeSD data to drive action

The BeSD tools focus on generating data and using findings to increase uptake of vaccines. Data may be used in a variety of ways at different levels of the programme, for planning, for monitoring and to guide intervention design in specific settings. Data should also be shared with NITAGs (National Immunization Technical Advisory Groups) to support their role in making sound, evidence-based recommendations.

The four BeSD domains (Fig. 1) represent the main factors that influence vaccine uptake in individuals. The survey priority indicators for tracking these factors over time can be found in the tool annexes of this guidebook.

Use the data generated from the tools to:

- ✓ inform the design and evaluation of interventions to increase uptake;
- ✓ develop targeted interventions to address context-specific drivers and barriers, particularly those experienced by disadvantaged population groups;
- ✓ evaluate effectiveness of strategies and track trends over time through routine BeSD assessments;
- ✓ advocate and mobilize resources; and
- ✓ contribute to triangulated or comparative analysis with other data sources to offer a more complete understanding of issues and guide programme planning.

This section describes how you can use BeSD data for these activities.

5.1 Using BeSD priority indicators

The BeSD survey priority indicators are helpful when planning to monitor changes over time or measure the impact of interventions. The priority indicators represent the domains in the BeSD framework and rely on survey items with strong psychometrics and associations with vaccine uptake. The priority indicators are framed around immunization programme gains, to align with existing immunization indicators such as coverage. **Low values for an indicator show a problem, and an intervention or other action is recommended**. For example, a country may decide to take action when an assessment reveals that only 60% of parents/caregivers know where to get their child vaccinated. Thresholds for action must be determined by each country, taking local context and other data into consideration.

5.2 Planning interventions

Four broad intervention areas are considered foundational to any immunization programme. These are:

1) community engagement
2) communication and education
3) service quality (e.g., provider recommendation, reminder/recall, inclusive services); and
4) supportive policies (e.g., requirements, incentives).

The BeSD priority indicators support tracking how these foundational interventions are working, where and for whom. Where interventions are not working, BeSD assessments can support understanding why that is, particularly through use of the qualitative interview guides. At a subnational level, these assessments can be conducted as part of a human-centred design or tailoring immunization programme process to diagnose the reasons for low uptake, choose tailored interventions and evaluate their effectiveness *(10, 11)*.

In addition to the four broad interventions listed above, other types of interventions that are effective for increasing uptake include those listed in Table 8. Interventions are listed in a domain based on available evidence and expertise. In some settings, an intervention may act on more than one domain. Adequate monitoring and evaluation of interventions, using BeSD indicators, will be critical in establishing the impact of interventions in specific settings and any changes over time. References refer to systematic reviews or meta-analyses that show the intervention led to higher vaccine uptake in low- and middle-income countries, where such data were available.

Table 8. Promising interventions by BeSD domain to guide planning

Domain where problem is identified	Interventions shown to increase vaccination
Thinking and feeling Motivation	Campaigns to inform or educate the public about vaccination, including approaches based in the health facility or community *(1–3, 5)* Dialogue-based interventions, including one-to-one counselling to encourage vaccination *(12, 13)*
Social processes	Community engagement *(12, 14)* Positive social norm messages *(6, 15)* Vaccine champions and advocates *(16, 17)* Recommendations to vaccinate from health workers *(18)*
Practical issues	Reduced out-of-pocket costs *(19)* Service-quality improvements *(5, 19, 20)* Reminder for next dose/recall for missed dose *(21–24)* On-site vaccination at work, home and school *(5, 17, 19, 25–27)* Default appointments *(6)* Incentives *(6, 19, 28, 29)* School and work requirements (mandates) *(19, 30)*

5.3 Selecting interventions when BeSD data are not available

Collect BeSD data ahead of intervention design, even if using just the BeSD priority indicators. Share findings with local experts, partners and community representatives (including disadvantaged groups and persons with disabilities) to contribute to a broader understanding of the reasons for low uptake and to discussions about intervention selection and design. You may need to prioritize target populations or other elements of implementation. Take care not to ascribe hunches or anecdotal stories as a diagnosis of the problem in place of measurable indicators.

5.4 Monitoring and evaluation of interventions using BeSD indicators

Use at least the BeSD priority indicators to facilitate ongoing monitoring and evaluation of interventions. This is vital to determine whether the intervention is achieving its expected outcomes and to guide continuous improvement to close gaps in coverage and increase equity.

Indicators are numbers or statements that reflect what was measured to help signify performance, change or impact. When using indicators remember to:

- ✓ use BeSD indicators alongside existing relevant immunization indicators;
- ✓ use as few indicators as possible;

- ✓ collect only the information most needed;
- ✓ check that the indicator selected really will measure the desired change; and
- ✓ analyse and use the information provided by the indicator to act or make decisions.

Table 9 offers an example framework to help identify inputs, outputs and outcomes that correspond to BeSD indicators and interventions from the COVID-19 surveys.

Table 9. Example of a monitoring and evaluation framework

DOMAIN and INDICATORS	INTERVENTION	INPUTS	ACTIVITY / OUTPUTS	OUTCOMES
Practical Issues **% of adults/ HCWs who know where to get vaccines for themselves** **% of adults/HCWs who believe that accessing vaccination for themselves is "very" or "moderately" easy**	Improve access to vaccination Mailed or phone offer of appointment Outreach Reminders, standing orders and walk-in clinics.	Messages to invite, remind, follow-up and inform Mechanisms for delivery of personal invitations	Messages are ready on schedule, pilot-tested, revised and ready for roll-out Mechanisms are available and ready to be put into action	↑ Know where to get vaccine ↑ Believe that accessing vaccination for themselves is "very" or "moderately" easy ↑ Readiness to seek vaccination ↓ Perceived barriers to access

HCWs: health-care workers

Finally, accountability is key throughout all assessments. To ensure accountability, consult with the participating communities and other stakeholders regularly, sharing indicator data to show progress and change over time.

5.5 Complementing BeSD data with other data sources

The BeSD tools support understanding *why* gaps in immunization coverage exist. **BeSD data can enable programmes to**:

- identify and address influences on behaviour;
- target and evaluate strategies in specific contexts;
- examine and understand trends over time; and
- better plan for future needs.

Complementing BeSD data with other sources of data serves to:

- Contextualize issues around vaccination confidence, demand and uptake.
- Identify reinforcing factors among different populations and socio-demographic groups. For example, both health workers and caregivers report that vaccine misinformation is an important issue in their community or context. This observation may provide insight into strategies for effectively reaching caregivers and health workers.
- Validate findings based on consistency of data collected using different methods and across different data sources (Fig. 2). Such triangulation can help to address the limitations of findings and biases associated with any one method.

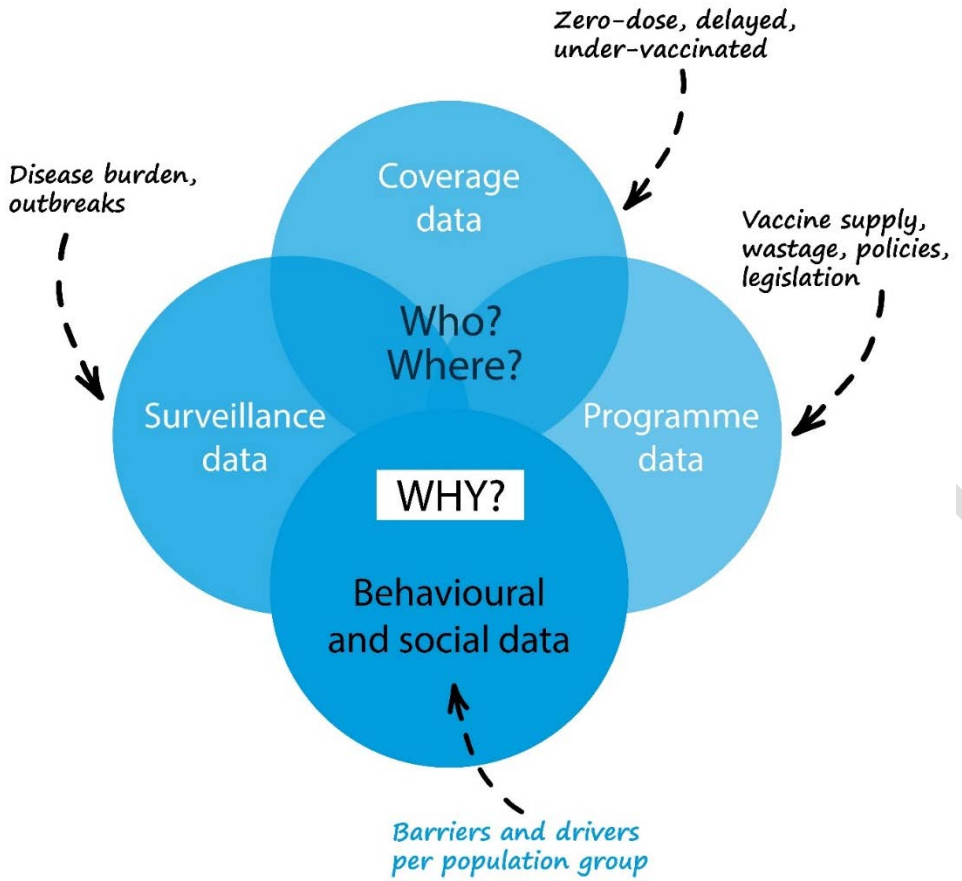


Fig. 2. Triangulation of insights on reasons for low uptake together with other programme data

Use BeSD data along with other data sources to understand key areas of focus and unique interventions that may be required:

- **Surveillance data**: Use vaccine-preventable disease (VPD) surveillance data to understand prevalence, incidence and related changes in VPDs in specific areas over time. Surveillance data showing a high disease burden may indicate populations for prioritization of BeSD data collection. The combination of different kinds of data can also help inform adaptation of vaccination campaigns following VPD outbreaks, for a more tailored and targeted approach that addresses the specific drivers or barriers uncovered.
- **Coverage data**: Use coverage data to narrow down population subgroups that merit further assessment using the BeSD tools (i.e., where coverage is low and a population is more susceptible to outbreaks, it will be important to conduct a BeSD assessment to understand the specific drivers and barriers to vaccination). Where coverage is particularly low, for example among zero-dose communities, qualitative assessments using the BeSD interview guides enable a richly detailed understanding of the contributors.
  Additionally, assess BeSD data from specific regions alongside vaccine coverage data from the same regions to identify trends and patterns in the relationship between determinants of uptake and vaccine coverage. If coverage data are available from different subpopulations, the resulting analyses will help to understand key differences in the pattern of these associations as well.
- **Census data**: Analyse BeSD data alongside census data in the specific country context on how uptake relates to major socio-demographic characteristics. This information in turn may help to

inform policy-level decisions by health authorities. For example, poor social norms around vaccination are specific to areas belonging to particular ethnic groups. This observation may indicate that more targeted interventions might improve vaccine uptake in these areas. Note that census data may not be up to date in resource-poor settings.

- **Other health system data:** Analyse BeSD data with other health data on maternal and child health services to highlight similar trends over time or geographic patterns across subpopulations of interest in uptake of other child health services compared with immunization services. This information may provide insight into whether low vaccine uptake is related to health system issues or behavioural and social issues, or a combination of both. Triangulation may offer useful insights when health system data are disaggregated by gender, age and disability status.
- **Social listening data**: Examine findings from BeSD data alongside data and trends from social listening data. Social listening means tracking content and exposure to conversations about vaccination in the public space or on social media and monitoring what themes emerge. These data can indicate the specific messages and information (including misinformation) people are exposed to across a range of sources. BeSD data look at the potential impact of such data on uptake, vaccine intentions and other contextually relevant variables.

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Annex 1: BeSD tools for childhood vaccination

1.1 Childhood vaccination priority indicators (version 1.0)

The five priority indicators for vaccination of children (younger than age 5) are presented in the table below. When it is not possible to use the full childhood vaccination survey, at least measure these priority indicators.

Domain	Construct	Priority question	Priority indicator
Thinking and feeling	**Confidence in vaccine benefits**	How important do you think vaccines are for your child's health? Would you say… ☐ Not at all important, ☐ A little important, ☐ Moderately important, *or* ☐ Very important	% of parents/caregivers who say that vaccines are "moderately" or "very" important for their child's health
Social processes	**Family norms**	Do you think most of your close family and friends want you to get your child vaccinated? ☐ NO ☐ YES	% of parents/caregivers who say most of their close family and friends want their child to be vaccinated
Motivation	**Intention to get child vaccinated**	[COUNTRY NAME] has a schedule of recommended vaccines for children. Do you want your child to get none of these vaccines, some of these vaccines or all of these vaccines? ☐ NONE ☐ SOME ☐ ALL	% of parents/caregivers who say they want their child to get all of the recommended vaccines
Practical issues	**Know where to get child vaccinated**	Do you know where to go to get your child vaccinated? ☐ NO ☐ YES	% of parents/caregivers who say they know where to get their child vaccinated
Practical issues	**Affordability**	How easy is it to pay for vaccination? When you think about the cost, please consider any payments to the clinic, the cost of getting there, plus the cost of taking time away from work. Would you say… ☐ Not at all easy, ☐ A little easy, ☐ Moderately easy, *or* ☐ Very easy	% of parents/caregivers who say vaccination is "moderately" or "very" easy to pay for vaccination for their child

1.2 Childhood vaccination survey for caregivers (version 1.0)

The BeSD Childhood Vaccination Survey is a globally standardized tool for assessing the drivers of vaccination for children. The survey is to be completed by parents and caregivers to children under age 5 (0–47 months).

The survey has 19 questions. When it is not possible to use the full childhood vaccination survey, at least measure the priority indicators. To support use of the survey and analyses, also included are a recommended consent script and socio-demographic questions; programmes should adapt the consent and demographic questions as needed but should not change the rest of the survey.

The "Indicator" column shows **priority** indicators; optional indicators are shown with a * (based on weaker performance in validation). The "Rationale" column contains important information for translating and locally adapting questions. Table cell colours indicate the BeSD domain (demographics, thinking and feeling, motivation, social processes and practical issues).

Trained interviewers should read the survey questions and response options aloud to respondents. Interviewers should not read aloud instructions in [square brackets] and ALL CAPITALS. Interviewers should emphasize underlined words. Instructions on how to adapt the survey for self-administration, such as an online survey, are in the BeSD data for action guidebook, section 3.5.

Construct	Question	Indicator	Rationale
Date	DAY /MONTH /YEAR OF INTERVIEW: ____ /_____ /_____	None	This is an administrative question for the interviewer to complete at the time of interview. To ensure comparability and tracking, this question must not be adapted.
Participant	PARTICIPANT ID: _____	None	This is an administrative question for the interviewer to record a unique identity for individual participants at the time of interview. To ensure comparability and tracking, this question must not be adapted.
Location	GPS COORDINATES: _____ CLUSTER NUMBER: _____ DISTRICT NAME: _____	None	This is an administrative question for the interviewer to complete at the time of interview. This question can be adapted to suit the survey methodology.

Construct	Question	Indicator	Rationale
Consent	Hello, I am [INTERVIEWER NAME] with [INSTITUTION OR ORGANIZATION NAME]. We are interviewing people to help improve children's vaccination services in [COUNTRY NAME]. I know you are busy, so this will take only a few minutes. Your participation is completely voluntary and anonymous. If you do not want to answer a question or wish to stop the interview, just let me know. Would you be willing to take the survey? ☐ YES ☐ NO IF "YES": Thank you very much. Do you have any questions for me before we begin? ADDRESS ANY QUESTIONS AND PROCEED. IF "NO": Thank you very much. END INTERVIEW.	None	This question serves as an example of text to be included to capture respondents' informed consent to their participation in the study.
Age	How old are you? ☐ _____ YEARS	Mean age % of parents/caregivers who are 18–34 years old % of parents/caregivers who are 35–54 years old	This question collects age in number of completed years; this will allow for stratified analysis by age of respondents.
Gender	This may seem obvious, but I have to ask the question. What is your gender? Would you say…	% of parents/caregivers who are women	This question collects gender identity of respondents to allow stratified analysis. The third response option can be included in

Construct	Question	Indicator	Rationale
	☐ Woman, ☐ Man, ☐ Nonbinary, *or would you* ☐ Prefer not to say?	% of parents/caregivers who are men	contexts where specific third-gender categories are culturally recognized; this response option can be adapted as appropriate based on in-country considerations or consultation.
Parent/caregiver	Are you the parent or primary caregiver of any children who are younger than 5 years old? ☐ YES ☐ NO IF "NO": Unfortunately, you are not eligible to participate in the survey. Thank you very much for taking the time to answer my questions. END INTERVIEW.	None	This question determines whether the respondent is responsible for any children under 5 years old. It should be used to screen out respondents who do not have children younger than age 5.
Number of children under 5	How many children do you have who are younger than 5 years old? ☐ _____ CHILDREN IF MORE THAN ONE CHILD: The next questions are about your youngest child.	% of parents/caregivers with two or more children	This question collects the number of children younger than 5 years old. If the respondent has more than one child under 5, they should be informed that the rest of the survey is about their youngest child.
Relationship to child	What is your relationship to your child? Would you say… ☐ Mother, ☐ Father, ☐ Grandparent, ☐ Uncle or aunt, ☐ Brother or sister, *or* ☐ Other? [IF "OTHER": Please specify _____]	% of parents/caregivers who are the mother % of parents/caregivers who are the father	This question assesses the caregiver's relationship to the child.

Construct	Question	Indicator	Rationale
Age of child	How old is your youngest child? ☐ Less than 1 year old, ☐ 1 year old, ☐ 2 years old, ☐ 3 years old, *or* ☐ 4 years old?	% of parents/caregivers reporting about a child younger than age 2	This question collects the age of the youngest child in number of completed years.
Gender of child	Is your youngest child…? ☐ Female, ☐ Male, ☐ Non-binary, *or would you* ☐ Prefer not to say?	% of children who are female % of children who are male	This question collects gender identity of respondents' youngest child to allow stratified analysis. The third response option can be included in contexts where specific third-gender categories are culturally recognized; this response option can be adapted as appropriate based on in-country considerations or consultation.
Vaccination status	[COUNTRY NAME] has a schedule of vaccines for children. As far as you know, has your child had none of these vaccines, some of these vaccines or all of these vaccines? ☐ NONE ☐ SOME ☐ ALL	% of parents/caregivers whose child had all recommended vaccines	This question collects reported vaccination status. In addition to this question, full vaccination status should be recorded as recommended in the *World Health Organization vaccination coverage cluster surveys: reference manual*, https://apps.who.int/iris/handle/10665/272820.
Intention to get child vaccinated	[COUNTRY NAME] has a schedule of vaccines for children. Do you want your child to get none of these vaccines, some of these vaccines or all of these vaccines? ☐ NONE ☐ SOME ☐ ALL	**Priority** % of parents/caregivers who say they want their child to get all of the recommended vaccines	This question assesses intention to get the child vaccinated. "Want" is similar to desire, prefer, like, plan and intend. It might identify a plan for future action but can also be about willingness. "Recommended" is similar to advised, suggested, standard or nationally recommended; it refers to the national

Construct	Question	Indicator	Rationale
			vaccination schedule of recommended vaccines for children. The text in square brackets is to be locally adapted to include the country name.
Confidence in vaccine benefits	How important do you think vaccines are for your child's health? Would you say… ☐ Not at all important, ☐ A little important, ☐ Moderately important, *or* ☐ Very important?	**Priority** % of parents/ caregivers who say vaccines are moderately or very important for their child's health	This question assesses positive attitude towards vaccination of the child. The main idea is that vaccination is good, important and valuable. A related idea is that vaccination is effective, prevents disease, saves lives and protects children who are vaccinated.
Confidence in vaccine safety	How safe do you think vaccines are for your child? Would you say… ☐ Not at all safe, ☐ A little safe, ☐ Moderately safe, *or* ☐ Very safe?	% of parents/caregivers who say vaccines are moderately or very safe for their child	This question assesses negative attitude towards vaccination of the child. The main idea is the belief that vaccination is safe and is not dangerous or harmful. "Do you think" is included so that respondents do not see the survey as a test or as demeaning them for what they may not know.
Confidence in health workers	How much do you trust the health workers who give children vaccines? Would you say you trust them… ☐ Not at all, ☐ A little, ☐ Moderately, *or* ☐ Very much?	% of parents/caregivers who say they trust the health workers who give children vaccines "moderately" or "very" much*	This question assesses confidence in people who provide vaccines. "Trust" refers to belief that the health worker will be competent, reliable and give good health care. "Health worker" will need local adaptation to indicate the medical professionals responsible for recommending and administering childhood vaccination (i.e. health provider, general

Construct	Question	Indicator	Rationale
			practitioner or paediatrician and assisting nurses or vaccinators).
Peer norms	Do you think most parents you know get their children vaccinated? ☐ NO ☐ YES	% of parents/caregivers who say most parents they know will get their children vaccinated	This question assesses social norms – beliefs about what other parents are doing. "Most parents you know" includes friends, people at work and people in the neighbourhood who the respondent may not have close social ties to. It does not include people the respondent has never met.
Family norms	Do you think most of your close family and friends want you to get your child vaccinated? ☐ NO ☐ YES	**Priority** % of parents/caregivers who say most of their close family and friends want their child to be vaccinated	This question assesses social norms – beliefs about what close social contacts want the respondent to do. "Close family and friends" include people with opinions the respondent would listen to or feel some degree of pressure to heed.
Religious leader norms	Do you think your religious leaders want you to get your child vaccinated? ☐ NO ☐ YES	% of parents/caregivers who say their religious leaders want their child to be vaccinated*	This question assesses social norms – beliefs about what opinion leaders want the respondent to do. "Religious leader" includes priests, clerics, imams, rabbis and others in similar roles.
Community leader norms	Do you think your community leaders want you to get your child vaccinated? ☐ NO ☐ YES	% of parents/caregivers who say their community leaders want their child to be vaccinated	This question assesses social norms – beliefs about what opinion leaders want the respondent to do. "Community" may refer to a neighbourhood or region or social group defined by a characteristic such as race or national origin.

Construct	Question	Indicator	Rationale
			"Community leader" includes people who represent a neighbourhood, region or subgroup of people.
Health worker recommendation	Has a health worker recommended your child be vaccinated? ☐ NO ☐ YES	% of parents/caregivers who say a health worker has recommended vaccination for their child	This question assesses whether the respondent recalls a health worker or health-care provider recommending vaccination. "Recommended" includes raising the topic during a clinic visit, saying the child is due and offering advice to get the child vaccinated. The term "health worker" must be locally adapted to indicate the medical professional most likely to/responsible for recommending childhood vaccination (i.e., health provider, general practitioner or paediatrician).
Received recall	Have you ever been contacted about your child being due for vaccination? ☐ NO ☐ YES	% of parents/caregivers who have been contacted about child being due for vaccination	This question assesses the mechanisms in place to call in children who are due for vaccines.
Mother's travel autonomy	If it was time for your child to get vaccinated, would the mother need permission to take your child to the clinic? ☐ NO ☐ YES	% of mothers who say they do not need permission to take child for vaccination*	This question assesses freedom of women to leave the home to get the child vaccinated. "Time to get vaccinated" is similar to the child being due for vaccines. "Clinic" refers to the clinic, doctor's office, primary care practice, vaccination clinic, health centre or mobile service that delivers the vaccines for the child.

Construct	Question	Indicator	Rationale
Know where to go to get vaccination	Do you know where to go to get your child vaccinated? ☐ NO ☐ YES	**Priority** % of parents/caregivers who say they know where to get their child vaccinated	This question assesses whether the respondent knows where to take the child for vaccination. The question is about knowing that the facility or vaccination site exists and where it is located. The question is not about ability to access or use the services.
Took child for vaccination	Have you personally ever taken your youngest child to get vaccinated? ☐ NO ☐ YES	% of parents/caregivers who say they have taken youngest child for vaccination*	This question assesses whether the respondent, personally, has been with the child when the child went to a vaccination clinic. This question allows us to disaggregate analysis by those who have a personal experience with the vaccination clinic and staff.
Vaccination availability	Have you ever been turned away when you tried to get your child vaccinated? ☐ NO ☐ YES	% of parents/caregivers who say they have never been turned away for child vaccination	This question assesses the experience of going to the vaccination clinic and not receiving vaccination for the child that day. "Turned away" refers to staff at the clinic saying the vaccine was not available, a sign saying the clinic was out of stock or being unable to see a vaccine provider because of other problems at the clinic.
Ease of access	How easy is it to get vaccination services for your child? Would you say… ☐ Not at all easy, ☐ A little easy, ☐ Moderately easy, *or* ☐ Very easy?	% of parents/caregivers who say it is "moderately" or "very" easy to get child vaccination services	This question assesses the degree to which vaccination is easy to get for the child. The question looks at ease of access in general and leads into the next question. "Easy" refers to achievable, possible without great effort, not hard and not difficult. "Vaccination services" refers to access to vaccination.

Construct	Question	Indicator	Rationale
Affordability	How easy is it to pay for vaccination? When you think about the cost, please consider any payments to the clinic, the cost of getting there, plus the cost of taking time away from work. Would you say… ☐ Not at all easy, ☐ A little easy, ☐ Moderately easy, *or* ☐ Very easy?	**Priority** % of parents/caregivers who say vaccination is "moderately" or "very" easy to pay for	This question assesses the perceived cost of vaccination. Cost is the monetary value associated with vaccination. "Easy to pay" refers to the total costs associated with vaccinating being something the respondent can afford to pay.
Reasons for low ease of access	What makes it hard to get vaccination services for your child? Would you say… [READ ALOUD ALL RESPONSE OPTIONS, PAUSING AFTER EACH TO ALLOW RESPONDENT TO ANSWER "YES" OR "NO" AFTER EACH RESPONSE OPTION. RESPONDENTS MAY SELECT MULTIPLE RESPONSE OPTIONS.] ☐ Nothing, it's not hard, [IF NOTHING, SKIP REST OF RESPONSES] ☐ Getting to the clinic is hard, ☐ The clinic opening times are inconvenient, ☐ The clinic sometimes turns people away without vaccinating, ☐ The waiting time in the clinic takes too long, *or* ☐ Is there something else? [RECORD ANSWER: _____]	% of parents/caregivers who say nothing makes it hard to access children's vaccination % of parents/caregivers who say getting to the clinic is hard % of parents/caregivers who say clinic opening times are inconvenient % of parents/caregivers who say the clinic sometimes turns people away % of parents/caregivers who say the waiting time takes too long	This question assesses the reasons why vaccination is difficult to get for the child. Respondents can choose multiple response options here. There is no skip logic for this question; it must be asked of all respondents. "Nothing, it's not hard" is an exclusive response option (it cannot be selected alongside other response options) available for those who do not think it is difficult to get vaccination services for their child. "Hard to get to" refers to geographical distance and barriers related to transportation. "Inconvenient" refers to opening hours that do not suit the respondent. "Turns people away" refers to the clinic sending people home without vaccination despite their having come to be vaccinated. "Takes too long" refers to the waiting times at the clinic.

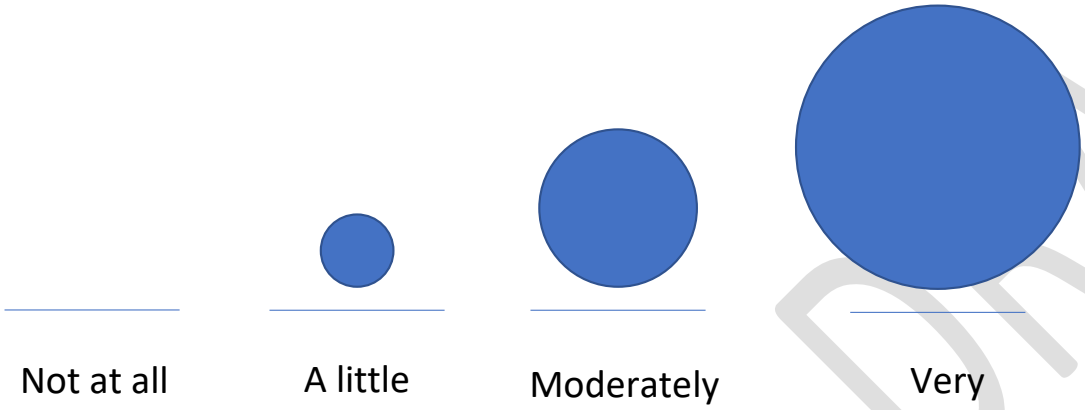
Construct	Question	Indicator	Rationale
Service satisfaction	How satisfied are you with the vaccination services? Would you say… ☐ Not at all satisfied, ☐ A little satisfied, ☐ Moderately satisfied, *or* ☐ Very satisfied?	% of parents/caregivers who say they are "moderately" or "very" satisfied with the vaccination services for their child	This question assesses satisfaction with vaccination services received during the last visit. "Satisfied" refers to how good the services and experience were for the respondent, and how pleased or happy the respondent felt about the visit and the interactions that took place. "Vaccination services" refers to work done by vaccination clinic staff who greet the patient, handle paperwork and payment, and administer the vaccine. "Not at all" is bad and not acceptable. "Not very" is okay, adequate and not bad. "Somewhat" is positive but not the best possible. "Very" is great, fantastic and outstanding.
Service quality	What is not satisfactory about the vaccination services? Would you say… [READ ALOUD ALL RESPONSE OPTIONS, PAUSING AFTER EACH TO ALLOW RESPONDENT TO ANSWER "YES" OR "NO" AFTER EACH RESPONSE OPTION. RESPONDENTS MAY SELECT MULTIPLE RESPONSE OPTIONS.] ☐ Nothing, you are satisfied, [IF NOTHING, SKIP REST OF RESPONSES] ☐ Vaccine is not always available, ☐ The clinic does not open on time, ☐ Waiting times are long,	% of parents/caregivers who say vaccine is not available % of parents/caregivers who say the clinic does not open on time % of parents/caregivers who say waiting times are long	This question assesses reasons why the respondent is not satisfied with the vaccination services. Respondents can choose multiple response options here. There is no skip logic for this question; it must be asked of all respondents. "Nothing, you are satisfied" is an exclusive response option (it cannot be selected alongside other response options) available for respondents who are satisfied with the vaccination services.

Construct	Question	Indicator	Rationale
	☐ The clinic is not clean, ☐ Staff are poorly trained, ☐ Staff are not respectful, ☐ Staff do not spend enough time with people, *or* ☐ Is there something else? [RECORD ANSWER: _____]	% of parents/caregivers who say the clinic is not clean % of parents/caregivers who say staff are poorly trained % of parents/caregivers who say staff are not respectful % of parents/caregivers who say staff do not spend enough time with people	"Vaccine is not always available" refers to people being turned away due to lack of vaccine (stock-outs). "The clinic does not open on time" refers to the clinic not operating according to the hours advertised. "Waiting times are long" is the perception that the service was poorly organized for time, and that staff were unable to provide efficient, quick service. "The clinic is not clean" refers to any complaint about the place where vaccines are given, including location and building structure. This includes lack of cleanliness and poor maintenance. This includes vaccine vials, needles, fridges for storing vaccines as well as furniture in the clinic, reception and waiting rooms, or even appearance of personnel, such as appropriate attire, clean appearance and uniforms. "Staff are poorly trained" is the perception that the service received was not as promised or that the quality of service was not reliable or consistent. The respondent may perceive that staff did not fulfil their role very well, that the staff were not well trained or prepared for their responsibilities, or that the staff lacked the confidence or skill to deliver the service expected.

Construct	Question	Indicator	Rationale
			"Staff are not respectful" refers to inability to inspire confidence, put parents at ease and communicate competence. It includes staff being discourteous, impolite and unable to reassure parents. Staff can show respect in verbal and non-verbal ways. "Staff do not spend enough time with people" is the perceived lack of empathy a respondent may experience from vaccination clinic staff, and perception of a rushed service or lack of time dedicated to reassuring parents and answering their questions.

1.3 Visual survey response scale

For surveys with lower-literacy respondents, consider using a visual response scale. It is designed for questions with four response options (such as “not at all”, “a little”, “moderately”, “very”). Interviewers should read the question aloud and point to the visual scale as they read the response options.



1.4 Childhood vaccination in-depth interview guides (version 1.0)

The BeSD tools for childhood vaccination provide a set of four adaptable qualitative interview guides intended for use with different audiences. These guides can be used for in-depth interviews with individuals. Questions should be adapted to suit the cultural context of the people being interviewed and the research question being investigated.

Interview guide for caregivers of children under 5

BeSD model construct	Question/[Instruction]	Rationale
General	Introduction: Hello, I am [INTERVIEWER'S NAME] with [INSTITUTION OR ORGANIZATION NAME]. We are interviewing people to help improve vaccination services in [NAME OF COUNTRY]. The interview is expected to take __ minutes. Your participation is completely voluntary and anonymous. The answers you give will be completely confidential. If you do not want to answer a question or wish to stop the interview, just let me know. Would you be willing to take part in an interview with me? [If audio recording the interview] Would you be happy for me to record our conversation?	- Clear introduction to ensure true informed consent for participation is obtained before proceeding.
	Tell me a little about yourself and your family. *Probe*: - Who lives in your household with you? - How old is your child/are your children? - Are your children up to date with their vaccines?	- Warm-up question. - Enables understanding of the participant's family situation and personal context.
Motivation **Social processes**	**Thinking back to the first time you had your child vaccinated, tell me why you decided that you would go ahead with it.** [If first vaccine was administered at birth, ask about the first time they took their child back for their next set of scheduled vaccines.] *Probe*: - Did anyone suggest it? - Who decided that you should take your child to be vaccinated? - Who usually takes your child(ren) to have their vaccines?	- Aim to understand how the caregiver came to the decision about whether or not to vaccinate their child. - Aim to understand who else was involved in the decision.

BeSD model construct	Question/[Instruction]	Rationale
Social processes	**Do you talk about vaccination with anyone else?** *Probe*: - Who do you talk to? - What do they say? - Do other parents you know vaccinate their children?	- Aim to understand what the social norms are for this caregiver (i.e., what the usual vaccination behaviour of other caregivers is in their community).
Practical issues	**Thinking back to the first time you took your child to be vaccinated, tell me how you knew it was time to do so?** *Probe*: - What kind of reminders do you use?	- Aim to understand what prompts the caregiver to seek vaccination for their child.
Practical issues	**Thinking about vaccination day for your child, tell me about what happens before you arrive at the place where your child gets the vaccine. Start with before you leave home.** *Probe*: - What do you need to do to prepare before you leave home? - How do you travel to the vaccination place? **Once you arrive at the vaccination place, tell me what happens next.** *Probe*: - Who do you talk to when you get there? - What happens in the waiting room or queue? - Do you need to pay a fee? - Are other health checks done while you're there? **What happens when it's your child's turn to get the vaccine?** *Probe*: - What happens first? - [Probe for each step until the vaccination is completed.] - What do the health workers talk to you about while you're there? How do you feel when you talk with them?	- Aim to understand the practical and logistical considerations the caregiver must address or overcome to get their child vaccinated. - Describe the process they follow on vaccination day. - [Note: "Vaccination place" should be substituted with the correct word for the particular vaccination service the caregiver uses, for example "hospital" or "clinic".]

BeSD model construct	Question/[Instruction]	Rationale
	After your child has had the vaccine, tell me what happens next. *Probe*: - What happens when you leave the vaccination place? - How do you travel home? - What happens after you arrive home?	
Practical issues	**What do you like about what happens on vaccination day?** *Probe*: - Ask about each step described by the caregiver in the question above. - [If there is something identified that they like] Why do you like it?	- Aim to understand positive aspects of the vaccination process described.
Practical issues	**What don't you like about what happens on vaccination day?** *Probe*: - [If the response is "nothing", list the steps in the process they describe and ask whether there is anything they don't like about them individually.] - Is there anything you find difficult? Why do you find it difficult?	- Aim to understand in detail any barriers to getting their child vaccinated.
Thinking and feeling	**Tell me how you feel about childhood vaccination?** *Probe*: - Why do you feel this way? - Do you think it's a good thing? Why? - Do you think it's important? Why? - Is there anything you feel isn't good about vaccination? Can you tell me more about it?	- Aim to understand underlying feelings about childhood vaccination in general.
Thinking and feeling	**How do you feel when your child is vaccinated?** *Probe*: - Do you think it's good for your child? Why? - Is there anything that worries you? Why does it worry you?	- Aim to understand their feelings when it comes to vaccinating their child specifically (different from the previous question, which aims to understand how they feel about vaccination in general).
General	**Is there anything else you'd like to say?**	- Aim to capture any other issues or thoughts that haven't been captured in previous questions.

Interview guide for health workers

Question/[Instruction]	Rationale
Introduction: Hello, I am [INTERVIEWER'S NAME] with [INSTITUTION OR ORGANIZATION NAME]. We are interviewing people to help improve vaccination services in [NAME OF COUNTRY]. *The interview is expected to take __ minutes. Your participation is completely voluntary and anonymous. The answers you give will be completely confidential. If you do not want to answer a question or wish to stop the interview, just let me know. Would you be willing to take part in an interview with me? [If audio recording the interview] Would you be happy for me to record our conversation?*	- Clear introduction to ensure true informed consent for participation is obtained before proceeding.
Tell me a little about yourself and what you do. *Probe*: - What are you responsible for? - How many days do you work in this role? - Where do you perform your duties?	- Warm-up question. - Enables understanding of the participant's professional role. - Understanding the breadth of the participant's responsibilities. - Understanding how many days per week the participant works and where they are situated physically (e.g., does the participant work at multiple sites?).
To what extent does your role involve immunization? *Probe*: - What parts of your job involve immunization? - Can you tell me more about that?	- To understand how much of the participant's role is immunization related. - To understand in some detail what those immunization-related responsibilities are.
I'd like to understand the process you follow to immunize a child, starting from the very beginning. *Probe*: - Does it involve work for you even before the family arrives at the centre for vaccination?	- This question is for workers who administer immunizations to children. - The aim is to understand the work processes followed by the participant: o May shed light on logistical or practical barriers they may encounter when delivering immunization services.

Question/[Instruction]	Rationale
- Can you summarize the procedure of immunization in around five steps, starting once a family arrives at the centre for vaccination? *[Note: Adjust this question for non-clinic settings if required.]* - Are there follow-ups or steps involved once they leave the centre? *[Note: Other probes, such as ongoing door to door, systems of recording vaccinations, making vaccination cards and so on, could be added as required.]*	o May shed light on facilitators that could be applied elsewhere. - [Note: The wording of this question is currently framed for a health worker in a clinic-type setting. The wording will have to be adjusted for the approach used in the setting being researched, for example outreach or mobile vaccination services.]
What do you find works in helping families stay up to date with immunization? *Probe*: - What helps them not miss doses or appointments? *[Note: This is to probe for practical issues.]* - What helps those who are hesitant about getting their children vaccinated?	- This question is designed to find out what, in the participant's experience, helps keep families up to date with immunizations for their children. - [Note: The question is intentionally broad and open-ended so that all possible answers are gathered.]
What do you find difficult when it comes to helping families stay up to date with immunization? *Probe*: - Which part of the process you described before do you find the hardest to complete? Why is that? - Can you give some examples of reasons people give when their child has fallen behind the vaccination schedule? - Can you give some examples of reasons that people give for refusing vaccines for their children?	- This question is designed to help identify and understand difficulties the participant faces in helping families to keep up to date with vaccinations. - [Note: The suggested probes are to help separate differences between difficulties in the process they describe above, and difficulties they think families experience.]
If you had the chance, what would you do to improve immunization services in your area?	- The aim is to identify any other issues or suggestions not identified in the previous line of questioning. - Closing question.

Interview guide for community influencers

Question/[Instruction]	Rationale
Introduction: Hello, I am [INTERVIEWER'S NAME] with [INSTITUTION OR ORGANIZATION NAME]. We are interviewing people to help improve vaccination services in [NAME OF COUNTRY].	- Clear introduction to ensure true informed consent for participation is obtained before proceeding.

Question/[Instruction]	Rationale
The interview is expected to take __ minutes. Your participation is completely voluntary and anonymous. The answers you give will be completely confidential. If you do not want to answer a question or wish to stop the interview, just let me know. Would you be willing to take part in an interview with me? *[If audio recording the interview]* Would you be happy for me to record our conversation?	
Tell me a little about yourself and your role here in the community. *Probe*: - To what extent does your work involve immunization? - Can you tell me more about that? - Who do you work with to do that work?	- Warm-up question. - Enables understanding of the participant's role in the community. - Understanding the breadth of the participant's responsibilities.
Can you take me through the process you follow when you work in a community? *Probe*: - *[Note: This probe is for participants who work with families.]* When you visit a family: o What do you talk about? o What information can you not leave without saying? o Do you follow up with the families afterwards? How do you do that? - *[Note: This question is for participants who work with other people and organizations; use as appropriate for the participant.]* o How do you help the front-line health workers in working with families? o How do you help with routine immunization?	- To understand the details of the participant's immunization-related activities. - [Note: Some participants may work directly with families; others work with NGOs (nongovernmental organizations) and other agencies. The suggested probe questions should be adjusted to suit the participant's setting and role.]
What do you find works in helping families stay up to date with their children's immunizations? *Probe*: - What helps them not miss doses or appointments? *[Note: This is to probe for practical issues.]* - What helps those who are hesitant about getting their children vaccinated?	- This question is designed to find out what, in the participant's experience, helps families keep up to date with immunizations for their children. - [Note: The question is intentionally broad and open-ended so that all possible answers are gathered].

Question/[Instruction]	Rationale
What makes it difficult for families stay up to date with immunization? Probe: - Can you give some examples of reasons people give when their child has fallen behind the vaccination schedule? - Can you give some examples of reasons that people give for refusing vaccines for their children? - Are you able to overcome these challenges? How?	- This question is designed to help identify and understand difficulties the participant sees for families in keeping up to date with vaccinations in their community.
If you had the chance, what would you do to improve immunization services in your area?	- Aim to identify any other issues or suggestions not identified in the previous line of questioning. - Closing question.

Interview guide for programme managers

Question/[Instruction]	Rationale
Introduction: Hello, I am [INTERVIEWER'S NAME] with [INSTITUTION OR ORGANIZATION NAME]. We are interviewing people to help improve vaccination services in [NAME OF COUNTRY]. We're seeking input from people like you who know the processes and the work well. Your views are crucial and very valuable. The interview is expected to take __ minutes. Your participation is completely voluntary and anonymous. The answers you give will be completely confidential. If you do not want to answer a question or wish to stop the interview, just let me know. Would you be willing to take part in an interview with me? [If audio recording the interview] Would you be happy for me to record our conversation?	- Clear introduction to ensure true informed consent for participation is obtained before proceeding.
Tell me a little about yourself and your current role. *Probe*: - To what extent does your work involve childhood immunization? - What kinds of immunization-related activities are you responsible for (e.g., surveillance, campaigns, communications)? - Can you tell me more about those?	- Warm-up question. - Enables understanding of the participant's overall current role. - Understanding the breadth of the participant's responsibilities. - Understanding the extent of their immunization-related activities and what those entail.

Question/[Instruction]	Rationale
What makes the provision of childhood immunization a success in your area? *Probe*: - Are there specific examples you can describe?	- This question is designed to find out what, in the participant's experience, helps keep families up to date with immunizations for their children. - [Note: The question is intentionally broad and open-ended so that all possible answers are gathered.]
What do you think are the difficulties when it comes to providing childhood immunization in your area? *Probe*: - Do you face difficulties with children falling behind the vaccination schedule in your area? Can you describe those difficulties? - Do you face difficulties with parents refusing vaccines for their children? - Are you able to overcome these challenges? How?	- This question is designed to help identify and understand difficulties the participant sees for families in keeping up to date with vaccinations in their jurisdiction.
If you had the chance, what would you do to improve the childhood immunization situation in your area?	- Aim to identify any other issues or suggestions not identified in the previous line of questioning. - Closing question.

1.5 Qualitative framework analysis template for caregivers, health workers, community influencers and programme managers

The qualitative framework is provided in an Excel template to support interpretation of qualitative results. The Excel template can be accessed here: https://docs.google.com/spreadsheets/d/1TGZS4gEjmmLJGC5i63rAfLa70xHdcDR9/edit?usp=sharing&ouid=110867530849518712256&rtpof=true&sd=true

Note that the analysis approach recommended is not a linear process. It will be necessary to move between coding the interviews and the framework summaries and adjusting the categories slightly as new data from subsequent interviews emerge.

Annex 2: BeSD tools for COVID-19 vaccination

2.1 COVID-19 vaccination priority indicators (version 1.0)

The five priority indicators for vaccination of COVID-19 among adults are provided in the table below. When it is not possible to use the full COVID-19 vaccination survey, at least measure these priority indicators.

Domain	Construct	Priority question	Priority indicator
Thinking and feeling	**Confidence in COVID-19 vaccine benefits**	How important do you think getting a COVID-19 vaccine is for your health? Would you say… ☐ Not at all important, ☐ A little important, ☐ Moderately important, *or* ☐ Very important?	% of adults/health workers who say a COVID-19 vaccine is moderately or very important for their health
Social processes	**Family norms**	Do you think most of your close family and friends want you to get a COVID-19 vaccine? ☐ NO ☐ YES	% of adults/health workers who say most of their close family and friends want them to get a COVID-19 vaccine
Motivation	**Intention to get vaccinated**	Do you want to get a COVID-19 vaccine? Would you say… ☐ No, you do not want to, ☐ Yes, you do want to, *or are you* ☐ Not sure?	% of adults/health workers who say they want to get a COVID-19 vaccine
Practical issues	**Know where to get vaccination**	Do you know where to go to get a COVID-19 vaccine for yourself? ☐ NO ☐ YES	% of adults/health workers who say they know where to get a COVID-19 vaccine for themselves
Practical issues	**Affordability**	How easy is it to pay for COVID-19 vaccination? When you think about the cost, please consider any payments to the clinic, the cost of getting there, plus the cost of taking time away from work. Would you say… ☐ Not at all easy, ☐ A little easy, ☐ Moderately easy, *or* ☐ Very easy?	% of adults/health workers who say COVID-19 vaccination is “moderately” or “very” easy to pay

2.2 COVID-19 vaccination survey for adults and health workers (version 1.0)

The BeSD COVID-19 Vaccination Survey is a globally standardized tool for assessing the drivers of COVID-19 vaccination. The survey is to be completed by adults and health workers.

The survey has 22 questions. When it is not possible to use the full COVID-19 vaccination survey, at least measure the priority indicators. To support use of the survey and analyses, also included are a recommended consent script and socio-demographic questions; programmes should adapt the consent and demographic questions as needed but should not change the rest of the survey.

The "Indicator" column shows **priority** indicators; optional indicators are shown with a * (based on weaker performance in validation). The "Rationale" column contains important information for translating and locally adapting questions. Countries may also adapt the term "COVID-19" throughout the survey where a colloquial term is better understood, such as "coronavirus". Table cell colours indicate the domain (demographics, thinking and feeling, motivation, social processes and practical issues).

Trained interviewers should read the survey questions and response options aloud to respondents. Interviewers should not read aloud instructions in [square brackets] and ALL CAPITALS. Interviewers should emphasize underlined words. Instructions on how to adapt the survey for self-administration, such as an online survey, are in the BeSD data for action guidebook, section 3.5.

Construct	Question and response options	Indicator	Rationale
Date	DAY /MONTH /YEAR OF INTERVIEW: ____ /_____ /_____	None	This is an administrative question for the interviewer to complete at the time of interview. To ensure comparability and tracking, this question must not be adapted.
Participant	PARTICIPANT ID: _____	None	This is an administrative question for the interviewer to record a unique identity for individual participants at the time of interview. To ensure comparability and tracking, this question must not be adapted.
Location	GPS COORDINATES: _____ CLUSTER NUMBER: _____ DISTRICT NAME: _____	None	This is an administrative question for the interviewer to complete at the time of interview. This question can be adapted to suit the survey methodology.

Construct	Question and response options	Indicator	Rationale
Area	IS THE AREA: ☐ RURAL ☐ URBAN	None	This is an administrative question for the interviewer to complete at the time of interview.
Consent	Hello, I am [INTERVIEWER NAME] with [INSTITUTION OR ORGANIZATION NAME]. We are interviewing people to help improve vaccination services in [COUNTRY NAME]. I will be asking you questions about COVID-19. I know you are busy, so this will take only a few minutes. Your participation is completely voluntary and anonymous. If you do not want to answer a question or wish to stop the interview, just let me know. Would you be willing to take the survey? ☐ YES ☐ NO IF "YES" TO S0: Thank you very much. Do you have any questions for me before we begin? ADDRESS ANY QUESTIONS AND PROCEED. IF "NO" TO S0: Thank you very much. END INTERVIEW.	None	This question serves as an example of text to be included to capture respondents' informed consent to their participation in the study.
Age	How old are you? _____ YEARS	% of adults/health workers who are 18–34 years old % of adults/health workers who are above 55 or more years old	This question collects age in number of completed years: this will allow stratified analysis by age of respondents. This question can also serve to screen in or screen out participants for inclusion based on the study sampling methodology.

Construct	Question and response options	Indicator	Rationale
Gender	This may seem obvious, but I have to ask the question. What is your gender? Would you say… ☐ Woman, ☐ Man, ☐ Non-binary, *or would you* ☐ Prefer not to say?	% of adults/health workers who are women % of adults/health workers who are men	This question collects gender identity of respondents to allow stratified analysis. The third response option can be included in contexts where specific third-gender categories are culturally recognized; this response option can be adapted as appropriate based on in-country considerations or consultation.
Occupation	Which of the following best describes your work during the COVID-19 pandemic? Would you say… ☐ Health worker, ☐ Essential services worker, ☐ Educator, ☐ Other worker, *or* ☐ None of the above?	% of adults who are health workers % of adults who are essential service workers	This question enables sorting of respondents for the right survey as needed. Inclusion of this question will allow analysis of intentions to be stratified by whether someone is in a priority occupational group or not. This question can also serve to screen in or screen out participants for inclusion based on the study sampling methodology. "Essential services worker" refers to other non-health front-line workers (e.g., police, transport service workers, grocery store staff). The categories may be locally adapted to ensure they are appropriate to the specific context and allow disaggregated data as needed. Some countries may choose to delineate between front-line and non-front-line health workers.
Health worker	[FOR HEALTH WORKERS ONLY] What is your current role? Would you say… ☐ Doctor, ☐ Nurse, ☐ Paramedic/first responder, ☐ Community health worker, ☐ Traditional healer, *or*	Varies by country	This question enables categorization of health workers into common roles or functions within the health system. If included, this question enables more detailed analysis of health worker roles and stratification of results. The response options offered should be adapted in-country at national or even

Construct	Question and response options	Indicator	Rationale
	☐ Other health worker?		subnational level to reflect the most appropriate role categorizations based on the types of health workers most likely to be at risk of COVID-19 infection/most exposed to COVID-19.
COVID-19 risk	Do you have a chronic condition? This could include, for example, obesity, diabetes, lung disease or another long-term condition. ☐ NO ☐ YES ☐ NOT SURE	% of adults/health workers who have a chronic condition (answered "yes")	This question assesses whether the respondent has any underlying condition, comorbidities or health conditions that make the respondent a higher priority for vaccination. Inclusion of this question allows stratification of results by comorbidities. This question can also serve to screen in or screen out participants for inclusion based on the study sampling methodology.
COVID-19 diagnosis	To your knowledge, have you ever had COVID-19? ☐ NO ☐ YES IF "YES": Was it… ☐ Mild, *or* ☐ Severe? Was it… ☐ Confirmed by a test, *or* ☐ Not confirmed by a test?	% of adults/health workers who have had COVID-19 (answered "yes") % of adults/health workers who have had COVID-19 confirmed by test	Previously having COVID-19 can be perceived as a reason to not vaccinate, and countries may want to stratify data on intentions to be vaccinated according to this. This question can also serve to screen in or screen out participants for inclusion based on the study sampling methodology. When a COVID-19 vaccine becomes available in-country, researchers may choose to include a question to assess whether the respondent has received a COVID-19 vaccine. If several are available in the country, a question that asks which vaccine the respondent received may also be added.
Perceived risk – self	How concerned are you about getting COVID-19? Would you say…	% of adults/health workers who say they are "moderately" or "very"	This question assesses the degree to which the respondent perceives a risk of getting COVID-19 themselves. "Concern" is similar to worry or

Construct	Question and response options	Indicator	Rationale
	☐ Not at all concerned, ☐ A little concerned, ☐ Moderately concerned, *or* ☐ Very concerned?	concerned about getting COVID-19*	thinking about a problem; it is not directly about fear or anxiety or emotion.
COVID-19 vaccine uptake	Have you received a COVID-19 vaccine? Would you say… ☐ No ☐ Yes, you received one dose, ☐ Yes, you received two doses, *or* ☐ Yes, you received three or more doses? ☐ NOT SURE	% of adults/health workers who received a COVID-19 vaccine (answered "yes")	This question assesses whether the respondent has ever received any dose of a COVID-19 vaccine. A "not sure" response option is included here as it is likely some adults may not easily be able to recall such information.
Intention to get vaccinated	Do you want to get a COVID-19 vaccine? Would you say… ☐ No, you do not want to, ☐ Yes, you do want to, *or are you* ☐ Not sure?	**Priority** % of adults/health workers who say they want to get a COVID-19 vaccine	This question assesses intention to receive a COVID-19 vaccine if advised to do so by a medical professional. Countries can choose to add an open-text follow-up question for those who answer "no": What is the main reason you would not get a COVID-19 vaccine if it were available to you? [OPEN-TEXT RESPONSE]
Confidence in COVID-19 vaccine benefits	How important do you think getting a COVID-19 vaccine is for your health? Would you say… ☐ Not at all important, ☐ A little important, ☐ Moderately important, *or* ☐ Very important?	**Priority** % of adults/health workers who say a COVID-19 vaccine is "moderately" or "very" important for their health	This question assesses positive attitude towards COVID-19 vaccination. The main idea is that vaccination is good, important and valuable. A related idea is that vaccination is effective, prevents disease, saves lives and protects those vaccinated.
Confidence in COVID-19	How safe do you think a COVID-19 vaccine is for you?	% of adults/health workers who say a	This question assesses negative attitude towards COVID-19 vaccination for themselves.

Construct	Question and response options	Indicator	Rationale
vaccine safety	☐ Not at all safe, ☐ A little safe, ☐ Moderately safe, *or* ☐ Very safe?	COVID-19 vaccine is "moderately" or "very" safe	The main idea is the belief that the vaccine is safe and is not dangerous or harmful.
COVID-19 vaccine – see friends and family	Do you think that getting a COVID-19 vaccine will allow you to see your family and friends again? ☐ NO ☐ YES	% of adults/health workers who say that getting a COVID-19 vaccine will allow them to safely see their family and friends again*	This question assesses whether freedom to see family and friends could be a motivator to get a COVID-19 vaccine.
Confidence in health workers	How much do you trust the health workers who would give you a COVID-19 vaccine? Would you say… ☐ Not at all, ☐ A little, ☐ Moderately, *or* ☐ Very much?	% of adults/health workers who say they trust the health workers who give COVID-19 vaccines "moderately" or "very much"*	This question assesses confidence in the people responsible for recommending and administering vaccines. "Trust" refers to belief that the health worker who gives vaccines will be competent, reliable and provide good health care. "Health worker" will need local adaptation to indicate the medical professionals responsible for recommending and administering adult vaccination (i.e., general practitioner, health provider or primary health-care physician and assisting nurses or vaccinators).
Peer norms	Do you think most adults you know will get a COVID-19 vaccine if it is recommended to them? ☐ NO ☐ YES	% of adults/health workers who say that most adults they know will get a COVID-19 vaccine (answered "yes")	This question assesses social norms – beliefs about what other people are doing. "Most adults you know" includes friends, people at work and people in the neighbourhood who respondents may have

Construct	Question and response options	Indicator	Rationale
			social ties to. It does not include people they have never met.
Workplace norms	Do you think most of the people you work with will get a COVID-19 vaccine? ☐ NO ☐ YES ☐ NOT CURRENTLY WORKING	% of adults/health workers who say that most of the people they work with will get a COVID-19 vaccine*	This question assesses social norms – beliefs about what other people are doing. "Most people you work with" includes all colleagues and people at their place of work who could be eligible for a COVID-19 vaccine. This question has been shown to be highly correlated with COVID-19 vaccine uptake. If you use this question, note that it does not collect data on the workplace norms of those who are unemployed at the time of data collection (those who select "I am not currently working").
Family norms	Do you think most of your close family and friends want you to get a COVID-19 vaccine? ☐ NO ☐ YES	**Priority** % of adults/health workers who say most of their close family and friends want them to get a COVID-19 vaccine	This question assesses social norms – beliefs about what close social contacts want the respondent to do. "Close family and friends" include people with opinions the respondent would listen to or feel some degree of pressure to heed.
Religious leader norms	Do you think your religious leaders want you to get a COVID-19 vaccine? ☐ NO ☐ YES	% of adults/health workers who say their religious leaders want them to get a COVID-19 vaccine (answered "yes" or "not sure")*	This question assesses social norms – beliefs about what opinion leaders want the respondent to do. "Religious leader" includes priests, clerics, imams, rabbis and others in similar roles.

Construct	Question and response options	Indicator	Rationale
Community leader norms	Do you think other community leaders want you to get a COVID-19 vaccine? ☐ NO ☐ YES	% of adults/health workers who say their community leaders want them to get a COVID-19 vaccine (answered "yes" or "not sure")	This question assesses injunctive social norms – beliefs about what opinion leaders want the respondent to do. "Community" may refer to a neighbourhood or region or a social group defined by a characteristic such as race or national origin. "Community leader" includes people who represent a neighbourhood, region or subgroup of people.
Health worker recommendation	Has a health worker recommended you get a COVID-19 vaccine? ☐ NO ☐ YES	% of adults/health workers who say a health worker has recommended they get a COVID-19 vaccine	This question assesses whether a health worker or health-care provider has advised the respondent to get a COVID-19 vaccine. "Recommended" includes raising the topic during a clinic visit, saying the person is due and offering advice to get vaccinated. The term "health worker" must be adapted to reflect local language (e.g., health-care provider, general practitioner, vaccinator).
Received recall	Have you ever been contacted about being due for a COVID-19 vaccine? ☐ NO ☐ YES	% of adults/health workers who say they have been contacted about being due for a COVID-19 vaccine (answered "yes")	This question assesses mechanisms in place to reach and remind adults due for vaccination. If these systems/mechanisms are not in place in-country, we recommend that this question not be included.
Gender equity – travel autonomy	If it was time for you to get a COVID-19 vaccine, would you need permission to go and get it? ☐ NO ☐ YES	% of adults/health workers who say they do not need permission to go and get a COVID-19 vaccine*	This question assesses freedom of the respondent to leave the home to get a COVID-19 vaccine. Data can be stratified by gender to assess women's travel autonomy.

Construct	Question and response options	Indicator	Rationale
Know where to get vaccination	Do you know where to go to get a COVID-19 vaccine for yourself? ☐ NO ☐ YES	**Priority** % of adults/health workers who know where to get a COVID-19 vaccine for themselves	This question assesses whether the respondent knows where to go for vaccination. The question is about knowing that the facility or vaccine provider exists and where it is located. The question is not about ability to access or use the services. If COVID-19 vaccines are not yet available in your country, adapt the question to: Do you know where to go to get yourself vaccinated? ☐ NO ☐ YES
On-site vaccination	Is a COVID-19 vaccine available for you to get at your place of work? Would you say… ☐ NO ☐ YES ☐ NOT CURRENTLY WORKING	% of adults/health workers who have access to a COVID-19 vaccine at their place of work (answered "yes")*	This question assesses availability or existence of vaccination services at work (on-site) for health workers only. This question can also be applied to adults in countries where it is not uncommon to offer adult vaccines in workplaces. A "not sure" response option is included here as some may not be aware of the presence of any on-site vaccination in their place of work. If COVID-19 vaccines are not yet available in your country, adapt the question to: Have any vaccines ever been available for you to get at your place of work? ☐ NO ☐ YES

Construct	Question and response options	Indicator	Rationale
Ease of access	How easy is it to get a COVID-19 vaccine for yourself? Would you say… ☐ Not at all easy, ☐ A little easy, ☐ Moderately easy, *or* ☐ Very easy?	% of adults/health workers who say getting COVID-19 vaccination is "moderately" or "very" easy	This question assesses the degree to which vaccination is easy for respondents to get for themselves. The question looks at ease of access in general and leads into the next question. "Easy" refers to achievable, possible without great effort, not hard and not difficult. "Vaccination services" refers to access to vaccination. If COVID-19 vaccines are not yet available in your country, adapt the question to: How easy is it to get vaccination services for yourself? ☐ Not at all easy ☐ A little easy ☐ Moderately easy, *or* ☐ Very easy
Affordability	How easy is it to pay for COVID-19 vaccination? When you think about the cost, please consider any payments to the clinic, the cost of getting there and the cost of taking time away from work. Would you say… ☐ Not at all easy, ☐ A little easy, ☐ Moderately easy, *or* ☐ Very easy?	**Priority** % of adults/health workers who say COVID-19 vaccination is "moderately" or "very" easy to pay for.	This question assesses the perceived cost of vaccination. Cost is the monetary value associated with vaccination. "Easy to pay" refers to the total costs associated with vaccination being something the respondent can afford to pay for.
Reasons for low ease of access	What makes it hard for you to get a COVID-19 vaccine? Would you say…	% of adults/health workers who say COVID-19 vaccination is not yet available for them	This question assesses the reasons why vaccination is difficult to get. Respondents can choose multiple response options here. There is

Construct	Question and response options	Indicator	Rationale
	[READ ALOUD ALL RESPONSE OPTIONS, PAUSING AFTER EACH TO ALLOW RESPONDENT TO ANSWER "YES" OR "NO" AFTER EACH RESPONSE OPTION. RESPONDENTS MAY SELECT MULTIPLE RESPONSE OPTIONS.] ☐ Nothing, it's not hard, [IF NOTHING, SKIP REST OF RESPONSES] ☐ COVID-19 vaccination is not yet available for me, ☐ Making an appointment is hard, ☐ The vaccination site is hard to get to, ☐ The opening times are inconvenient, ☐ The waiting time takes too long, ☐ I am unable to leave work duties, ☐ Sometimes people are turned away without vaccination, *or* ☐ Is there something else? [RECORD ANSWER: _____]	% of adults/health workers who say making an appointment is hard % of adults who say they can't go on their own % of adults/health workers who say the vaccination site is hard to get to % of adults/health workers who say vaccination opening times are inconvenient % of adults/health workers who say the waiting time takes too long % of health workers who say they are unable to leave work duties % of adults/health workers who say sometimes people are turned away without vaccination	no skip logic for this question; it must be asked of all respondents. Response options explained: "Nothing, it's not hard" is an exclusive response option (it cannot be selected alongside other response options) available for those who do not think it is difficult to get COVID-19 vaccines. "COVID-19 vaccination is not yet available for me" is to capture people who are not yet eligible for a COVID-19 vaccine according to their country guidelines. "Hard to get to" refers to geographical distance and difficult or inconvenient logistics of getting to the place where COVID-19 vaccines are offered. "Inconvenient" refers to opening hours that do not suit the respondent. "Takes too long" refers to the waiting times at the place of vaccination. "Unable to leave work duties" refers to health workers being unable to make time for vaccination alongside their work responsibilities. "Turns people away" refers to the clinic sending people home without vaccination when they specifically had come for vaccination. If COVID-19 vaccines are not yet available in your country, adapt the question to:

Construct	Question and response options	Indicator	Rationale
			What makes it hard for you to get vaccines? REMOVE THE RESPONSE OPTION: COVID-19 vaccination is not yet available for me.
Service satisfaction	How satisfied are you with COVID-19 vaccination services? Would you say… ☐ Not at all satisfied, ☐ A little satisfied, ☐ Moderately satisfied, *or* ☐ Very satisfied?	% of adults/health workers who say they are "moderately" or "very" satisfied with COVID-19 vaccination services (answered "yes")	This question assesses satisfaction with vaccination services received during the last visit. "Satisfied" refers to how good the services and experience were for respondents, and how pleased or happy they felt about the visit and the interactions that took place. "Vaccination services" refers to work done by vaccination clinic staff who greet patients, handle paperwork and payment, and administer the vaccine. "Not at all" is bad and not acceptable. "Not very" is okay, adequate and not bad. "Somewhat" is positive but not the best possible. "Very" is great, fantastic and outstanding.
Service quality	What is not satisfactory about the COVID-19 vaccination services? Would you say… [READ ALOUD ALL RESPONSE OPTIONS, PAUSING AFTER EACH TO ALLOW RESPONDENT TO ANSWER "YES" OR "NO" AFTER EACH RESPONSE OPTION. RESPONDENTS MAY SELECT MULTIPLE RESPONSE OPTIONS.] ☐ Nothing, you are satisfied [IF NOTHING, SKIP REST OF RESPONSES]	% of adults/health workers who say vaccine is not available % of adults/health workers who say the vaccination site does not open on time	This question assesses reasons why the respondent is not satisfied with the vaccination services. Respondents can choose multiple response options here. There is no skip logic for this question; it must be asked of all respondents. "Nothing, I am satisfied" is an exclusive response option (it cannot be selected alongside other response options) available for

Construct	Question and response options	Indicator	Rationale
	☐ Vaccine is not available, ☐ The vaccination site does not open on time, ☐ Waiting times are long, ☐ The vaccination site is not clean, ☐ Staff are poorly trained, ☐ Staff are not respectful, ☐ Staff do not spend enough time with people, *or* ☐ Is there something else? [RECORD ANSWER: _____]	% of adults/health workers who say waiting times are long % of adults/health workers who say the vaccination site is not clean % of adults/health workers who say staff are poorly trained % of adults/health workers who say staff are not respectful % of adults/health workers who say staff do not spend enough time with people	respondents who are satisfised with the vaccination services. "Vaccine is not available" refers to the lack of COVID-19 vaccine stock at the vaccination site/clinic. "The vaccination site does not open on time" means that the service operating hours were not functioning as scheduled or advertised. "Waiting times are long" is the perception that the service was poorly organized for time, or that staff were unable to prioritize efficient, quick service. "The vaccination site is not clean" refers to any complaint about the place where vaccines are given, including location and building structure. This also includes lack of cleanliness and poor maintenance. This could include vaccine vials, needles, fridges for storing vaccines as well as furniture in the clinic, reception and waiting rooms, or even appearance of personnel, such as appropriate attire, clean appearance and uniform. "Staff are poorly trained" is the perception that the service received is not as promised or that the quality of service is not reliable or consistent. The respondent may perceive that staff did not fulfil their role very well, that staff were not well trained or prepared for their responsibilities, or that staff lacked the

Construct	Question and response options	Indicator	Rationale
			confidence or skill to deliver the service expected. "Staff are not respectful" refers to inability to inspire confidence, put respondents at ease and communicate competence. It includes staff being discourteous, impolite and unable to reassure respondents. Staff can show respect in verbal and non-verbal ways. "Staff do not spend enough time with people" is the perceived lack of empathy a respondent may experience from vaccination clinic staff, and perception of a rushed service or lack of time dedicated to reassuring respondents and answering their questions.

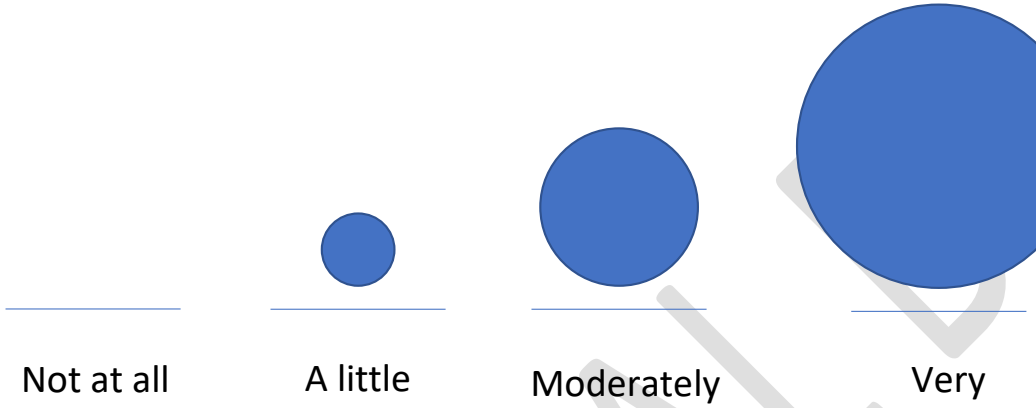
In addition to the BeSD survey questions in the table above, countries may choose to add questions about provision of COVID-19 vaccines, including the two below. These questions are just for health workers and should only be included in data collection if they will provide valuable descriptive data for the immunization programme.

Construct	Question and response options	Indicator	Rationale
Willingness to recommend vaccine to others	Would you recommend a COVID-19 vaccine to eligible individuals? Would you say… ☐ No, you do not want to, ☐ Yes, you do want to, *or are you* ☐ Not sure?	% of health workers who say they would recommend a COVID-19 vaccine to eligible individuals (answered "yes")	This question assesses health workers' willingness to recommend or promote a COVID-19 vaccine to persons who are eligible candidates for COVID-19 vaccines. If COVID-19 vaccines are not yet available in your country, adapt the question to: Would you recommend a COVID-19 vaccine to eligible individuals when it becomes available? Would you say…

Construct	Question and response options	Indicator	Rationale
			☐ No, ☐ Yes, *or are you* ☐ Not sure?
Ability to answer patient questions	How confident are you that you could answer patient questions about getting a COVID-19 vaccine? Would you say… ☐ Not at all confident, ☐ A little confident, ☐ Moderately confident, *or* ☐ Very confident?	% of health workers who say they are "moderately" or "very" confident they could answer patient questions about getting a COVID-19 vaccine	This question measures health workers' confidence in their ability to support the information needs of patients about a COVID-19 vaccine once it becomes available. If COVID-19 vaccines are not yet available in your country, adapt the question to: How confident are you that you could answer patient questions about getting a COVID-19 vaccine, once it is available? Would you say… ☐ Not at all confident, ☐ A little confident, ☐ Moderately confident, *or* Very confident?

2.3 Visual survey response scale

For surveys with lower-literacy respondents, consider using a visual response scale. It is designed for questions with four response options (such as “not at all”, “a little”, “moderately”, “very”). Interviewers should read the question aloud and point to the visual scale as they read the response options.



2.4 COVID-19 vaccination in-depth interview guide for adults and health workers (version 1.0)

The questions below are designed to be asked in a context where a COVID-19 vaccine is available. In contexts where multiple vaccines are available for use, questions should be modified and refer to "the COVID-19 vaccine**s**". In this instance it may be useful to understand whether perceptions, norms and willingness to accept a COVID-19 vaccine depend on which vaccine is being offered; interviewers should use probes for all vaccines available in the local context.

If these questions are to be used in a context where a COVID-19 vaccine is not yet available, the questions will need to be modified accordingly. For example, the COVID-19 vaccine confidence question "How do you feel about the COVID-19 vaccine?" would be modified for a pre-vaccine roll-out context by adjusting the wording to "How do you think you'll feel about the COVID-19 vaccine when it becomes available?"

Some questions will be worded differently, depending on whether the interviewee has had the vaccine or not. In these questions wording for both scenarios is included. Choose the wording that is appropriate for the interviewee.

Table cell colours indicate the domain (thinking and feeling, motivation, social processes and practical issues).

Construct	Adult	Health worker	Rationale
General	Tell me a little about yourself.	Tell me a little about yourself. Tell me a little about your role.	- Warm-up question. - Orients interviewer to participant's situation.
Thinking and feeling			
Perceived COVID-19 risk – to self	Tell me, how concerned are you about getting COVID-19? *Probe*: - Why do you feel that way? - How likely do you think it is? - How severe do you think it would be?	Tell me, how concerned are you about getting COVID-19? *Probe*: - Why do you feel that way? - How likely do you think it is? - How severe do you think it would be?	- Understand the participant's perceived risk due to COVID-19 (disease, not vaccine). - Will tie in with later question about getting COVID-19 vaccine when available.
Perceived risk – to patients	N/A	Tell me what you think about the risk that you could give COVID-19 to your patients	- Understand participant's perceived risk of infecting others.

Construct	Adult	Health worker	Rationale
COVID-19 stigma (social processes)	N/A	Being a health-care worker, how are you usually treated by others in the community? *Probe*: - Have you noticed anything different in how you're treated since the pandemic?	- Enables probing for the presence of/experience of stigma.
COVID-19 vaccine information	What have you heard about the COVID-19 vaccine(s)? *Probe*: - Have you heard anything that worries you? - Who did you hear this from? - Do you think it's true? Why? - Have you heard anything that makes you feel positive about the vaccines that are being developed?	What have you heard about the COVID-19 vaccine(s)? *Probe*: - Have you heard anything that worries you? - Who did you hear this from? - Have you heard anything that makes you feel positive about the vaccines that are being developed?	- Ask what they know about the vaccine – enables probing for positive or negative information.
COVID-19 vaccine confidence	How do you feel about the COVID-19 vaccine(s)? *Probes*: - *If multiple vaccines are available,* what are the perceptions of each? - Relate back to perceived COVID-19 risk and how important it is. - Importance in protecting others. - Alignment with spiritual or religious beliefs. *Ask for all COVID-19 vaccines available.* - What are your thoughts about the safety of the vaccine? *Ask for all COVID-19 vaccines available.*	How do you feel about the COVID-19 vaccine(s)? *Probes*: - *If multiple vaccines are available*, what are the perceptions of each? - Relate back to perceived COVID-19 risk and how important it is. - Importance in protecting others. - Alignment with spiritual or religious beliefs. *Ask for all COVID-19 vaccines available*. - What are your thoughts about the safety of the vaccine? *Ask for all COVID-19 vaccines available*.	- Elicits the participant's confidence in the vaccine; probe questions will cover the different aspects, such as safety and importance.

Construct	Adult	Health worker	Rationale
	- Thoughts or concerns about how "new" the vaccines are (try to understand if this links to safety, efficacy or anything else). - Thoughts on whether it works. *Ask for all COVID-19 vaccines available.*	- Thoughts or concerns about how "new" the vaccines are (try to understand if this links to safety, efficacy or anything else). - Thoughts on whether it works. *Ask for all COVID-19 vaccines available.*	
COVID-19 vaccine confidence in providers	N/A	N/A	- Trust in health providers will be covered under service satisfaction below.
Motivation			
COVID-19 vaccine intention	Have you thought about getting a COVID-19 vaccine? What did you decide? (Why?) *Follow on to next question (combine).*	Have you thought about getting a COVID-19 vaccine? What did you decide? (Why?) *Follow on to next question (combine).*	- Elicits what their intentions and decisions are towards the vaccine. On probing "Why?" responses may be repetitive of questions answered above; this can serve as a good cross check to previous answers given and allow for deeper understanding of motivation.
Social processes			
COVID-19 vaccine – decision process	Take me through how you will or have decided whether to get a COVID-19 vaccine. *Probe*: - Was anyone else involved in the decision? - Who else did you discuss it with?	Take me through how you will or have decided whether to get a COVID-19 vaccine. *Probe*: - Was anyone else involved in the decision? - Who did you discuss it with? - Is it a requirement from your employer?	- Covers decision autonomy, but also the decision-making process more broadly, with a view to understanding what kinds of social processes might be involved.

Construct	Adult	Health worker	Rationale
COVID-19 vaccine – safe to see family and friends	(If already had the vaccine) Has getting a COVID-19 vaccine changed things for you? (If hasn't had the vaccine) How do you think getting a COVID-19 vaccine might change things for you? *Probe*: - See family and friends - Going out in public - Going back to work.	(If already had the vaccine) Has getting a COVID-19 vaccine changed things for you? (If hasn't had the vaccine) How do you think getting a COVID-19 vaccine might change things for you? *Probe*: - See family and friends - Going out in public.	- This question explores ways a COVID-19 vaccine might impact people.
COVID-19 vaccine stigma	N/A	*If they answered in the affirmative to the stigma question above, ask*: Do you think having the COVID-19 vaccine will help/has helped with the stigma we spoke about earlier? Why?	- This question is only relevant if the participant describes any kind of stigma in the question above. Suggest not asking if they don't report having experienced or heard of it happening.
COVID-19 vaccine – travel autonomy	N/A	N/A	- Travel autonomy covered in practical issues below.
COVID vaccine - Descriptive social norms - Family norms - Religious leader norms - Workplace norms	If a COVID-19 vaccine is recommended by health-care workers, what do you think other people will do? *Probe*: - Family and friends - Religious or community leaders recommend? - *If more than one vaccine available:* Is this true for all COVID-19 vaccines or does it depend on which vaccine is recommended?	If a COVID-19 vaccine is recommended by health-care workers, what do you think other people will do? Probe: - Family and friends - Religious or community leaders recommend? - What do you think your work colleagues will do? - *If more than one vaccine available*: Is this true for all COVID-19 vaccines or does it depend on which vaccine is recommended?	- Elicits what they anticipate will be the social norms regarding uptake of COVID-19 vaccination.

Construct	Adult	Health worker	Rationale
Provider recommendation	What do you think your health-care provider's recommendation will be to you about the COVID-19 vaccine(s)?	What do you think your health-care provider's recommendation will be to you about the COVID-19 vaccine(s)?	- Anticipated recommendations.
General provider recommendation (any adult vaccine)	N/A	N/A	- General provider recommendation covered in practical issues below.
Practical issues			
Ever gone to get vaccines	Did you have any vaccines as a child? What do you remember about it? Probe: - Experiences, good and bad. Have you ever had a vaccine as an adult? Have you ever had one recommended to you by a health-care worker? *If previously vaccinated as an adult, ask:* Thinking about when you got that vaccine, what did you think was good about what happened in the clinic? Was there anything that wasn't good?	Have you ever had a vaccine as an adult? Have you ever had one recommended to you by a health-care worker? What about your employer? *If previously vaccinated as an adult, ask:* When you got that vaccine, what did you think was good about what happened in the clinic? Was there anything that wasn't good? What do you think might work better for you next time?	- Start with past general vaccination experiences, including, if applicable, service satisfaction in past experiences.

Construct	Adult	Health worker	Rationale
COVID-19 vaccine - On-site vaccine availability - Access - General vaccination – know where to get vaccines - Vaccination availability - General vaccine – affordability - General vaccine – service satisfaction - General vaccine – service quality	Can you take me through how you would get/how you got a COVID-19 vaccine? Start at the beginning. *Probe*: - Would/did you need to ask permission? - Where would/did you go to get it? - How would/did you get there? - What other things would/did you need to do (e.g., find care for young children, find someone to take care of livelihood/get up earlier to take care of household duties)? - Would there be/was there any cost involved for you (not just for vaccine, but things like transport)? - How much do you trust the health-care worker who will give you the vaccine? What would make it easy for you to get a COVID-19 vaccine if it was recommended and available? / What would make it easier for you to get a COVID-19 vaccine?	Can you take me through how you would get/how you got a COVID-19 vaccine? Start at the beginning. *Probe*: - Would/did you need to ask permission? - Where would/did you go to get it? Is the vaccine available at your workplace? - How would/did you get there? - Would/did you have to do it in your own time (not while you're on duty)? - Would there be/was there any cost involved for you (not just for vaccine, but things like transport)? - How much do you trust the health-care worker who will give you the vaccine? What would make it easy for you to get a COVID-19 vaccine if it was recommended and available? / What would make it easier for you to get a COVID-19 vaccine?	- Ask for a narrative of how they might access the vaccine, covering things like cost, missed workdays, transport, any permissions needed, etc. - Also cover what they feel might make accessing the vaccine easier for them.
Close	Is there anything else you'd like to say?	Is there anything else you'd like to say?	- Leave option for unexpected findings or elaboration of things expressed previously.

2.5 Qualitative framework analysis template for BeSD COVID-19 in-depth interview

The qualitative framework is provided in an Excel template to support interpretation of qualitative results. The Excel template can be accessed here: https://docs.google.com/spreadsheets/d/1UCcKO20dQRDBNOclwGwPin3sD_MiPTMy/edit?usp=sharing&ouid=110867530849518712256&rtpof=true&sd=true.

Note that the analysis approach recommended is not a linear process. It will be necessary to move between coding the interviews and the framework summaries, adjusting the categories slightly as new data from subsequent interviews emerge.

Annex 3: Guidance for adapting the BeSD tools

3.1 Adapting the BeSD surveys

For the BeSD surveys, a process of cognitive interviewing is recommended to improve the quality of translations and support careful adaptation of survey questions and corresponding response options.

How to carry out cognitive interviewing to test and locally adapt the surveys

This is a brief guide to using cognitive interviewing to improve BeSD surveys. **Cognitive interviewing is a process for improving the quality of a survey**, to ensure questions and response options are understood as intended, are well adapted to a local context and measure what they are designed to measure. **Recruit participants for cognitive interviewing from the target population.** In this case, parents or caregivers to one or more children under the age of 5.

Schedule separate interviews with participants and follow the steps below for each survey question and its response options, one question at a time. Assume 2–3 minutes' interview length per question. Where possible, aim to conduct two rounds of interviews with four to eight respondents per round. However, conducting even one round of interviews with as few as four people can offer meaningful insights to improve the survey significantly.

1) Ask the respondent the question (including response options) and allow them to answer.
2) Ask the respondent about the question they just answered, using probes to understand whether…
   - **The question is easy to understand and makes sense:**
     "In your own words, what is this question asking?" or *"What does this question mean to you?"* to check the survey question was well understood.
   - **The ideas or words in the question and response options are easy to understand:**
     Ask generally, "*Did this question make sense to you? Why/why not?"* or probe around specific words or concepts that may be difficult to understand. *"What do you think of when you hear the phrase '<u>getting vaccines</u>'?"*
   - **The response options make sense and allow for meaningful answers:**
     "Do the response options fit in with the sort of answer you want to give?"
   - **There are any response options that are missing:**
     "*Was there anything missing from the list of response options*?" to check the options are adequate.
   - **The question and response options are relevant in the country or region:**
     Ask generally, "*Did the response options offered make sense to you? Why/why not?*" or probe around specific words or concepts that could be interpreted differently: *"What do you think of when you hear the phrase 'vaccination clinic'?"*

If using **the visual response scale,** if questions are being asked in person (not self-administered), the interviewer should point to the corresponding part of the visual analogue scale when that response option is being verbalized. This helps respondents understand the meaning and the connection with the circles.

After conducting the first round of cognitive interviews, review the feedback from participants. Were the questions understood as intended? Did the response options allow them to answer meaningfully? Are the questions appropriate in the local setting? If needed, adapt questions and response options using the insights. Table A3.1 offers an example for organizing survey questions and cognitive interview insights when considering revisions. Document the findings and recommendations or adaptations made.

Table A3.1. Example cognitive interview probes, findings and recommendations

Survey question	Probes	Example of findings	Recommendations
How safe do you think vaccines are for your child? Would you say… ☐ Not at all safe ☐ A little safe ☐ Moderately safe, *or* ☐ Very safe	- What does the word "safe" mean to you? - Did the response options offered make sense to you? Why/why not?	- Respondents not sure of the degree of difference on the response scale. - Visual scale helpful.	- Be sure interviewers have a printed visual scale to use at <u>every</u> interview. - Wording to clarify that "vaccines" is general, and question is not about any one specific vaccine.
How much do you trust the [health-care providers] who would give your child vaccines? Would you say you trust them… ☐ Not at all ☐ A little ☐ Moderately, *or* ☐ Very much	- What does the term "health-care provider" mean to you? - Who would normally give you your vaccines?	- "Health-care provider" associated with clinic management; not those responsible for administering vaccine. - "Vaccinator" suggested by respondents as more appropriate term.	- Rephrase question: How much do you trust the **vaccinators** who would give your child vaccines? Would you say you trust them… ☐ Not at all ☐ A little ☐ Moderately, *or* ☐ Very much

It is very important to maintain the intended meanings of each question in the process of translation and potential question adaptation. The rationale provides a description of the question so as to clarify its intended meaning along with question-specific recommendations for local adaptions. Refer to the question rationale provided with the BeSD Childhood Vaccination Survey.

It is also essential to test the modified questions and responses by conducting another round of cognitive interviews with a new group of participants, repeating the process until the questions and response options are understood as intended.

3.2 Adapting the BeSD interview guides

The series of questions offered in the BeSD in-depth interview guides are designed as a menu for researchers to choose from, depending on what topics require in-depth understanding. Using all of the questions listed in the guide will result in an interview that may be almost 2 hours in length, and thus a significant time commitment from participants with large amounts of data to analyse. Choose questions that will best answer the specific research question for the project.

Questions should be ordered in such a way that the interview flows more like a conversation than a survey. The order of questions in the suggested interview guide results in a fairly conversational interview in English and follows a general order of starting with a "warm-up" question, followed by thoughts and

feelings, what respondents think they will do, the social processes involved and practical issues. This will change, depending on the language and cultural setting.

Once a draft qualitative interview guide is developed, pilot test it with two or three people who are fluent in the language that the interview will be conducted in. During these pilot interviews, be mindful of whether the interview flows well (like a conversation) and adjust the order of questions if needed.

More information on interview guide development can be found in:

- Roberts RE. Qualitative interview questions: guidance for novice researchers. Qualitat Rep. 2020;25(9):3185–203.
- Kvale S, Brinkmann S. Interviews: learning the craft of qualitative research interviewing. 3rd ed. Thousand Oaks (CA): SAGE; 2015.

Annex 4: Guidance for GPS data collection

What are GPS data?

The Global Positioning System (GPS) data include a set of coordinates that identify a point in physical space, in this case, to identify the location of a surveyed site using longitude, latitude, altitude and the time surveyed. The benefits of GPS data collection are substantial because it makes it possible after the survey to link the BeSD data with other data sets containing similar geographic information, such as MICS and DHS. Typical examples are to use databases that include geographic location information on health facilities, schools, road networks and many other geographically located attributes.

Benefits of collecting GPS data

With the use of GPS, it becomes possible to carry out further analyses of BeSD data sets by expanding and triangulating them with information available from other databases. The collection of GPS data is part of the general approach to develop geographical information systems (GIS) which can help with microplanning, mapping services and populations, and even target population estimates. GPS data are usually collected with the cluster or area geographic location data, such as the administrative units of the sampled area and its urban vs rural characteristics.

In DHS practice, for instance, the GPS location of the centre of each cluster is recorded during either the fieldwork or listing stage of the survey. To protect the confidentiality of our respondents, the locations are displaced, sometimes termed “geo-masked” or “geo-scrambled”. UNICEF recommends that GPS data not be shared in publicly available data sets, but rather that interested parties submit a formal request for access and use to the national statistical office.

Operational considerations

- GPS data collection can almost always be done without hiring additional **personnel**. The allocation of roles and responsibilities may vary according to the survey and what data are already available. However, each field team should have a person who is responsible for collecting the GPS points (**the GPS operator**) and an overall **GPS coordinator** at the implementing agency headquarters.
- The responsibilities of the **GPS operators** are as follows: capture and record the GPS waypoint at the centre of the survey site; complete the GPS data collection form, including the GPS waypoint name/number, latitude, longitude, altitude and GPS unit number; communicate with the GPS coordinator; and ensure that unit and accessories are handled properly during fieldwork.
- The responsibilities of the **GPS coordinator** are as follows: obtaining materials (hardware, software, data, training/other field materials); preparing the GPS units (GPS units are relatively inexpensive and generally available in countries); training GPS operators; and data collection/processing.

More detailed description and guidance on GPS data collection is available at https://mics.unicef.org/tools including tools for MICS GPS Data Collection, and MICS GPS Data Collection Questionnaire.

Annex 5: Guidance for collecting vaccination status

To capture routine immunization coverage, and in order to standardize procedures across surveys, WHO recommends the following hierarchy of evidence of vaccination as outlined in the *World Health Organization vaccination cluster surveys reference manual*:

1) **Home-based records** (vaccination cards). The best evidence is a legible date of vaccination on the home-based record (vaccination card) with a day, a month and a year.

2) **Health centre records.** It will be necessary to search for evidence of vaccination status in health facility records for children in the cluster whose caretaker says that they received some routine vaccinations locally, and if:
   - the caretaker does not show interviewers the vaccination card;
   - the card indicates some doses with a tick mark, but no date; or
   - the caretaker says that the child received some routine doses that are not recorded on the card.

3) **Recall, or verbal history of vaccination.** If there is no home-based record of vaccination, or if it is incomplete, the next level of evidence is a verbal *history* of vaccination by the caretaker (vaccination recall). Start by asking the caretaker the place of the injection (on the body) for injectable vaccines or act out putting drops in the mouth to ask about oral polio vaccine or rotavirus vaccines. Ask when the vaccine was received in relation to other documented vaccinations. Plan to use helpful visual aids matching the national vaccination practices when asking this question. Also ask the caretaker where the person went to receive the vaccination (e.g., clinic, outreach site, hospital, school, home). A child might have been vaccinated in a health centre different from the nearest one. In such a case it will not be possible to look for the record at the closest health centre.

For the complete *World Health Organization vaccination cluster surveys reference manual*, see:

- https://apps.who.int/iris/handle/10665/272820.

For further recommendations on harmonization vaccination coverage measures in household surveys, see:

- https://www.who.int/immunization/monitoring_surveillance/Surveys_White_Paper_immunization_2019.pdf?ua=1.

Annex 6: Example report templates and charts

This annex contains templates and examples for reporting on and visualizing BeSD data. These resources are non-prescriptive and aim to offer a helpful starting point for users of the BeSD tools.

Example table. Intention to accept vaccine across socio-demographic characteristics

	Total *n* = (%)	**Intention to get the recommended vaccine *n* (%)**	***P* value**
Gender Woman Man Non-binary Declined to respond			
Age (years) of caregiver 18–29 30–49 50–69 70+			
District D 1 D 2			
Employment Health worker Essential services worker Other			
Completed years of education 0 1–5 6–12 12+			

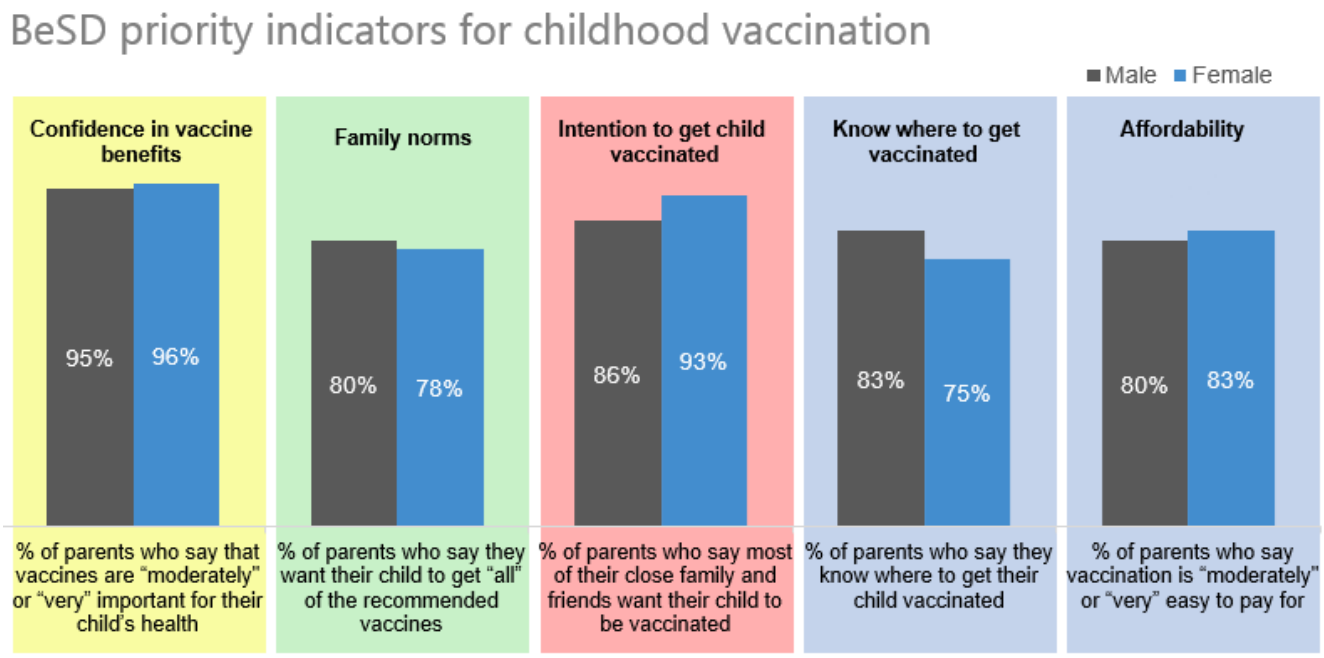
Example table. Univariate analysis and multivariate logistic regression model of vaccine acceptance and demographic variables

	Vaccine acceptance *n* (%)	**Unadjusted ORs (95% CI)**	***P* value**	**Adjusted ORs (95% CI)**	***P* value**
Gender of caregiver Woman Man Non-binary Declined to respond					
Age (years) 18–29 30–49 50–69 70+					
District D 1 D 2					
Completed years of education 0 1–5 6–12 12+					

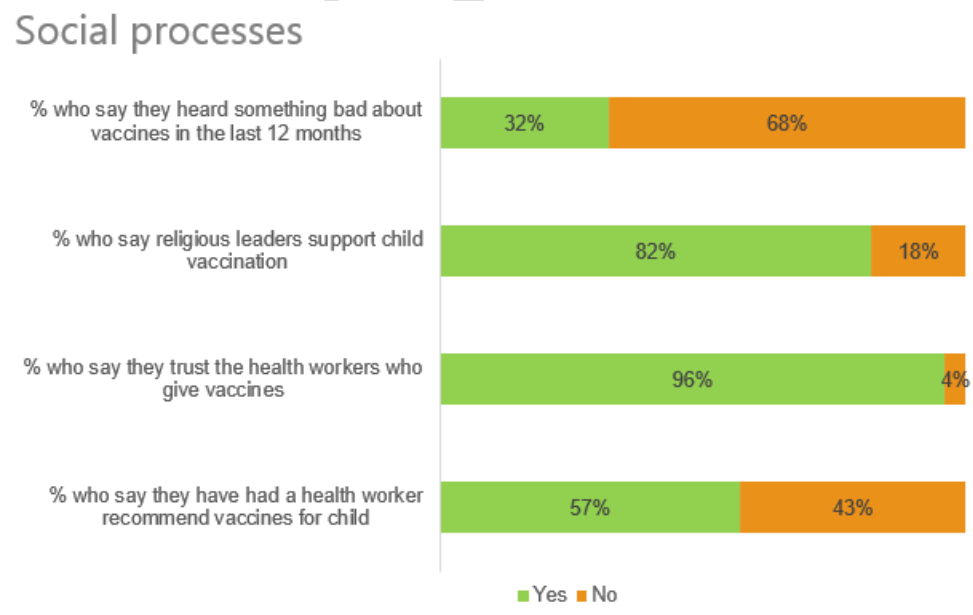
CI: confidence interval; OR: odds ratio.

6.1 BeSD data visualizations

The charts below offer initial examples of ways in which data may be represented visually. (Each visualization would also have a sample size indicated.)



Total sample (n=304); male (n=239), female (n=165).



BeSD childhood vaccination survey. All respondents (n=304).

6.2 BeSD reporting template

The adaptable template presented in this section offers an initial example of how to report BeSD findings.

Instructions for use:

- *Please fill in the following fields based on the guidance provided for each section. Either enter text directly or copy and paste from another document.*
- *Please provide full source citation and URLs; where relevant, include data visualizations and good-quality photographs.*

Country:
Date of investigation (months and year):
Focus area: e.g., childhood vaccination among migrant communities in…
Title:
Principal investigator full name and contact information:
Abstract: *Please provide a 1–2 short paragraph abstract/summary of the data-gathering activities, adding contextual relevance. Describe what the study was about and, briefly, how it was carried out. Describe in a few sentences the main findings and recommendations or next steps.*
Introduction: *a)* ***Problem and situation analysis.*** ***What was the research question?*** *Briefly describe the initial situation or challenge that was the basis for this work. Cite any comparative statistics or other sources to support this contextualization.*
Plan: *b)* ***Research methods.*** ***How did you plan to assess and address the problem?*** *Briefly describe the methods used and research protocol developed, including any rationale for decisions made on tools use, sampling, mode of implementation, etc. If the group had a working hypothesis, state this up front and clarify how the hypothesis would be tested.* Be sure to include: • overall research design, and sampling approach with justification • recruitment methods • how the data were handled, including how missing or incomplete data were dealt with • what analysis was done and why • how the interviews were conducted and recorded • ethical considerations and approval.

Investigate:

c) ***Evidence and analysis.***
What did the research reveal, and was this different from what you had expected to find? *Describe the findings resulting from the BeSD surveys or interviews.*

For BeSD survey reports:

- the response rate of the survey
- characteristics of the sample (e.g., age, gender, geographic location)
- the percentage of respondents who report willingness or intention to accept vaccines
- report on the BeSD priority indicators (descriptive statistics)
- association of vaccine uptake with priority indicators (and other BeSD survey constructs if measured) and demographics.

For BeSD in-depth interviews study reports:

- Describe how many interviews were undertaken and over what time period.
- Tell the story of the results, and how they relate to the research questions.
- Focus on the concepts and themes, and how they relate to the research questions.
- Give example quotes to illustrate the concept or theme.
- Describe any links between themes and concepts identified but take care to justify how and why these links were made, using the data as evidence.

Act:

What did you do with the findings? *Describe the intervention or strategy, how it was selected and developed and who was involved in the process. Describe how the intervention contributes to the overall outcomes. How were planning and preparation undertaken collaboratively with communities?*

This section could include the following topics as relevant:

a) ***Intervention***
What is the intervention? What or who does it involve? How was it decided on? Include any visuals to support a description of the intervention.

b) ***Partnerships, local structures, services and resources***
Describe the partnerships and collaboration mechanisms, the local structures, services, initiatives and resources that are available/unavailable to support implementation of the intervention. To what extent have stakeholders been involved?

c) ***Monitoring and evaluation***
What is the plan for tracking the progress and impact of the intervention selected? What measures, tools and procedures are being considered to gather feedback, monitor progress and evaluate results based on baselines?

d) *Describe* ***key successes and challenges*** *during implementation. What is the potential for* ***replication and scaling up****? (Optional)*

e) *Progress and results*

APLICABLE ONLY WHERE AN INTERVENTION HAS ALREADY BEEN IMPLEMENTED. In summary (3–4 paragraphs) describe the current situation in terms of progress so far. Provide (quantitative and qualitative) evidence from monitoring and evaluations used to validate results (see hierarchy of results below) and conclusions. What were the outcomes? What were the lessons learned in seeking to achieve the outcomes, and how can we factor these into the next programming cycle to ensure sustainability and scale-up?

- *Behaviour and social change*
- *Policy change*
- *Institutional/structural change*
- *Improved (access and quality) service delivery.*

Next steps:

Describe any planned next steps in implementation or any challenges in strategy as a result of this good practice to date (2–3 paragraphs).

Attachments:

- *Provide related data tables, charts and visualizations as available.*
- *Provide a list of available related literature about the situation/issue (with links, if possible).*
- *Provide any relevant high-quality photos.*
- *You are welcome to include quotes from staff, partners or members of the community.*
- *You are welcome to suggest additional persons to contact for more information.*

Annex 7: WHO policy on data collected in Member States

Policy on use and sharing of data collected in Member States by WHO outside the context of public health emergencies

Data are the basis for all sound public health actions and the benefits of data sharing are widely recognized, including scientific and public health benefits. Whenever possible, WHO wishes to promote the sharing of health data, including but not restricted to surveillance and epidemiological data.

In this connection, and without prejudice to information sharing and publication pursuant to legally binding instruments, by providing data to WHO, the Ministry of Health of your Country:

- confirms that all data to be supplied to WHO have been collected in accordance with applicable national laws, including data protection laws aimed at protecting the confidentiality of identifiable persons;
- agrees that WHO shall be entitled, subject always to measures to ensure the ethical and secure use of the data, and subject always to an appropriate acknowledgement of your Country:
    I. to publish the data, stripped of any personal identifiers (such data without personal identifiers being hereinafter referred to as "the Data") and make the Data available to any interested party on request (to the extent they have not, or not yet, been published by WHO) on terms that allow non-commercial, not-for-profit use of the Data for public health purposes (provided always that publication of the Data shall remain under the control of WHO);
    II. to use, compile, aggregate, evaluate and analyse the Data and publish and disseminate the results thereof in conjunction with WHO's work and in accordance with the Organization's policies and practices.

Except where data sharing and publication are required under legally binding instruments (IHR [International Health Regulations], WHO Nomenclature Regulations 1967, etc.), the Ministry of Health of your Country may in respect of certain data opt out of (any part of) the above, by notifying WHO thereof, provided that any such notification shall clearly identify the data in question and clearly indicate the scope of the opt-out (in reference to the above), and provided that specific reasons shall be given for the opt-out.

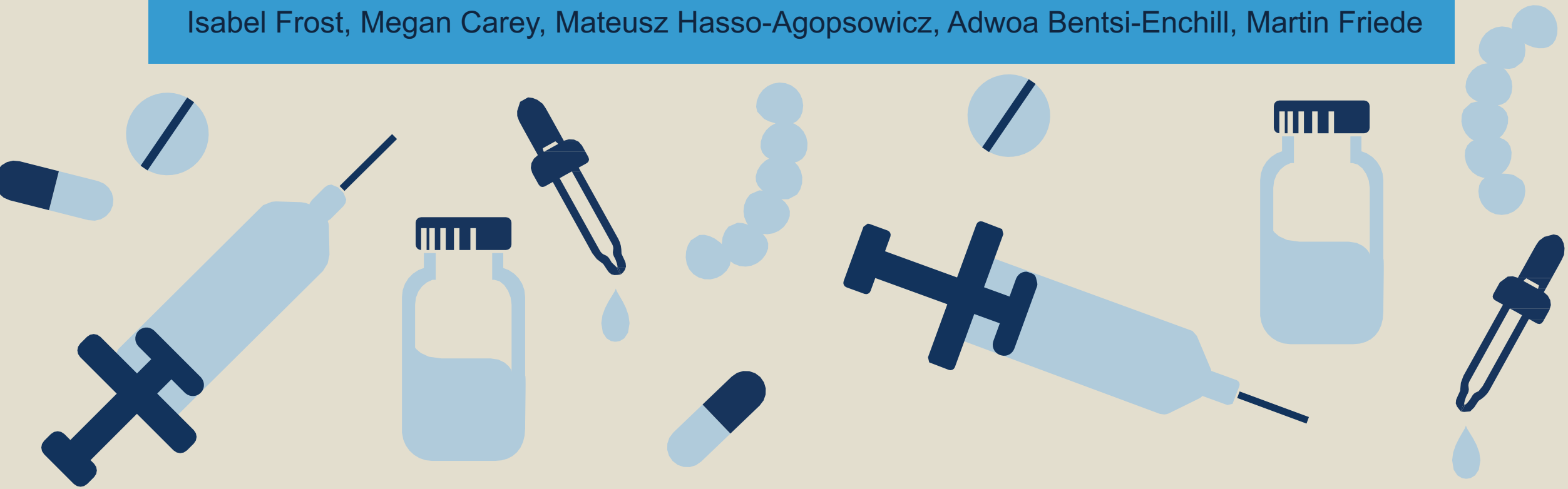
World Health Organization

Session 3

Developing a guidance on methodologies to measure the impact of vaccines in preventing antimicrobial resistance (AMR)

Development of guidance to measure the impact of vaccines on AMR

Isabel Frost, Megan Carey, Mateusz Hasso-Agopsowicz, Adwoa Bentsi-Enchill, Martin Friede



World Health Organization

Vaccines Against AMR

The problem of AMR...

4.95 million deaths
associated with bacterial AMR in 2019

28 million
people projected to fall into poverty worldwide due to AMR with up to **US$1 trillion global increase in healthcare cost** by 2050

...and the role of vaccines

- prevent AMR infections and reduce transmission of AMR
- reduce occurrence of disease symptoms associated with antibiotic use

- Under current coverage:
  - **PCV** prevents 23.8 million episodes of antibiotic-treated illness prevented among children under 5 yrs in LMICs every year;
  - **Rotavirus** vaccine prevents 13.6 million Lewnard *et al.*, 2020 *Nature*
- Universal coverage with both of these vaccines could prevent 40 million additional episodes
- **Influenza** vaccine reduces days of antibiotic use in adults by 28.1% Buckley *et al.*, 2019 *Clin Microbiol Infect.*
- In **typhoid** outbreak setting, Pakistan, TCV effectiveness was 95% (93–96) against culture-confirmed *S* Typhi, and 97% (95–98) against XDR *S* Typhi Yousafzai *et al.*, 2021 *Lancet GH*

Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Murray *et al.* 2022 *Lancet*
Drug-resistant infections: a threat to our economic future World Bank Report 2017

World Health Organization

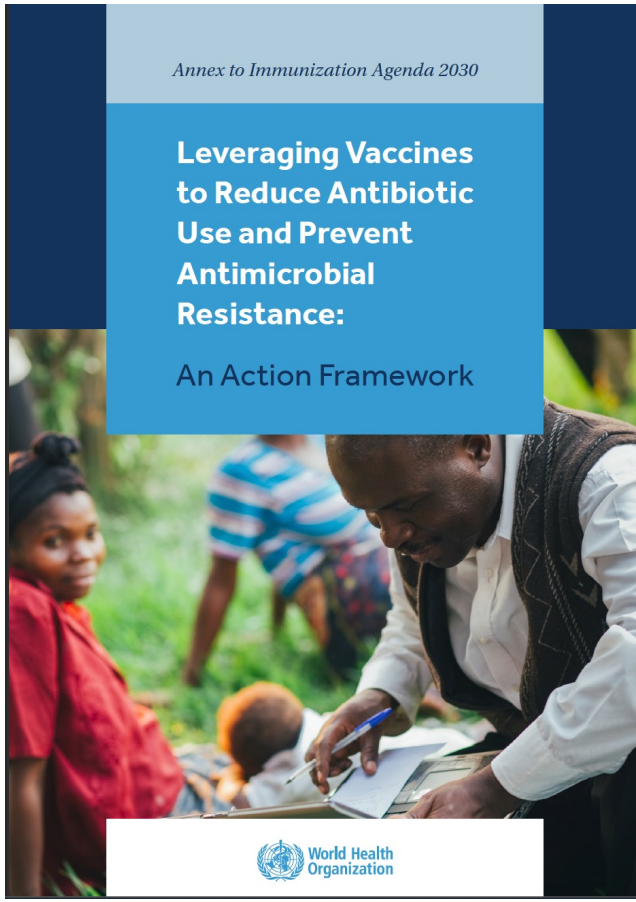
Vaccines Against AMR

WHO Program on Vaccines and AMR

The Immunization Agenda 2030

- envisions a world where everyone, everywhere, at every age, fully benefits from vaccines to improve health and well-being.
- **calls for research to understand the full value of vaccines**, beyond mortality, to guide decisions around vaccine development, introduction and use.
- highlights **critical role of vaccines in preventing AMR**

Action Framework on leveraging vaccines to reduce AMR published as supplement to IA2030



Action framework

Strategic Goals:

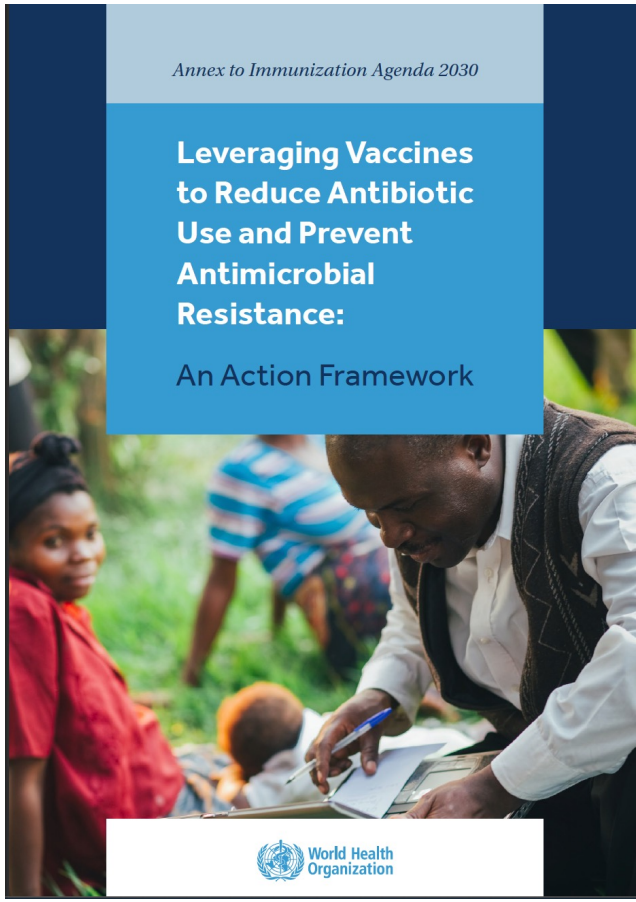
Expanding use of licensed vaccines to maximize impact on AMR

Develop new vaccines that contribute to prevention and control of AMR

Expanding and sharing knowledge of vaccine impact on AMR

Calls for:

- **Improved methodologies to increase collection and analysis of relevant data to assess vaccine impact on AMR, including antimicrobial use**
- **For normative bodies to provide guidance for …evaluation of vaccine impact on AMR and antibiotic use.**



Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance: A World Health Organization Action Framework
Vekemans *et al.* Clin Infect Dis. 2021 Aug 15; 73(4): e1011–e1017.

Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance: An Action Framework; Annex to Immunisation Agenda 2030

World Health Organization

Vaccines Against AMR

Measuring vaccine impact on AMR is complex

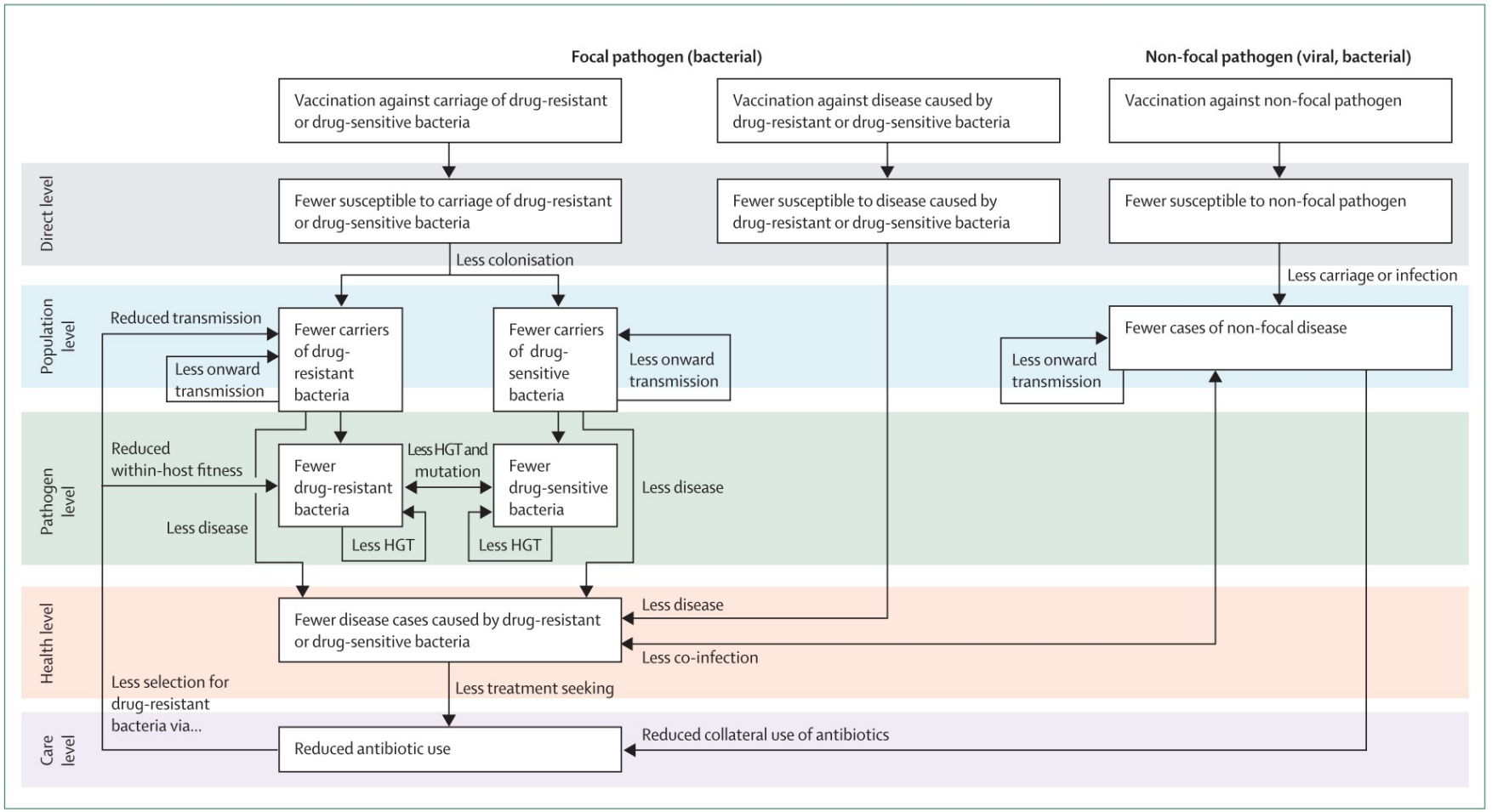


Figure 2: **Pathways through which vaccination against focal bacteria and non-focal bacteria and viruses can control antibiotic resistance. HGT=horizontal gene transfer.**

- Role of vaccines to combat AMR is **complex and varies by context**: geography (high/low-resource settings), vaccine, target population, pathogen type (viral /bacterial /parasitic /fungal), etc.
- Resulting **heterogeneity in studies**, both in terms of data collection, types of indicators, and analysis
- **Creates difficulties in: comparing results** between studies, prioritizing funding and research, decision-making for vaccine use, including AMR indicators in clinical trials

Use of mathematical modelling to assess the impact of vaccines on AMR. Atkins *et al.* 2017 *Lancet Infectious Diseases*

World Health Organization

Vaccines Against AMR

Existing guidance

- **Guidelines on vaccine efficacy** and conduct of clinical trials have been produced by many official bodies including WHO, FDA (US), EMA (EU), PHE (UK), NMPA (China) and others.
  - AMR was mentioned 3/19 documents reviewed, also included guidance on laboratory work that could be applicable to measuring AMR;
- **Guidelines on measuring AMR and antibiotic consumption**
  - Multiple produced by WHO AMR division

Gap identified: **need for guidance that builds on existing documents to bridge the gap between measuring vaccine effectiveness/efficacy and burden of AMR to assess impact of vaccines on AMR**

GLASS whole-genome sequencing for surveillance of AMR, WHO, 2021
GLASS method for estimating attributable mortality of AMR BSI, WHO, 2021

World Health Organization

Vaccines Against AMR

Guidance on methodologies to measure the impact of vaccines on AMR

*There is a need to develop **guidance** for the harmonization of methodologies to **measure the impact of vaccines on antimicrobial resistant infections and antibiotic use.***

Deliverables

Stakeholder consultation

Meeting to discuss expected project outcomes, develop/iterate workstreams, agree pathogen scope, and develop detailed methodology.

Needs analysis

Series of interviews, to understand needs, challenges and opportunities relating to harmonization of methodologies.

Landscape analysis

Literature review of existing methodologies.

Stakeholder consultation

Meeting to consolidate findings and develop final guidance document.

World Health Organization

Vaccines Against AMR

Scope: Indicators of AMR burden

Indicators of AMR include the following (others may be identified in the study):

Proposed

- **Prevalence** of AMR (% of infections that are resistant to antimicrobials in a given time),
- **Incidence** of infections caused by AMR pathogens (DRI, the number of resistant infections over time),
- Number of **deaths** due to AMR pathogens
- Antibiotic **consumption**,
- **Economic** burden,

Likely to be beyond scope

- Impact on **equity and social justice**,
- Impact on the **microbiome**,
- **Evolution** of resistant strains,
- Impact on the occurrence of **secondary infections** due to AMR pathogens.

Scope: Stratification of AMR indicators

Stratify and evaluate the appropriateness of methodologies:

Stratification	Example categories	Example considerations
Pathogen type	Enteric; Sexually Transmitted; Nosocomial; Respiratory	• Different types of sampling are possible • Different epidemiological considerations • Sampling in community vs hospital setting
Type of study	Phase 2; Phase 3; post licensure	• Emergence of resistant strains can be measured in an epidemiological study post vaccine licensure but is unlikely to be measured during a clinical trial • Size of study and type of sampling
Pathogen Family	Bacteria; viruses; parasites; fungi	• For viruses more likely to consider averted antibiotic consumption rather than resistant strains
Context	Local Epidemiology; High/Low resource settings	• E.g., the impact of a typhoid vaccine should be measured in countries with high burden of resistant typhoid • Different availability of local research tools and expertise

Case Studies:

Typhoid

- Challenging AMR burden
- New vaccine being introduced to countries

TB

- High AMR burden
- Late stage vaccine

Malaria

- Growing AMR threat
- Late stage vaccine

World Health Organization

Vaccines Against AMR

1 Virtual Stakeholder Consultation 14/15 March

Aims:

- To **discuss and iterate on the work plan** on generating guidance to measure the impact of vaccines on AMR, specifically focusing on:
  - Agreement on the **high-level approach** to develop the guidance;
  - Agreement on the **scope of the guidance**: included vaccines, type of studies, and indicators to measure AMR;
  - Agreement on the **methodological approach to conduct a landscape analysis** of needs, opportunities and challenges in measuring the impact of vaccines in preventing AMR;
  - Agreement on the **methodological approach to conduct a literature review** to identify ways of measuring the impact of vaccines in preventing AMR.

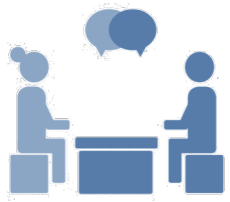
Output: *meeting report with developed and endorsed workstreams required to complete this project, as well as a detailed approach to conduct the needs and landscape analyses*

2 Needs Analysis Stakeholder Interviews

Aim: *To understand **needs, challenges and opportunities** relating to harmonization of methodologies to measure the impact of vaccines on AMR.*

- **40-50 Interviews** of
  - **Principal Investigators, clinicians, study coordinators** (industry/academia), who write protocols and manage research projects from Phase 2 to post-licensure studies.
  - **Funders, policymakers, regulators, Implementation program/EPI focal points** to understand needs in terms of connecting to policy/approval/funding and considering vaccine effectiveness
- **Globally representative** to ensure diverse needs in different contexts incorporated.
- Analysis by themes and suitability of indicators, findings will inform landscape analysis and final guidance

2 Needs Analysis Stakeholder Interviews



Questions to interviewees will cover:

Needs:

- What are the **required data outputs** needed to facilitate decisions about vaccine development, introduction and use?
- What are **the pros/cons of different indicators** in different settings?
- What guidance is needed to **harmonise the collection of such data** outputs?
- **Policymakers/ funders/ regulators data needs** for decision-making?

Challenges:

- What are the **current challenges** that prevent or hinder the harmonization of methodologies to measure the impact of vaccines on AMR and antibiotic use?

Opportunities:

- Where are **the opportunities for harmonizing methods** to measure the impact of vaccines on AMR and antibiotic use (aka low-hanging fruit)?

3 Landscape analysis Systematic review

Aim	• Search for studies of vaccine impact on AMR • Assess suitability of methodologies
Inclusion /Exclusion Criteria	• From past 20 years • Impact on human health only (exclude animals but include some aspect of environment, e.g. Hospital sewage samples and foodborne pathogens). • Modelling out of scope; focus on primary data collection. • Grey literature: documents relating to measuring AMR (without vaccine impact) including previous WHO reports
Stratify data	• Pathogen type (enteric/respiratory/etc); type of study; pathogen family (virus/parasite/bacteria/fungi); context (high/low resource/local epidemiology)
Search terms	vaccine AND ((antimicrobial OR antibiotic) AND (resistance OR resistant))
Databases	PubMed, Web of Science, etc.
Extract data	Pathogen; vaccine; phase of development of vaccine; hospital/community; low/high resourced setting; country; type of study (economic/health burden); study funder (academic/ government/ industry/ etc); experimental methods; indicators

4 Face-to-face stakeholder consultation generating guidance

Face-to-face Expert Consultation

- **20-30 experts**: Members of the VAC-AMR working group, representatives from related organizations, research institutions, pharmaceutical companies, funders, and policy and decision makers.
- Present **findings from needs analysis and landscape analysis**
- Use findings and expert consensus to **generate guidance**

Online Public Consultation

- **Draft guidance will be shared on the WHO's website** for 3 weeks, disseminated widely among AMR and vaccine experts, academia, industry and funders, to review the proposed approach.
- **Comments will be considered** for incorporation into the guidance.

Generate Guidance document

- Combining **Needs Analysis, Landscape Analysis and Guidance**.
- WHO **report** and peer reviewed **publication**

World Health Organization

Vaccines Against AMR

Case study Typhoid Conjugate Vaccines

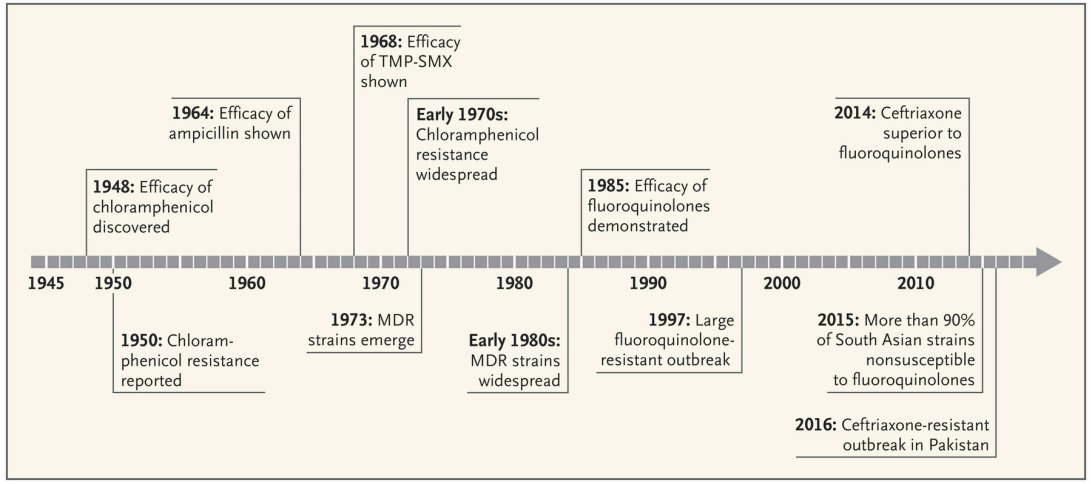
Justification:

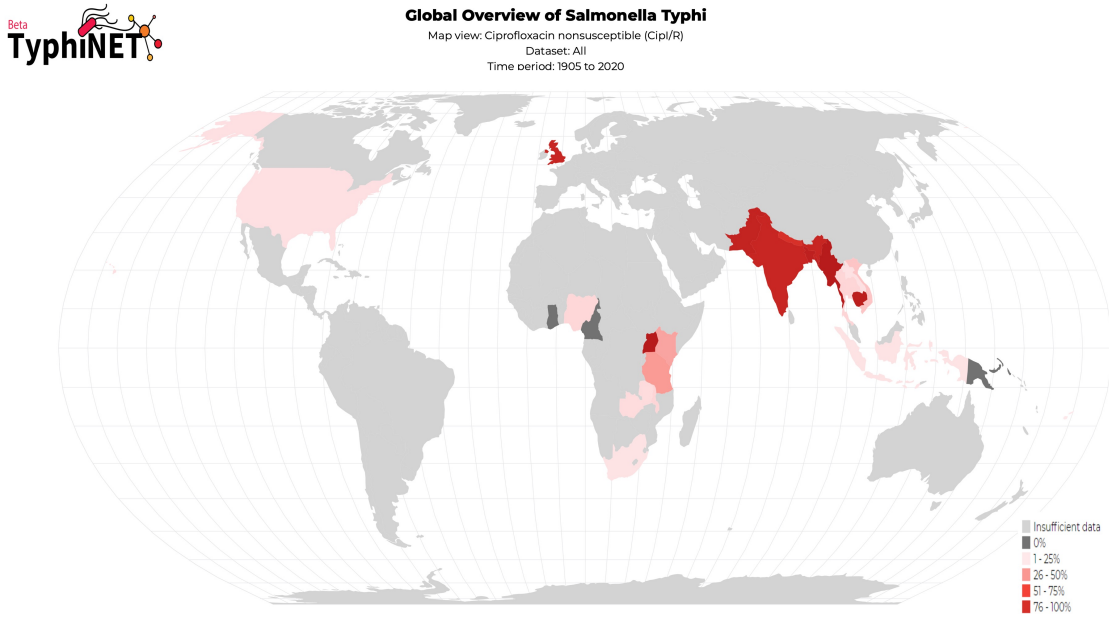
- Two Typhoid Conjugate Vaccines (TCVs) are now WHO prequalified– Typbar-TCV® (2017) and TYPHIBEV ® (2020)
    - Countries are just starting to introduce, so now is a good time to develop guidance to help countries assess impact on AMR
- There is a robust vaccine development pipeline, with several additional vaccine candidates in late-stage development
    - Manufacturers could still incorporate additional AMR-driven endpoints into clinical trial design and internal prioritization discussions
- AMR poses a significant threat to effective typhoid control and drug-resistant strains of Salmonella Typhi (S. Typhi) are very common, particularly in South Asia

Antimicrobial Resistance

- **Multidrug resistance** (MDR; resistant to chloramphenicol, trimethoprim-sulfamethoxazole, ampicillin) became widespread in the 1990s
- **Fluoroquinolones** became first-line treatment, but resistance became common in South and Southeast Asia in the 2000s
- This led to use of **third-generation cephalosporins** for treatment of typhoid in Asia, but the emergence and spread of **extensively-drug resistant** (XDR; MDR + resistant to fluoroquinolones, and third-generation cephalosporins) typhoid in Pakistan left azithromycin as the only available oral antimicrobial in South Asia
- The recent emergence of **azithromycin-resistant typhoid** in Bangladesh, Pakistan, India, and Nepal threatens effective oral treatment of typhoid in the region
- **We are rapidly approaching the end of effective oral antibiotics for treatment of typhoid fever**

Timeline of AMR in *S.* Typhi



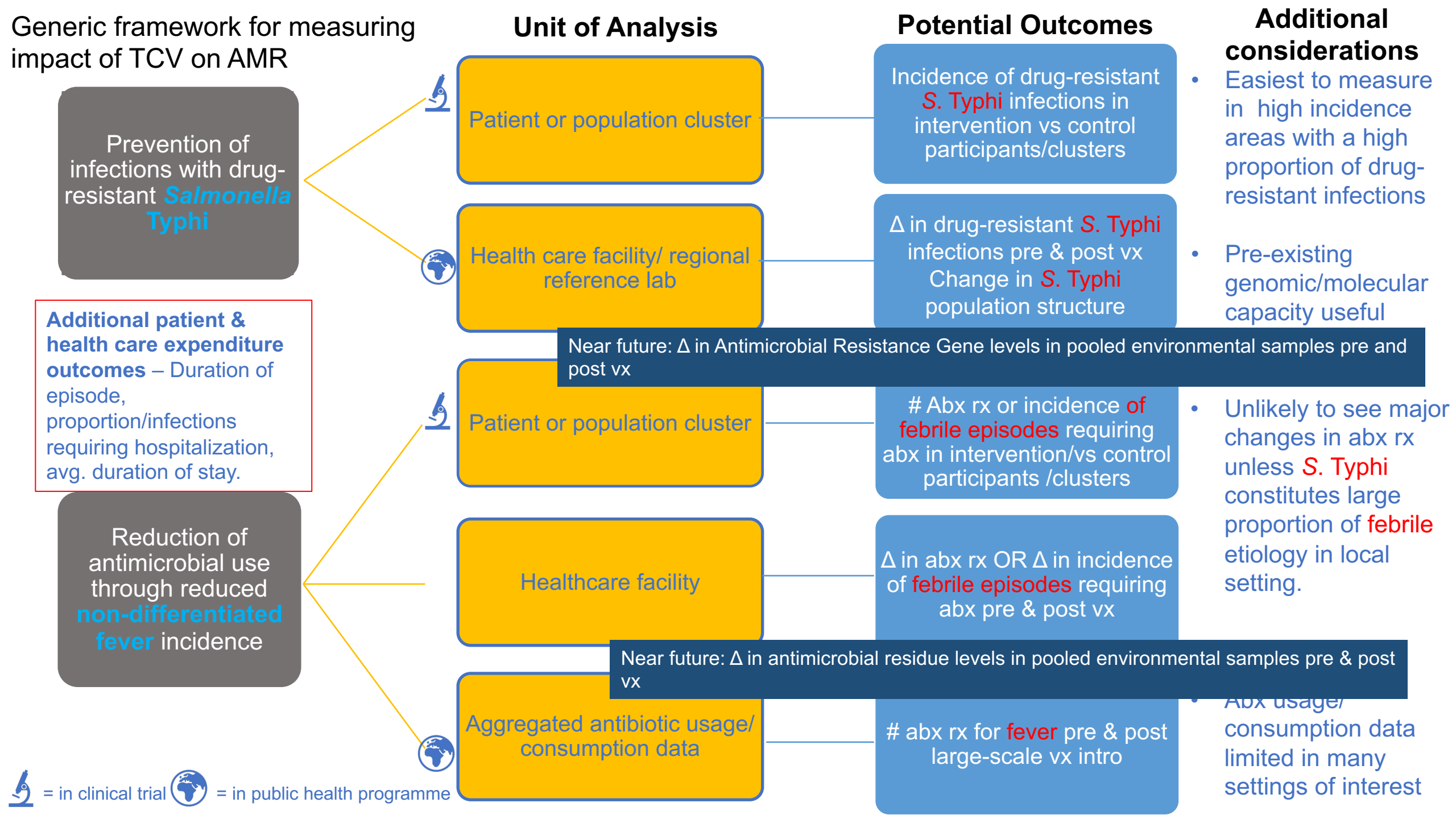


Figures from: Andrews JR, Qamar FN, Charles RC, Ryan ET. **Extensively drug-resistant typhoid—are conjugate vaccines arriving just in time?** N Engl J Med 2018; 379:1493–5. and TyphiNET Beta (typhi.net)

World Health Organization

Vaccines Against AMR

Generic framework for measuring impact of TCV on AMR



Questions for IVIR-AC

- Does IVIR-AC agree with the proposed scope in terms of pathogens, classes of pathogens, indicators of AMR, and study types?
- Is the selection of case study pathogens appropriate?
- Is the methodological approach to developing the needs analysis, landscape analysis and guidance appropriate?
- Is the approach proposed for typhoid appropriate?

Project Timeline

Task	Output	Timing
1. Kick off meeting	Meeting report	March 2022
2. Interview stakeholders	Needs analysis	May-August 2022
3. Review Literature	Landscape analysis	May-August 2022
4. Expert Consultation	Guidance	October 2022
5. Public Consultation	Add comments to guidance	November 2022
	Draft technical document combining needs analysis, landscape analysis and guidance, in addition to peer reviewed publication	December 2022

Annex to Immunization Agenda 2030

Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance:

An Action Framework

World Health Organization

Annex to Immunization Agenda 2030

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ISBN XXXXX-XXXXXXX

Suggested citation. Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance: An Action Framework: World Health; 2020. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at xxxxxx

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Design and layout by Lushomo.

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Printed in Switzerland.

Contents

List of illustrations

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 sub-national 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 consul-tative 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 dis-cussions 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 institu-tions, 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 oppor-tunity 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 contribu-tors: 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	ACTIONS	AUDIENCE
1 Increase coverage of vaccines with impact on AMR.	**1a.** Countries should implement existing vaccine-related recommendations of the Global Action Plan on AMR.	
	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.	
2 Update recommendations and normative guidance in both the vaccine and AMR sectors to include the role of vaccines to control AMR.	**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.	
	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.	
	2c. 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.	
	2d. 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.	
3 Improve awareness and understanding of the role of vaccines in limiting AMR through effective communication, education and training.	**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.	

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

GOAL

Develop new vaccines that contribute to prevention and control of AMR

OBJECTIVES	ACTIONS	AUDIENCE
4 Bridge the funding gap for R&D of new vaccines with potential for global AMR impact.	**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.	
5 Develop regulatory and policy mechanisms to accelerate approval and use of new vaccines that can reduce AMR.	**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 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&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 labeling 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.	

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

GOAL

Expand and share knowledge of vaccine impact on AMR

OBJECTIVES	ACTIONS	AUDIENCE
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

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]

---

1 Gapminder [Internet]. [cited 2020 Feb 26]. Available from: www.gapminder.org/data/

2 OECD. Stemming the Superbug Tide Just A Few Dollars More. OECD Publ. 2018.

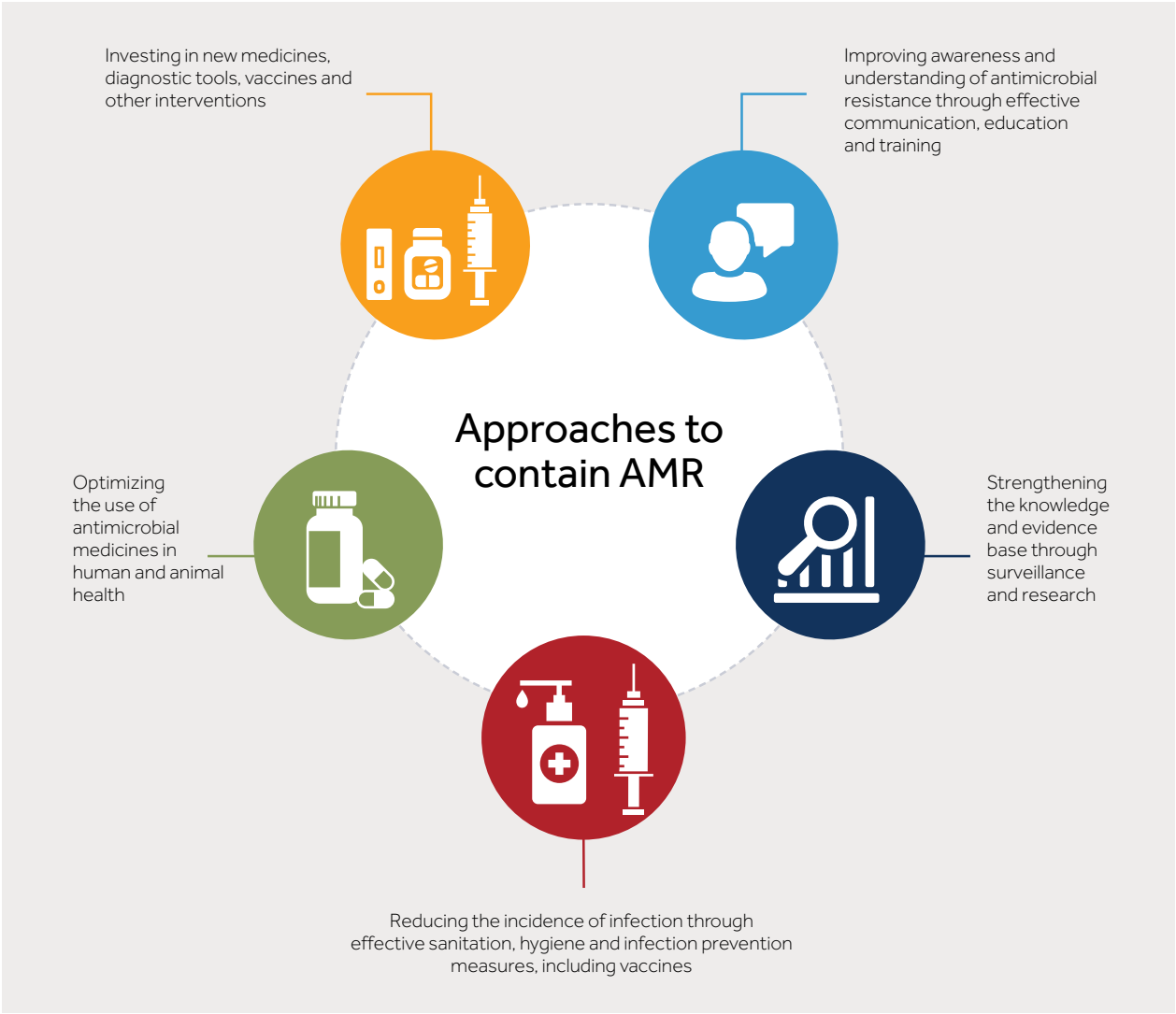
3 de Kraker MEA, Stewardson AJ, Harbarth S. Will 10 Million People Die a Year due to Antimicrobial Resistance by 2050? PLoS Med. 2016; 13(11).

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,[4] 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.[5]

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.[6] 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

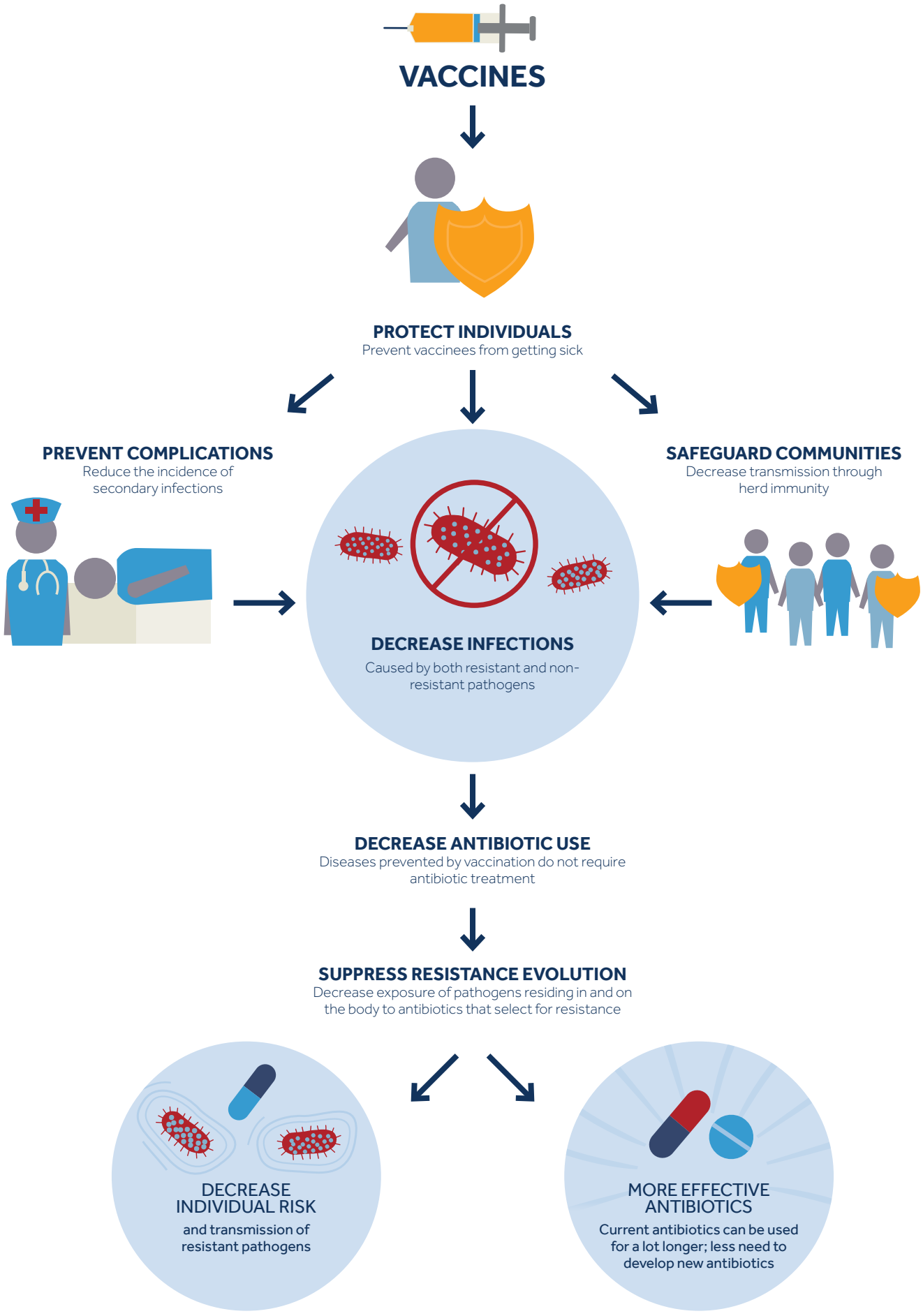


4 World Health Organization. Global action plan on antimicrobial resistance. WHO Press. 2015.

5 Interagency Coordination Group on Antimicrobial Resistance. No time to wait: securing the future from drug-resistant infections. 2019.

6 Kallberg C, Ardal C, Blix HS, Klein E, Martinez EM, Lindbæk M, et al. Introduction and geographic availability of new antibiotics approved between 1999 and 2014. PLoS One. 2018; 13(10).

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

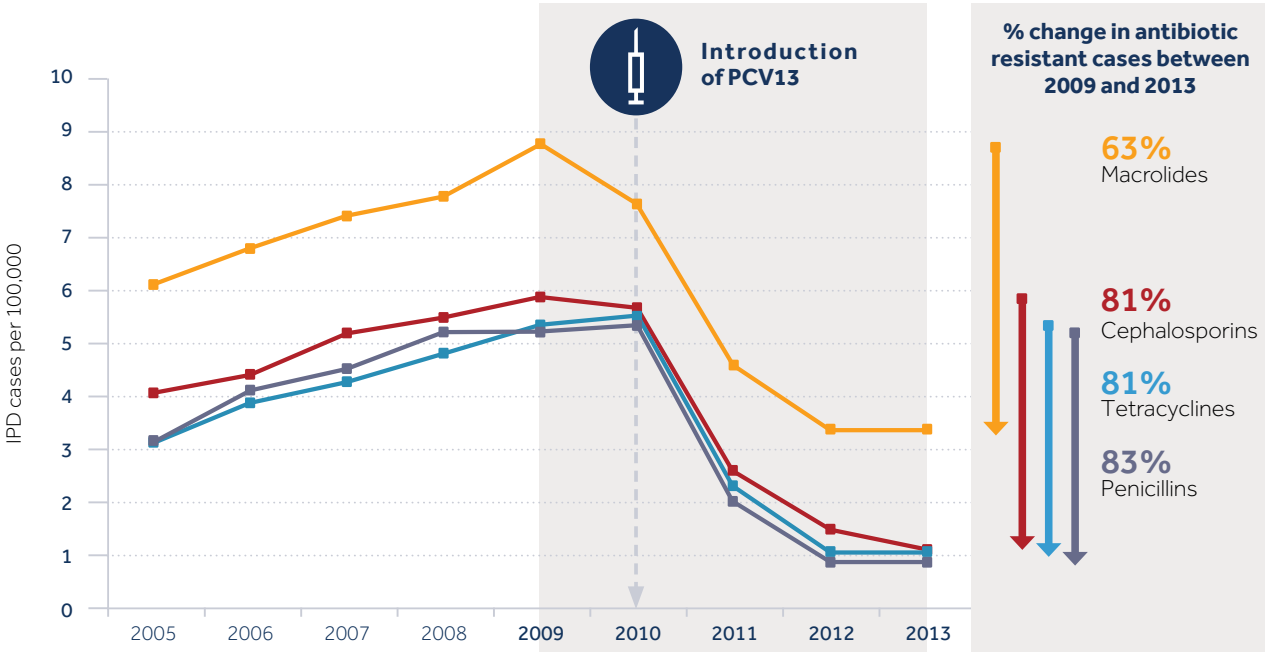
The most direct way in which vaccines contribute to prevention and control of AMR is by reducing the incidence of disease from resistant pathogens (Fig. 2). Vaccines against *S. pneumoniae*, Hib, *Salmonella* Typhi, *Bordetella pertussis,* tuberculosis (TB), and *Neisseria meningitidis* can prevent morbidity and mortality due 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

Fig. 3. Impact of pneumococcal vaccine on rates of drug-resistant invasive pneumococcal disease (IPD) in the United States of America[a, b]



IPD: invasive pneumococcal disease; PCV: pneumococcal conjugate vaccine.

a Jansen KU, Knirsch C, Anderson AS. The role of vaccines in preventing bacterial antimicrobial resistance. Nat Med. 2018;24(1):10-9.

b Tomczyk S, Lynfield R, Schaffner W, Reingold A, Miller L, Petit S, et al. Prevention of Antibiotic-Nonsusceptible Invasive Pneumococcal Disease with the 13-Valent Pneumococcal Conjugate Vaccine. Clin Infect Dis. 2016; 62(9).

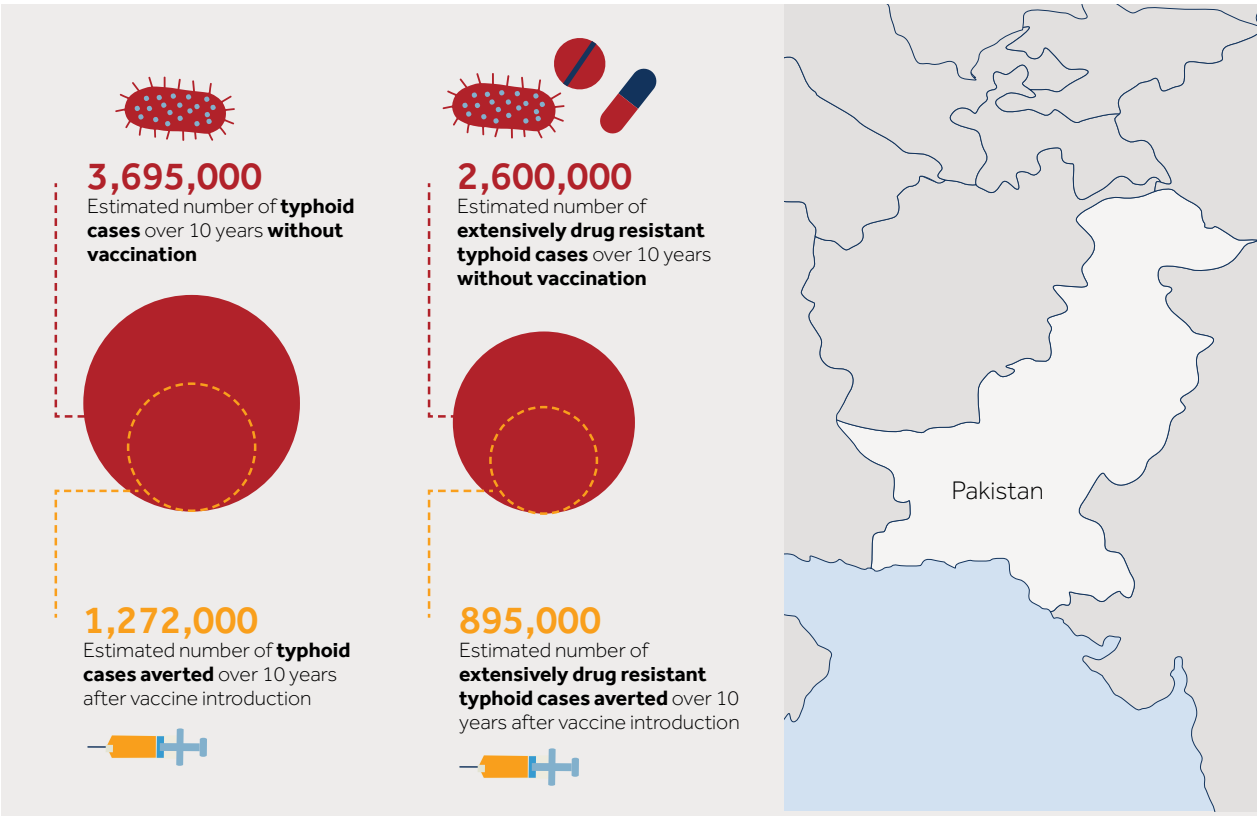
7 Klugman KP, Black S. Impact of existing vaccines in reducing antibiotic resistance: Primary and secondary effects. Proceedings of the National Academy of Sciences of the United States of America. 2018;115(51).

8 Jorgensen JH, Doern G V., Maher LA, Howell AW, Redding JS. Antimicrobial resistance among respiratory isolates of *Haemophilus influ-enzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* in the United States. Antimicrob Agents Chemother. 1990;34(11).

9 World Health Organization. Typhoid vaccine: WHO position paper - March 2018. Wkly Epidemiol Rec. 2018;37(2)

10 World Health Organization (WHO). Pakistan first country to introduce new typhoid vaccine into routine immunization programme [Internet]. 2019 [cited 2020 Feb 26]. Available from: http://www.emro.who.int/pak/pakistan-news/pakistan-first-country-to-introduce-new-typhoid-vaccine-into-routine-immunization-programme.html

Fig. 4. Estimated impact of typhoid vaccine on drug-sensitive and -resistant typhoid in Pakistan



The estimated number of typhoid cases over 10 years without vaccination, and the estimated number of typhoid cases averted over 10 years after vaccine introduction was calculated assuming vaccine efficacy of 82% at 1 year of follow-up.[a] The estimated number of extensively drug resistant typhoid cases over 10 years without vaccination, and the estimated number of extensively drug resistant typhoid cases averted over 10 years after vaccine introduction were calculated assuming that 70.4% of reported cases in Sindh Province, Pakistan were extensively drug resistant.[b]

[a] Bilcke J, Antillón M, Pieters Z, Kuylen E, Abboud L, Neuzil KM, et al. Cost-effectiveness of routine and campaign use of typhoid Vi-conjugate vaccine in Gavi-eligible countries: a modelling study. Lancet Infect Dis. 2019;19(7)

[b] Federal Disease Surveillance and Response Unit Pakistan. WEEKLY FIELD EPIDEMIOLOGY REPORT. 2020;2(02).

(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.[11, 12] As expressed in the Global Action Plan on AMR[13] and in a 2019 report to the UN Secretary-General,[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.[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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11 World Organisation for Animal Health (OIE). Report of the meeting of the OIE Ad Hoc group on prioritisation of diseases for which vaccines could reduce antimicrobial use in animals. Paris; 2015.

12 World Organisation for Animal Health (OIE). Report of the meeting of the OIE Ad Hoc group on prioritisation of diseases for which vaccines could reduce antimicrobial use in cattle, sheep, and goats [Internet]. 2018. Available from: https://www.oie.int/fileadmin/SST/adhocreports/Diseases%20for%20which%20Vaccines%20could%20reduce%20Antimicrobial%20Use/AN/AHG_AMUR_Vaccines_ruminants_May2018.pdf

13 World Health Organization. Global action plan on antimicrobial resistance. WHO Press. 2015.

14 Interagency Coordination Group on Antimicrobial Resistance. No time to wait: securing the future from drug-resistant infections. 2019.

15 World Health Organization. Global Antimicrobial Resistance Surveillance System (GLASS) Report Early implementation. 2017.

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.[a] 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.[b] 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 fimbrial 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.

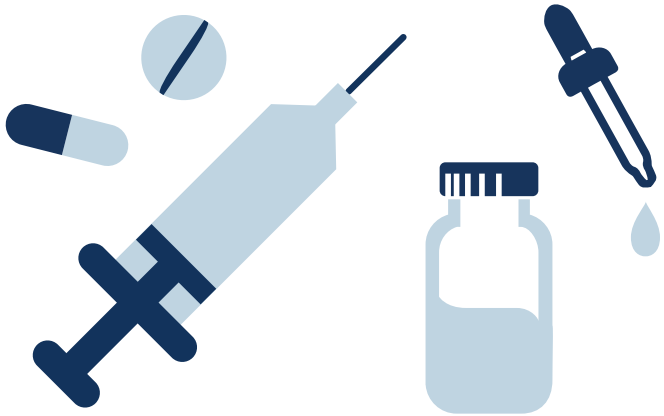
The **"collect data, explore alternatives"** cluster is composed of pathogens for which significant gaps remain, or alternative control strategies may be preferable. *S.* Paratyphi has low incidence and low associated mortality and morbidity. Uptake of a standalone vaccine is unlikely and combination 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.

[a] Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibi-otics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3).

[b] Vaccines to tackle drug resistant infections: An evaluation of R&D opportunities. 2018.

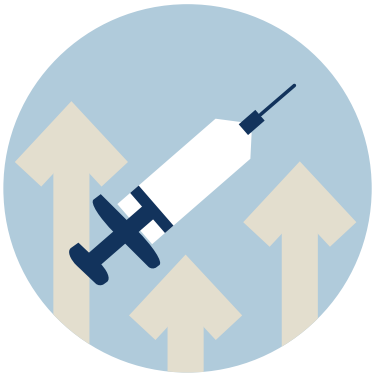
2. Strategic vision

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

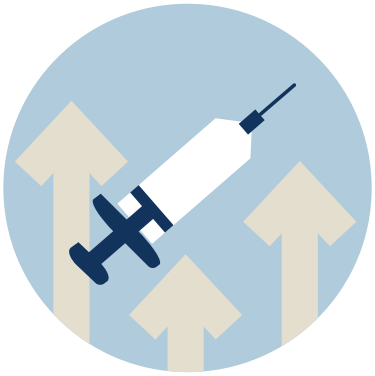
Specific objectives and priority actions in three goal areas will significantly enhance the contribution of vaccines to the control of AMR. These goals are:



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



Goal 1.

Expand use of licensed vaccines to maximize 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).[16] 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[17] 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

16 World Health Organization. Global action plan on antimicrobial resistance. WHO Press. 2015.
17 World Health Organization (WHO). Immunisation Agenda 2030: A Global Strategy to Leave No One Behind. 2020.

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

Vaccine	WHO recommendation	Global coverage in 2018[a]	WHO coverage target[b]	Vaccine impact on AMR
PCV	All children, through routine immunization.	47%	90% nationally, 80% at district level.	Reduces resistant and non-resistant pneumococcal disease; reduces antibiotic use in children.[c]
TCV	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.	NA	Access to be prioritized in settings with high endemicity and high levels of AMR.	Modelling suggests vaccine use will proportionally reduce incidence of resistant and non-resistant typhoid, including number of chronic typhoid carriers.[d]
Hib vaccine	All children, through routine immunization.	72%	90% nationally, 80% at district level.	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 <5 years.[c]
Influenza vaccines	All pregnant women, children 6-59 months, adults >65 years, people with chronic medical conditions and health-care workers.	NA	Varies according to risk group.	Good evidence that influenza vaccine reduces antibiotic use by reducing misuse of antibiotics and treatment of secondary bacterial infections.[e]
Rotavirus vaccine	All children, through routine immunization.	35%	90% nationally, 80% at district level.	Expected to reduce antibiotic use but no confirmatory data available.
Measles vaccine	All children, through routine immunization.	69%	90% nationally, 80% at district level	Expected to reduce antibiotic use against secondary bacterial complications, but no confirmatory data available.

NA: not available; PCV: pneumococcal conjugate vaccine; TCV: typhoid conjugate vaccine; WHO: World Health Organization.

[a] World Health Organization (WHO). Global and regional immunization profile. 2019.

[b] WHO. Global Vaccine Action Plan 2011-2020 [Internet]. Available from: https://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/

[c] 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).

[d] Bilcke J, Antillón M, Pieters Z, Kuylen E, Abboud L, Neuzil KM, et al. Cost-effectiveness of routine and campaign use of typhoid Vi-conjugate vaccine in Gavi-eligible countries: a modelling study. Lancet Infect Dis. 2019;19(7).

[e] Buckley BS, Henschke N, Bergman H, Skidmore B, Klemm EJ, Villanueva G, et al. Impact of vaccination on antibiotic usage: a system-atic review and meta-analysis. Clinical Microbiology and Infection. 2019;25(10).

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.

2c. 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.

2d. 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.

Fig. 5. Visuals from the International Vaccine Institute's advocacy campaign about the contribution of vaccines in the fight against AMR[a]

[a] International Vaccine Institute. IVI: World antibiotic awareness week 2019 [Internet]. 2019 [cited 2020 Feb 26]. Available from: https://www.ivi.int/world-antibiotic-awareness-week-2019/

Goal 2.

Develop new vaccines that contribute to prevention and control of AMR

New vaccine R&D is an integral part of the Global Action Plan on AMR.[18] Addressing AMR will require new tools and technologies to complement currently available strategies and interventions.[19] Few new antimicrobials have been developed recently or are anticipated to be available soon, and all are threatened by the emergence of resistance.[20] 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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18 World Health Organization. Global action plan on antimicrobial resistance. WHO Press. 2015.

19 World Health Organization (WHO). Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries. A WHO practial toolkit. 2019.

20 Årdal C, Balasegaram M, Laxminarayan R, McAdams D, Outterson K, Rex JH, et al. Antibiotic development — economic, regulatory and societal challenges. Nat Rev Microbiol. 2019;18(5).

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

Target pathogen and disease	Burden	AMR-related impact	Vaccine outlook
M. tuberculosis, tuberculosis (TB)	A quarter of global population latently infected;[a] in 2019, 10 million people fell ill with TB and 1.4 million died.[b]	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.[b]	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.[c]
N. gonorrhoeae, pelvic inflammatory disease, infertility	78 million new cases per year among people aged 15-49 years;[d] can cause infertility and other severe sequelae.	Once universally susceptible to antibiotics, strains resistant to every current class of antibiotic have emerged; complete treatment failure has been reported.[e]	*N. gonorrhoeae* shares 80-90% of its genetic sequence with *N. meningitidis*, a common cause of meningitis. There is some evidence that type B *N. meningitidis vaccine* partially protects against some *N. gonorrhoeae,* suggesting a vaccine is feasible.[f]
Plasmodium falciparum, malaria	228 million cases worldwide in 2018, 405 000 deaths.[g] Important driver of antibiotic use for non-specific febrile illness in high endemicity areas.	Artemisinin resistance emerged in South-East Asia in early 2000s; several artemisinin combination therapies now failing.[g] Potential to reduce malaria-driven antibiotic use.	RTS,S/AS01 vaccine provides partial protection in young children, showing that a vaccine is feasible.[h] RTS,S/AS01 is in pilot implementation through routine immunization programmes in Ghana, Kenya and Malawi. Other candidates continue to be developed.
RSV, respiratory disease	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.	Potential to reduce RSV-driven antibiotic use.	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.
Enterotoxigenic Escherichia coli (ETEC) and *Shigella* Gastroenteritis	ETEC caused 51 186 deaths globally including 18 669 deaths in children under 5 years old in 2016.[i] *Shigella* caused 212 438 deaths globally including 63 713 in children under 5 years old in 2016.[i] Contributors to long-term morbidity such as malnutrition and stunting.	High and growing rates of multidrug resistance.	Several candidate vaccines are in development. Controlled human infection models may be able to accelerate clinical development.

BCG: bacille Calmette-Guérin (vaccine); RSV: Respiratory Syncytial Virus.

[a] Houben RMGJ, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLOS Med. 2016;13(10).

[b] World Health Organization (WHO). Global Tuberculosis Report 2020. 2020.

[c] Tait DR, Hatherill M, Der Meeren O Van, Ginsberg AM, Van Brakel E, Salaun B, et al. Final analysis of a trial of M72/AS01E vaccine to prevent tuberculosis. N Engl J Med. 2019;381(25).

[d] Newman L, Rowley J, Hoorn S Vander, Wijesooriya NS, Unemo M, Low N, et al. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. PLoS ONE. 2015;10(12).

[e] Eyre DW, Sanderson ND, Lord E, Regisford-Reimmer N, Chau K, Barker L, et al. Gonorrhoea treatment failure caused by a *Neisseria gonorrhoeae* strain with combined ceftriaxone and high-level azithromycin resistance, England, February 2018. Eurosurveillance. 2018;23(27).

[f] Azze RFO. A meningococcal B vaccine induces cross-protection against gonorrhea. Clin Exp Vaccine Res. 2019;8(2)

[g] World Health Organization (WHO). World Malaria Report 2019. 2019.

[h] Olotu A, Fegan G, Wambua J, Nyangweso G, Leach A, Lievens M, et al. Seven-year efficacy of RTS, S/AS01 malaria vaccine among young african children. N Engl J Med. 2016;374(26).

[i] Khalil IA, Troeger C, Blacker BF, Rao PC, Brown A, Atherly DE, et al. Morbidity and mortality due to *shigella* and enterotoxigenic *Escherichia coli* diarrhoea: the Global Burden of Disease Study 1990-2016. Lancet Infect Dis. 2018;18(11).

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.

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.

Wellcome and the EDCTP Partnership calls for proposals. Calls for proposals for vaccine development and/or evaluation of the impact of vaccines on AMR were issued by both Wellcome and the EDCTP in 2019. For more information see https://wellcome.ac.uk/funding/schemes/impact-vaccines-antimicrobial-resistance and http://www.edctp.org/call/new-drugs-and-vaccines-for-priority-pathogens-in-antimicrobial-resistance-2019/.

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.

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/

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.

BOX 5 Regulatory pathways

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.

Goal 3.

Expand and share knowledge of vaccine impact on AMR

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.[21] 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.

[21] Buckley BS, Henschke N, Bergman H, Skidmore B, Klemm EJ, Villanueva G, et al. Impact of vaccination on antibiotic usage: a systematic review and meta-analysis. Clinical Microbiology and Infection. 2019;25(10).

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/

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/

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/

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

https://www.cdc.gov/drugresistance/intl-activities/amr-challenge.html

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/

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

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/

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/

COMBACTE fights antimicrobial resistance by speeding up the development of new antibiotics.

European Commission

https://ec.europa.eu/info/research-and-innovation/research-area/health-research-and-innovation/antimicrobial-drug-resistance-amr_en

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

http://www.fao.org/antimicrobial-resistance/en/
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

https://www.who.int/antimicrobial-resistance/interagency-coordination-group/en/
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.

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

https://www.gov.uk/government/publications/uk-5-year-action-plan-for-antimicrobial-resistance-2019-to-2024

The five-year action plan of the UK government articulates its ambitions and actions to tackle AMR for the years 2019-2024.

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.

Vaccines for AMR

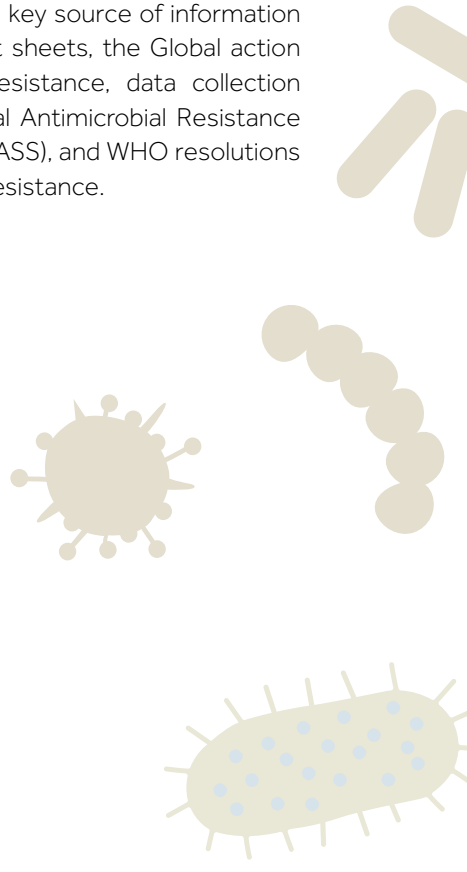
https://vaccinesforamr.org/

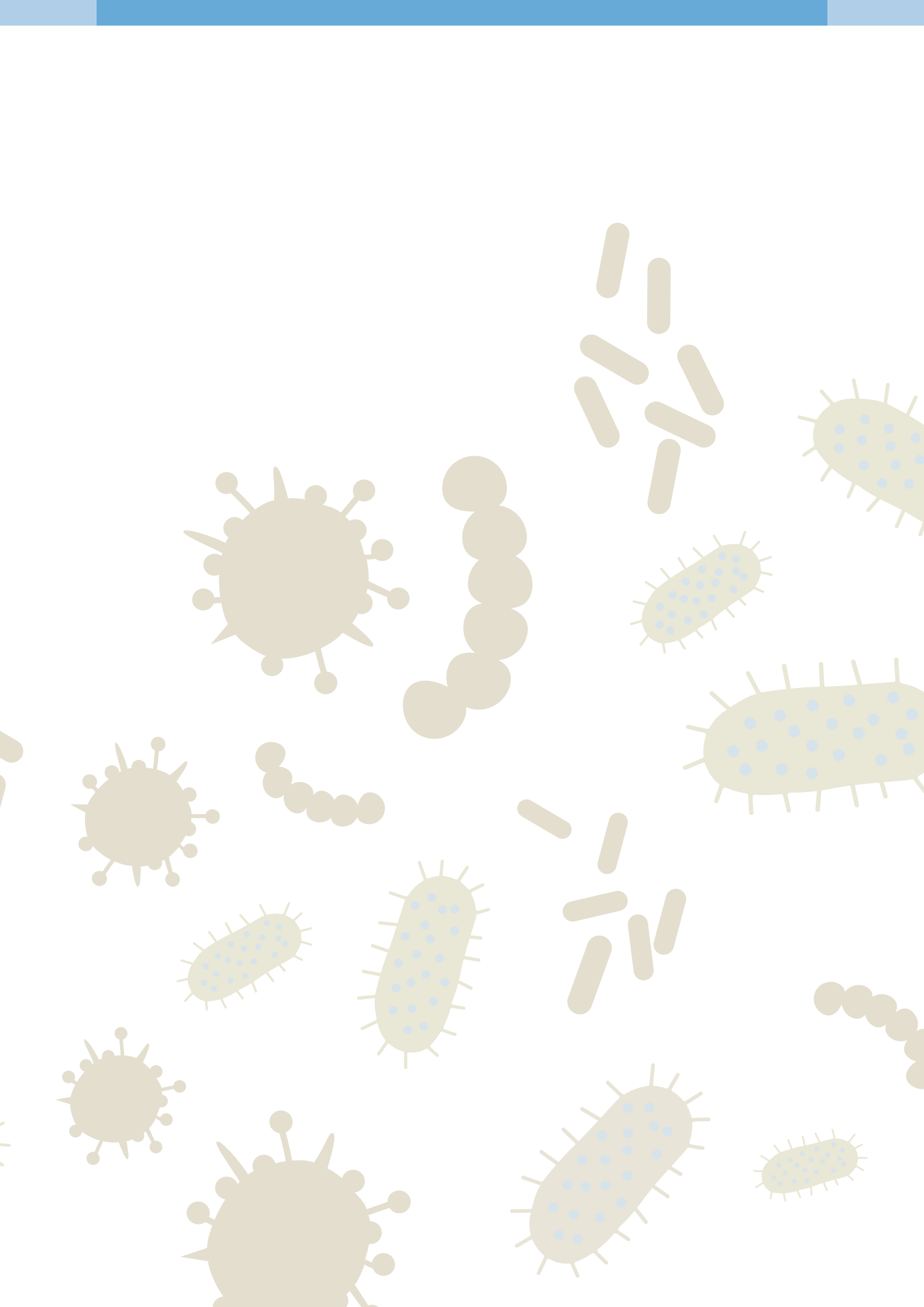
Report commissioned by Wellcome Trust, "Vaccines to tackle drug resistant infections: An evaluation of R&D opportunities".

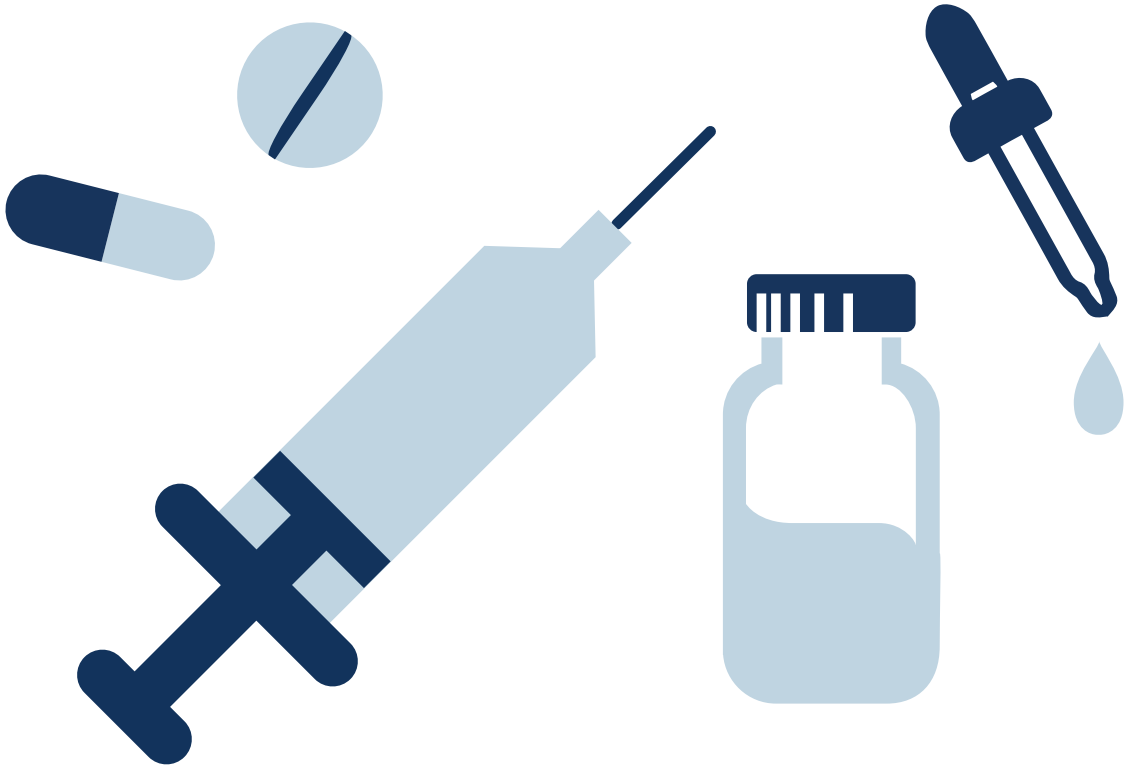
WHO and AMR

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.







World Health Organization

World Health Organization

Session 4
Evaluation of a modelling approach to assess the public health value and preferred product characteristics of a Therapeutic Vaccine for Human Papilloma Virus (HPV)

Defining the potential role of a therapeutic HPV vaccine to reduce cervical cancer mortality amongst women in LMICS

9 March 2022

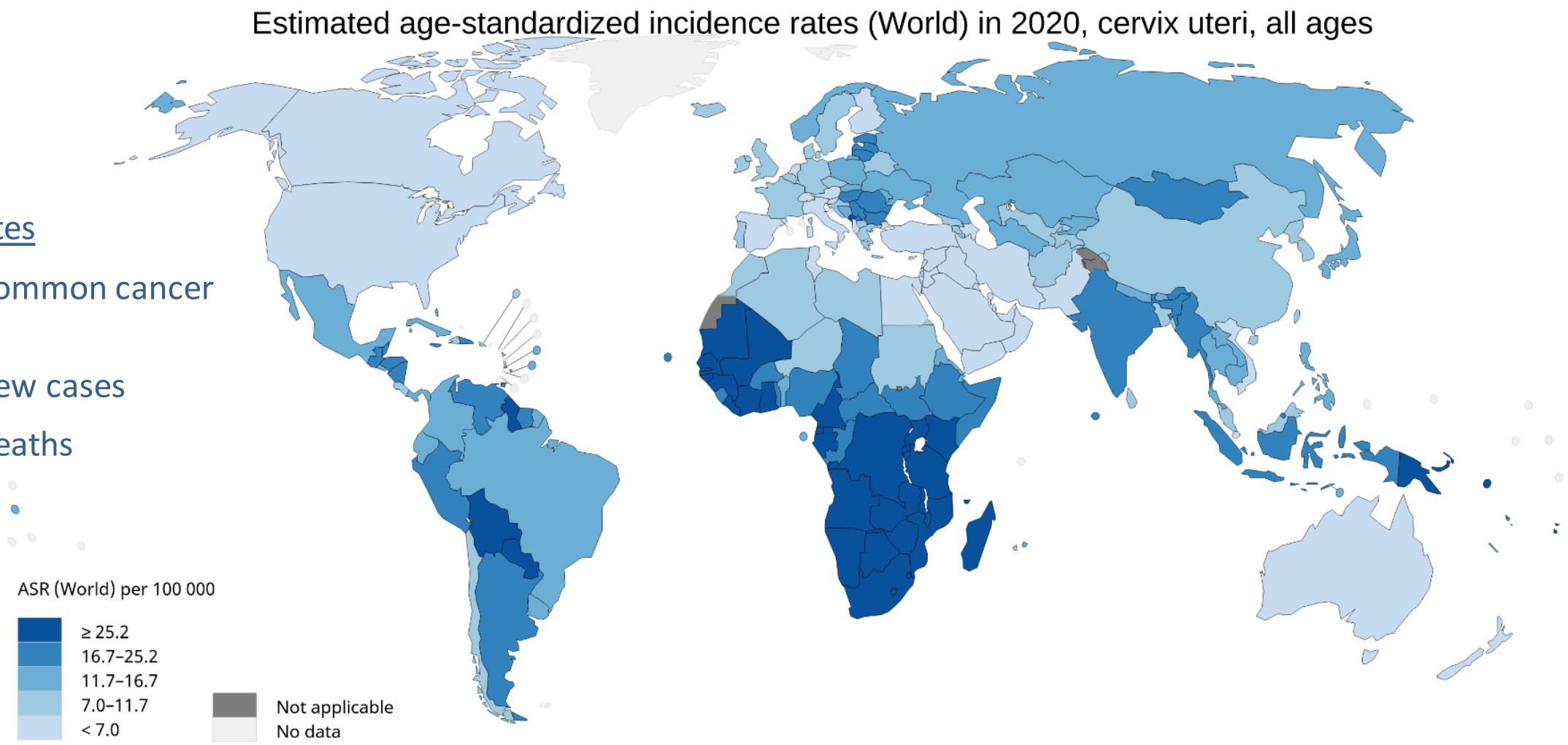

The Teal Sisters, Zambia, survivors and advocates for cervical cancer elimination

Cervical cancer: priority global health concern

World Health Organization

2020 estimates

- 4th most common cancer in women
- 604,000 new cases
- 342,000 deaths

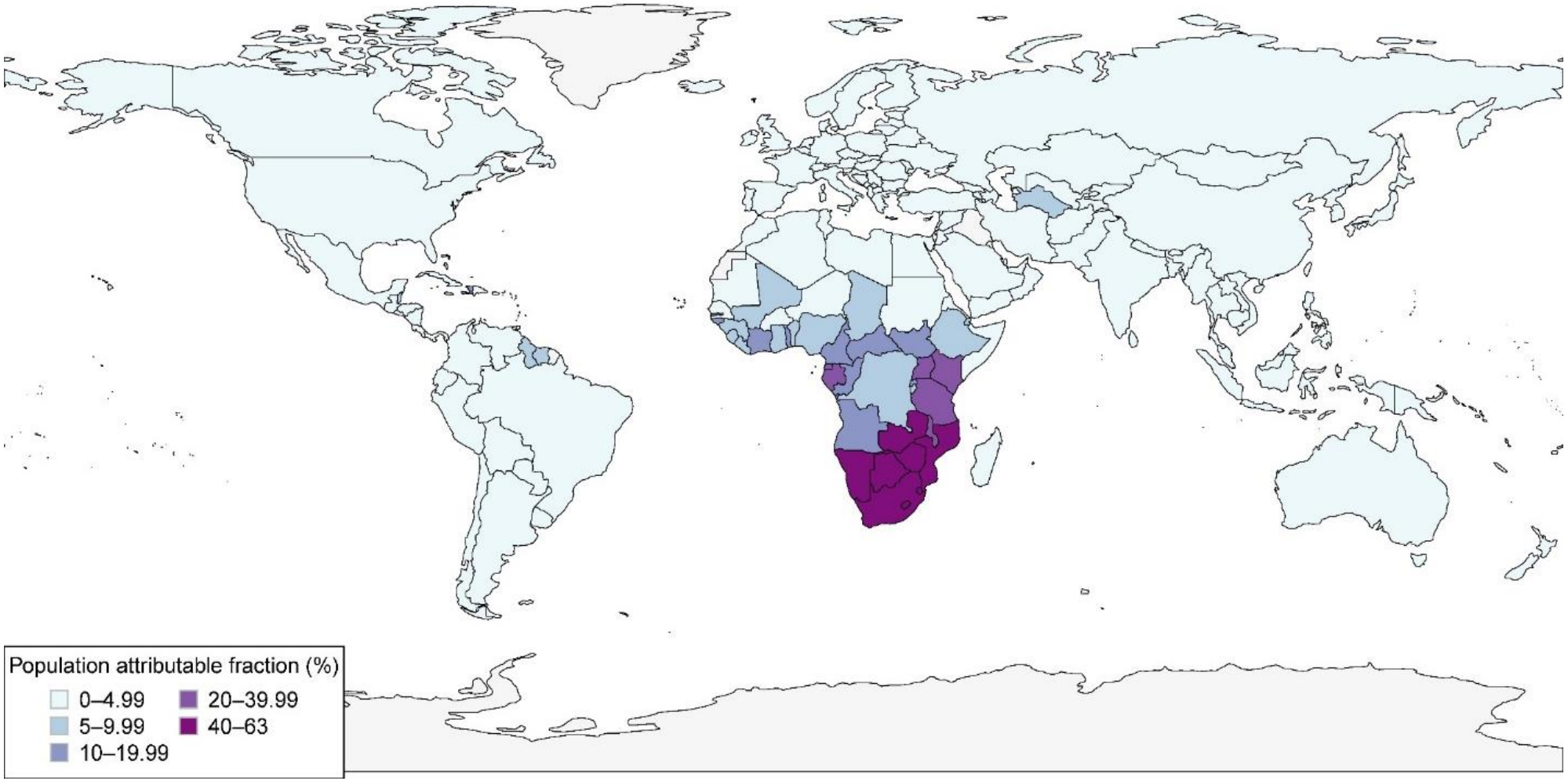


Data source: GLOBOCAN 2020
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization

Population attributable fraction of women with cervical cancer living with HIV, 2018

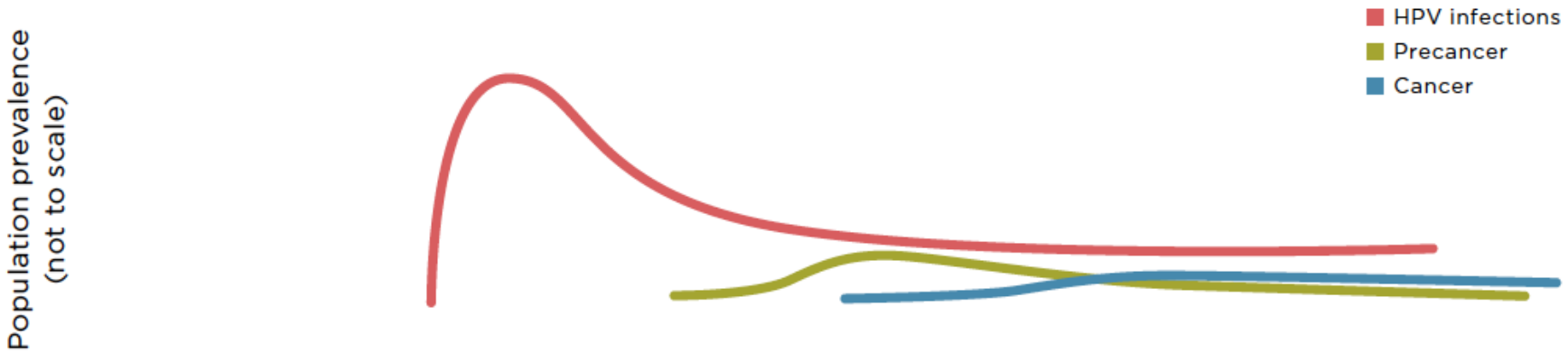
World Health Organization

Risk for cervical cancer among women living with HIV is 6x higher



Source: Stelzle D, Tanaka LF, Lee KK, et al. Estimates of the global burden of cervical cancer associated with HIV. Lancet Glob Health 2021;9(2):e161-e169.

WHO life-course approach to cervical cancer control



PRIMARY PREVENTION	SECONDARY PREVENTION	TERTIARY PREVENTION
Girls 9-13 years • HPV vaccination **Girls and boys, as appropriate** • Health information and warnings about tobacco use* • Sexuality education tailored to age & culture • Condom promotion/provision for those engaged in sexual activity • Male circumcision	**Women >30 years of age** **Screening and treatment as needed** • "Screen and treat" with low cost technology VIA followed by cryotherapy • HPV testing for high risk HPV types (e.g. types 16, 18 and others)	**All Women as needed** **Treatment of of invasive cancer at any age** • Ablative surgery • Radiotherapy • Chemotherapy

WHO Global Strategy to Eliminate Cervical Cancer

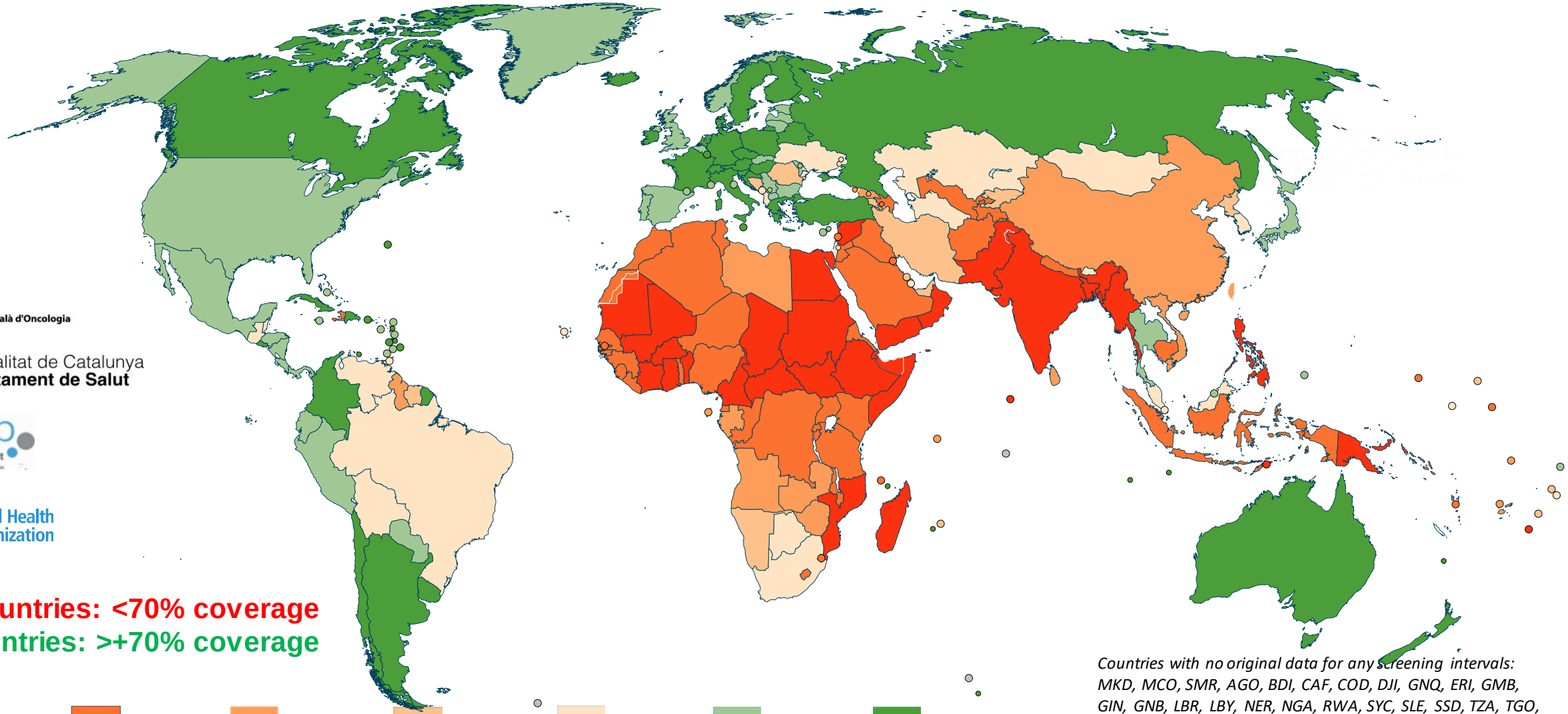
- Elimination threshold: 4 cases per 100 000 women
- Recent modelling: 62 million lives could be saved by 2120 if targets met (Lancet, 2020)

Reaching WHO Cervical Cancer Elimination Strategy targets

- Still have a long way to go to reach CxCa Elimination Strategy 2030 targets
  - Critical to address women who did not receive prophylactic vaccine in early adolescence
  - Complexity of HPV screening/treatment approach is a barrier in LMICs

Ever in lifetime screening coverage (2019), women aged 30-49 years by country

World Health Organization



ICO Institut Català d'Oncologia

Generalitat de Catalunya
Departament de Salut

human reproduction programme hrp research for impact

World Health Organization

126 countries: <70% coverage

76 countries: >+70% coverage

0-9% | 10-19% | 20-34% | 35-49% | 50-69% | 70-89% | 90-100%

Countries with no original data for any screening intervals: MKD, MCO, SMR, AGO, BDI, CAF, COD, DJI, GNQ, ERI, GMB, GIN, GNB, LBR, LBY, NER, NGA, RWA, SYC, SLE, SSD, TZA, TGO, ATG, PAN, SUR, VEN, ASM, COK, NIU, WSM, VUT, AFG, BHR, KHM, PRK, PSE, YEM

New innovations are needed to address gaps

Goal:

<u>To reduce CxCa deaths over next 30-40 yrs</u> - if screening and treatment and Px targets can't be met.

Can Tx vaccines help fill the gaps?

Current status:

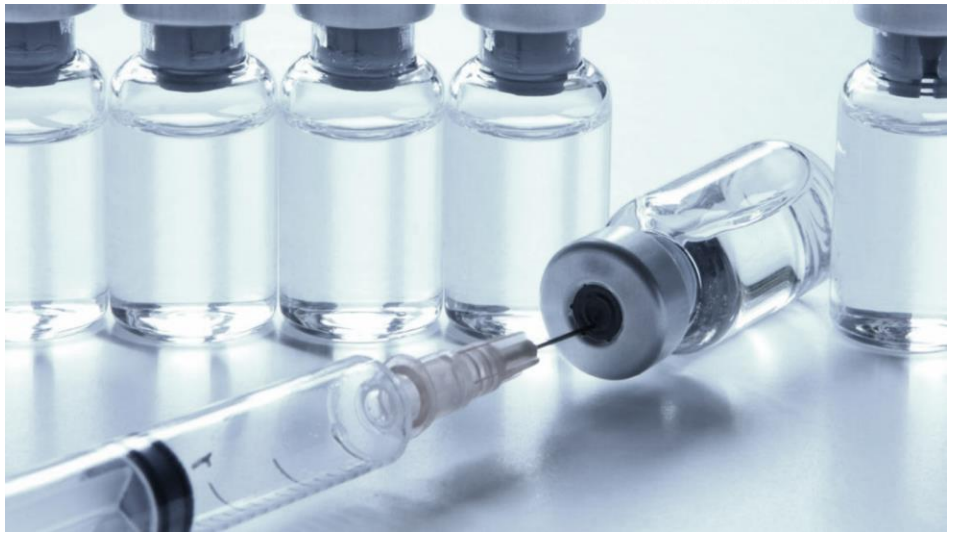
Several therapeutic (Tx) HPV vaccine candidates are in early clinical development:

- May clear hrHPV infection and/or regress CIN2/3 lesions

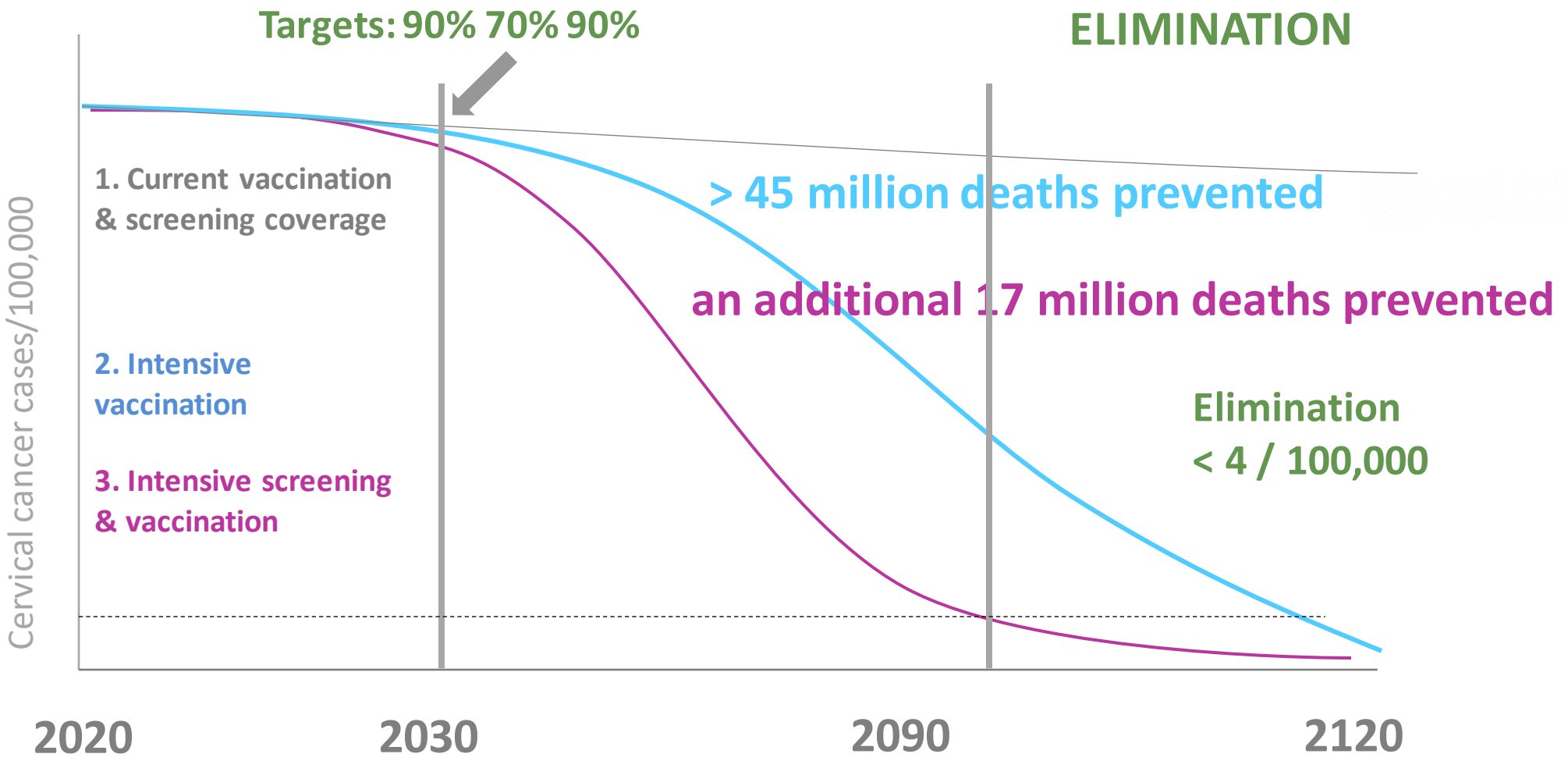
Tx HPV vaccine's role within broader CxCa efforts

Important to understand:

- **What is their added value** relative to scale-up of existing interventions?
- **How would Tx HPV vaccines be used?** How does this influence **attributes that would optimize impact?**
- What are their **likely attributes?** How does this affect **potential value and optimal use?**



Strategy to Achieve Elimination



Source: Brisson, Canfell et al, Lancet 2020

Global activities to understand potential value and define PPCs of TxV

Full value of vaccines assessment

- What is the public health need the vaccine would address?
- How valuable would the vaccine be?

Preferred product characteristics

- What should the vaccine look like to optimize its benefits?
- Who will get it and how will it be used?

Activities

1. Initial stakeholder consultation (Oct 2021): guiding principles to assess value and define PPCs
2. Modeling: impact and cost-effectiveness of TxV
3. End-user survey, additional lit reviews as needed
4. Follow-up stakeholder consultation in Fall 2022, incorporation of modelling and additional data
   - Presentation to WHO PDVAC
   - Public consultation to finalize PPC document (Dec 2022)

Modelling approach and proposed use-cases

A modelling approach will be used to identify:

- the potential impact of TxV
- the attributes TxV would need in order to have the desired impact

Under a range of assumptions about the broader CxCa prevention environment over time:

Use Case 1: Population-level vaccination of all adult females in a given age cohort

Use Case 2: Targeted usage of TxV within a screening and treatment scenario, for women with positive oncogenic HPV status

Sami Gottlieb, WHO
Raymond Hutubessy, WHO
Nathalie Broutet, WHO
Holly Prudden, WHO Consultant

Sharon Achilles, BMGF
Celina Schocken, BMGF Consultant
Eleanore Edson, BMGF
Peter Dull, BMGF
Jamie Cohen, BMGF
Kelle Moley, BMGF

Karen Canfell, Uni of Sydney
Amy Pagotto, Uni of Sydney
Kate Simms, Uni of Sydney
Adam Keane, Uni of Sydney
Michael Caruana, Uni of Syd
Michaela Hall, Uni of Sydney

Evaluation of a modelling approach to assess the public health value and preferred product characteristics of a therapeutic vaccine (TxV) for human papillomavirus (HPV)

IVIR-AC Meeting, March 9th, 2022

Karen Canfell, on behalf of the project team

Professor and Director, The Daffodil Centre, A Joint Venture between Cancer Council NSW and the University of Sydney, Australia

1. Overview of the modelling platform *(Policy1-Cervix)*

The *Policy1-Cervix* platform

Involved in **three global consortia** – CCEMC (WHO funded), CISNET (US-NIH funded) and CCGMC (Covid impact on cancer; a global consortium with IARC and others)

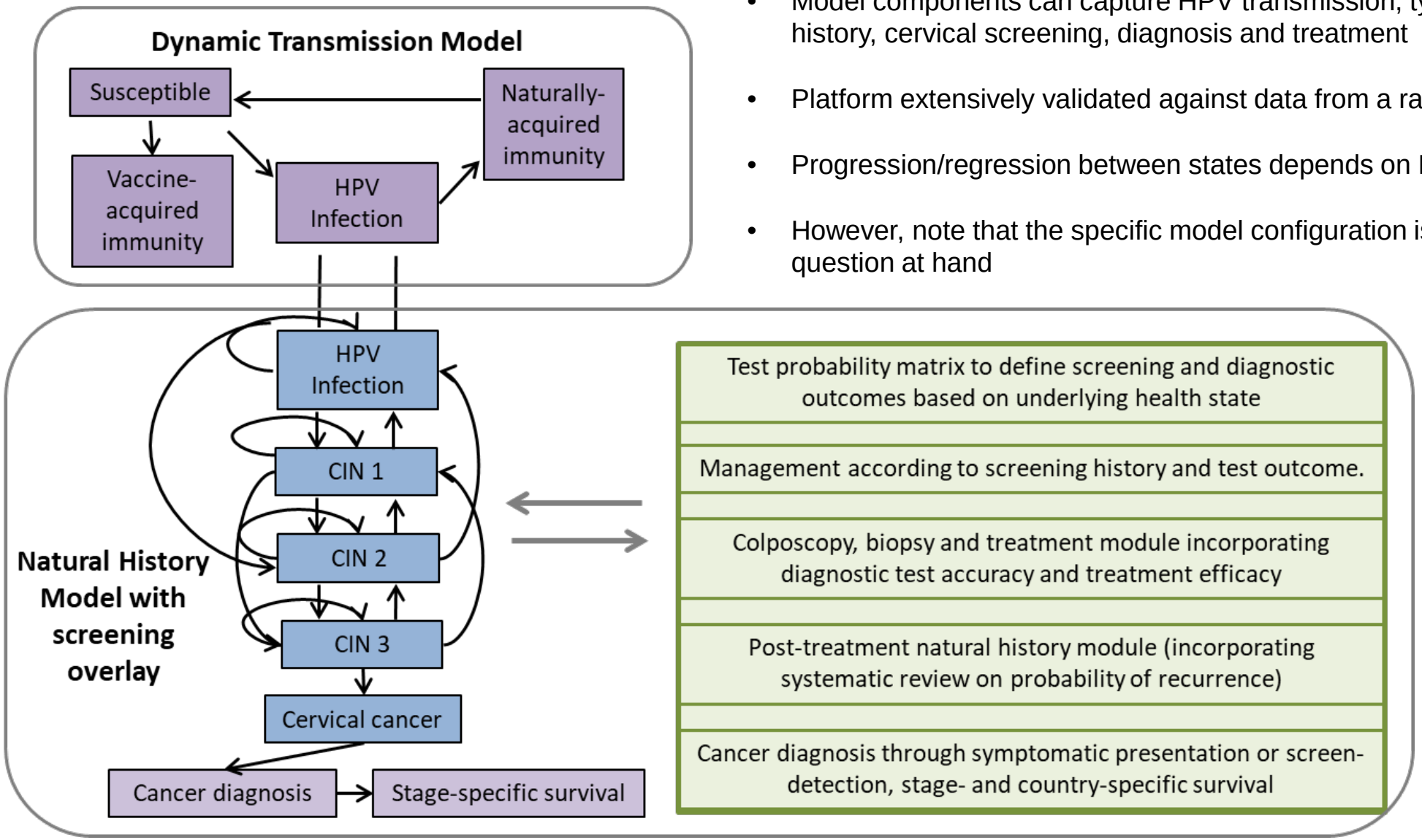
Policy1-Cervix has been used to evaluate the **impact of HPV vaccination, cervical screening and cancer treatment** in a range of settings, including:

- **Multiple HPV vaccine evaluations** (including male vaccination, next generation vaccine, vaccination in mid-adults, lives lost due to vaccine hesitancy in Japan).
- **Transition from cytology to primary HPV screening** in Australia, New Zealand and England – used to directly inform government policy (e.g Renewal of Australian screening program in 2018)
- **Multiple LMIC country-level evaluations** including rural and urban China, PNG, Malaysia, Tanzania, others.
- **First modelling of elimination** in any country (Australia) and elimination globally. Also, the timeline to cervical cancer elimination in USA (CISNET), for 78-LMICs (as part of the CCEMC) and Tanzania.
- The benefits, harms and cost-effectiveness of alternative test technologies, screening ages and frequencies **to inform updated 2021 cervical screening guidelines** for WHO.

1. Canfell/ Kim/ Brisson et.al. Lancet 2020
2. Brisson/Kim/Canfell et.al Lancet 2020
3. Burger/Smith et.al. Lancet PH 2020
4. Simms/Hanley/Smith et.al. Lancet PH 2020
5. Hall et.al. PlosOne 2020
6. Yuill et.al. JID 2020
7. Smith et al, MJA 2016
8. Smith et al, BMC HSR 2016
9. Smith et al, BMC HSR 2016
10. Simms et al Lancet Onc 2019
11. Lew et al, PLoS One 2016
12. Simms et al, Int J Cancer 2016
13. Simms et al, Lancet PH 2016
14. Simms et al, PLoS One 2017
15. Lew/Simms et al, Lancet PH 2017
16. Velentzis et al, Int J Cancer 2017
17. Hall et al, PLoS One 2018
18. Hall et al, Lancet PH 2018
19. Smith and Canfell, BMC RN 2014
20. Kitchener et al, HTA UK 2014
21. Smith and Canfell, PLoS One 2014
22. Canfell et.al, Vaccine, 2011
23. Legood et al, BMJ, 2012
24. Keane et.al. Cancer Epidemiology, 2021

Policy1-Cervix:

Core natural history model

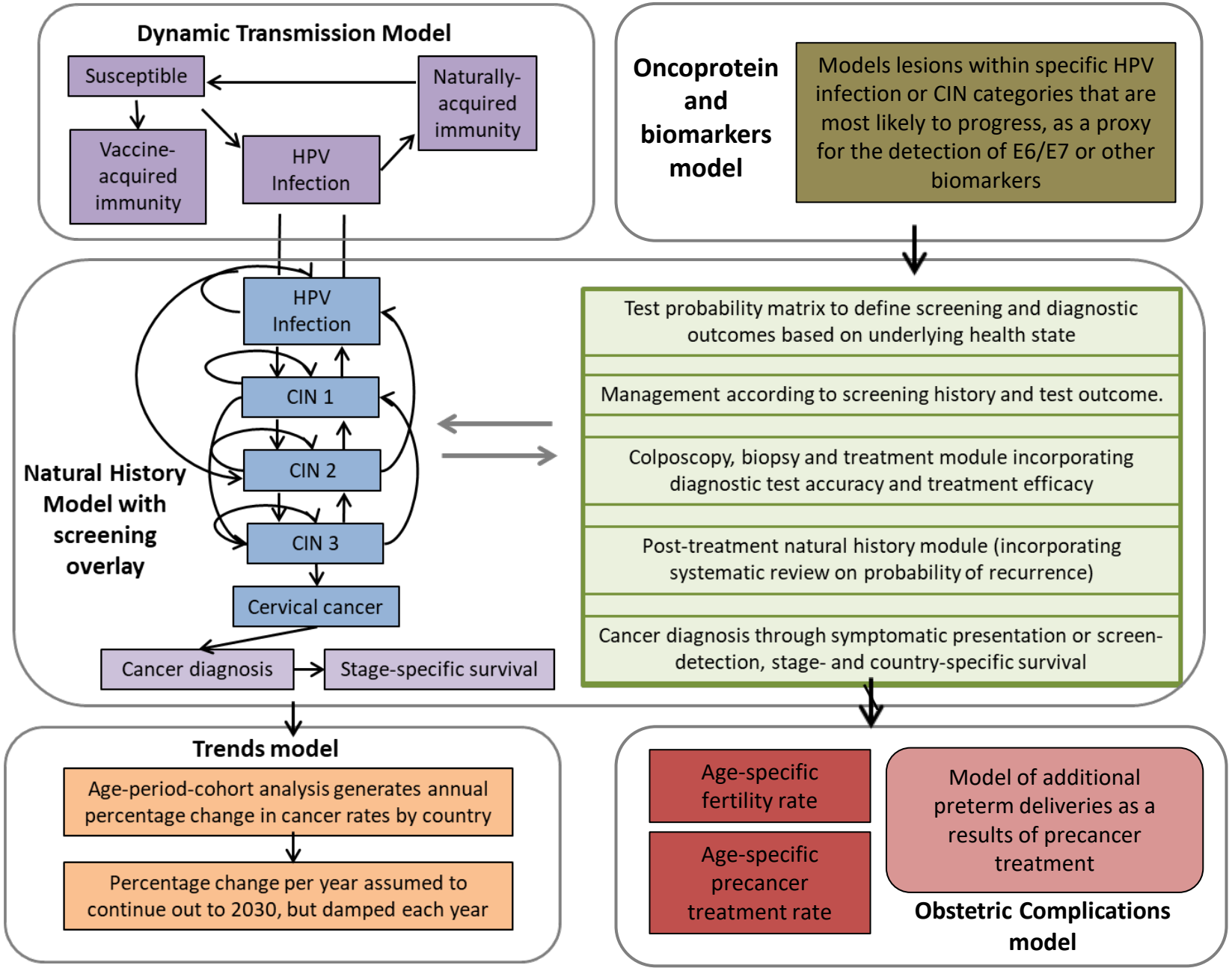


- *Policy1-Cervix* is a model platform including elements/components to capture sexual behaviour, HPV transmission, HPV/CIN/cancer natural history, cervical screening and vaccination.
- Model components can capture HPV transmission, type-specific natural history, cervical screening, diagnosis and treatment
- Platform extensively validated against data from a range of countries
- Progression/regression between states depends on HPV type
- However, note that the specific model configuration is adapted to the research question at hand

Policy1-Cervix:

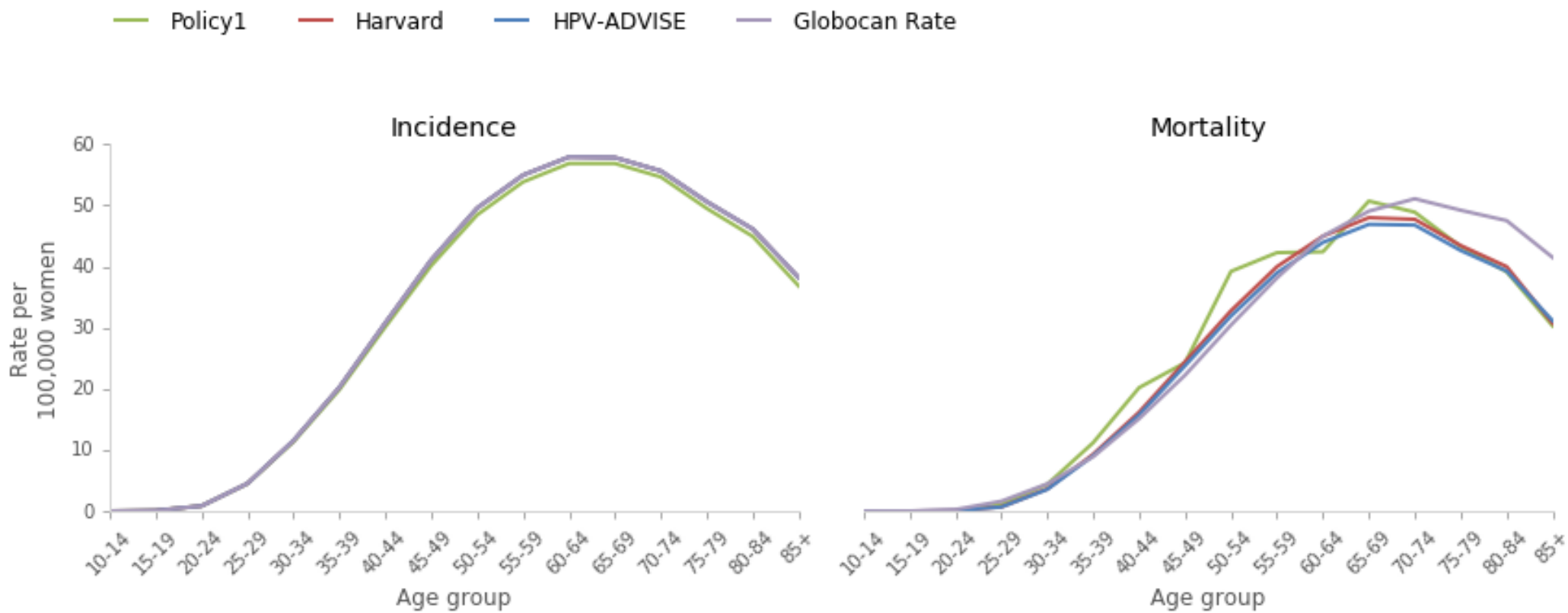
Full module ecosystem

- **Trends module** informed by APC modelling, captures background secular changes in cervical cancer rates (e.g sexual behaviour changes, HPV co-factor exposure)
- **Obstetric complications module** estimates additional low birth weight or preterm delivery events.
- **Oncoprotein and biomarkers module** allows for the evaluation of interventions that target E6/E7 or other biomarkers.
- The **Policy1-Cervix_HIV model** models HIV-HPV interactions and natural history progression for women living with HIV



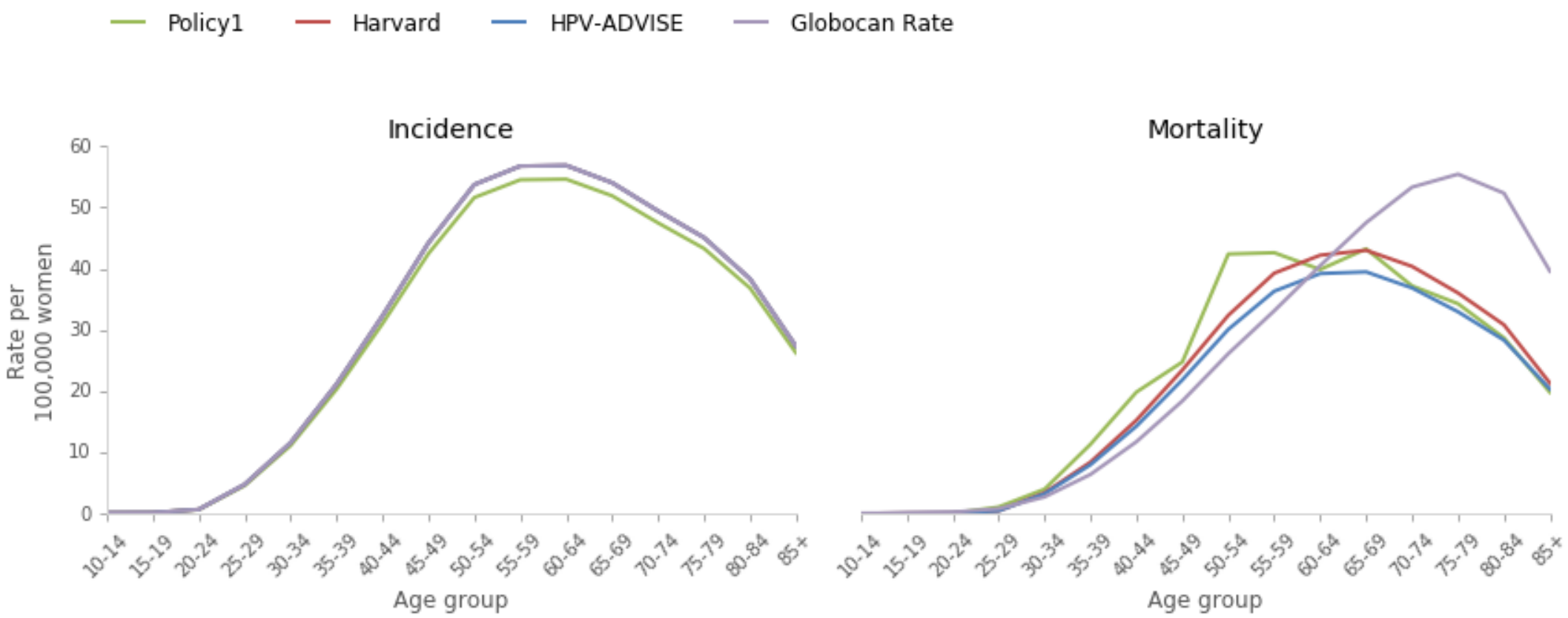
Policy1-Cervix: Calibration across 78 LMICs

- The model was directly calibrated to GLOBOCAN estimates of age-specific cervical cancer incidence in 6 regions, namely (i) East Asia and Pacific; (ii) Europe & Central Asia; (iii) Latin America & Caribbean; (iv) Middle East & North Africa; (v) South Asia; and (vi) Sub-Saharan Africa (listed in subsequent slides)
- It was then validated against the GLOBOCAN estimates of age specific cervical cancer mortality
- As part of the CCEMC comparative modelling exercise it was compared to two other models outputs for two other models, namely the Harvard model (Harvard University, USA) and HPV-ADVISE (Laval University, Canada).



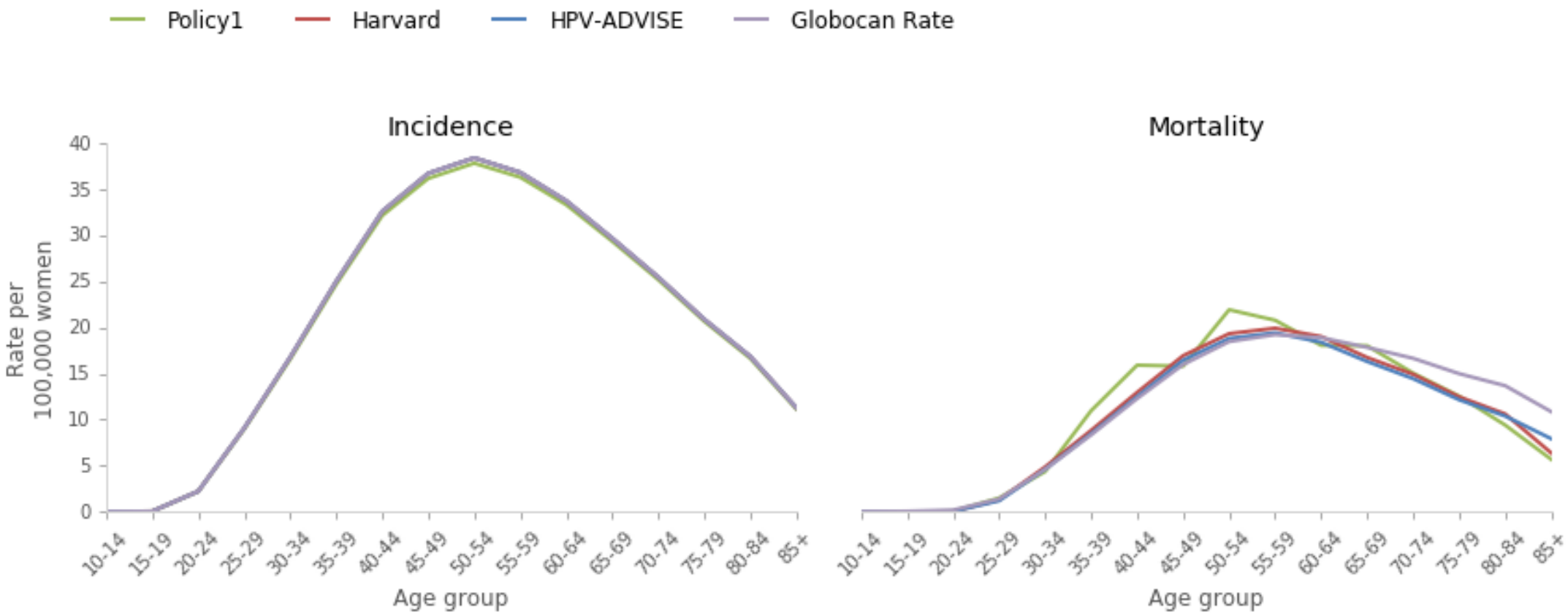
See Brisson et al and Canfell et al Lancet 2020

Policy1-Cervix: Calibration/validation in East Asia & Pacific



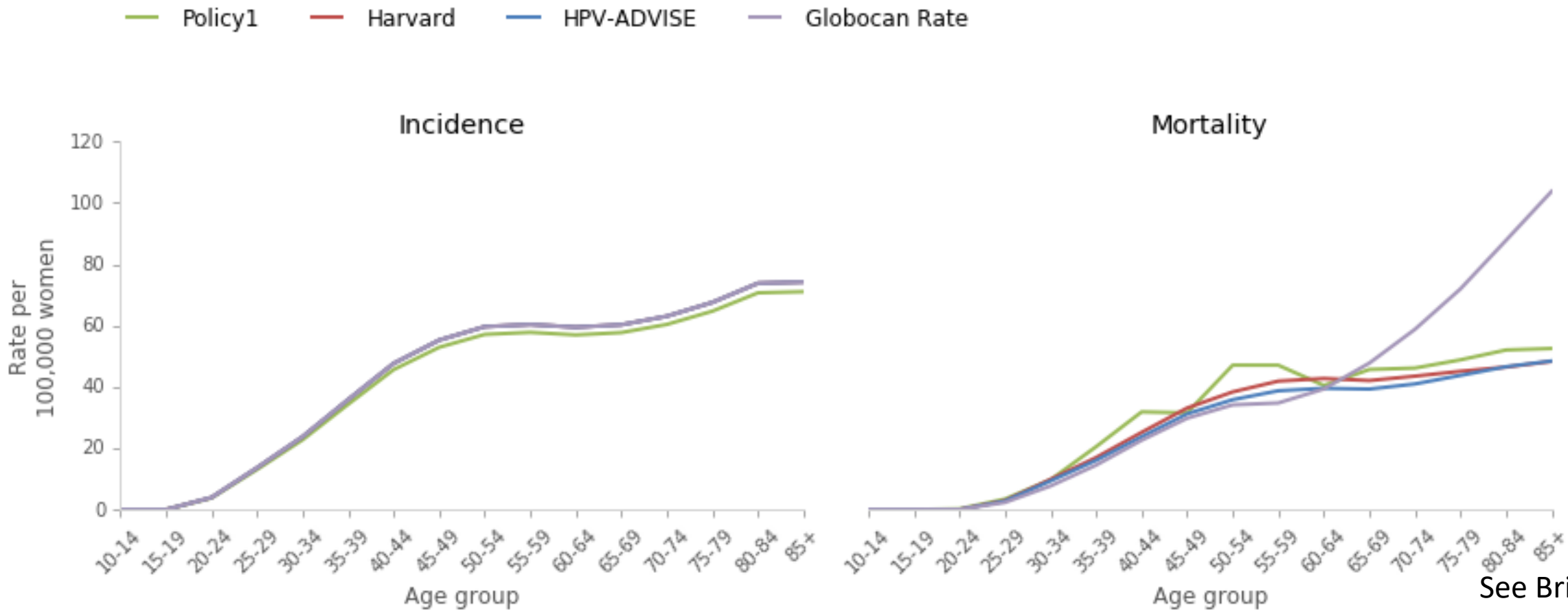
See Brisson et al and Canfell et al Lancet 2020

Policy1-Cervix: Calibration/validation in Europe & Central Asia



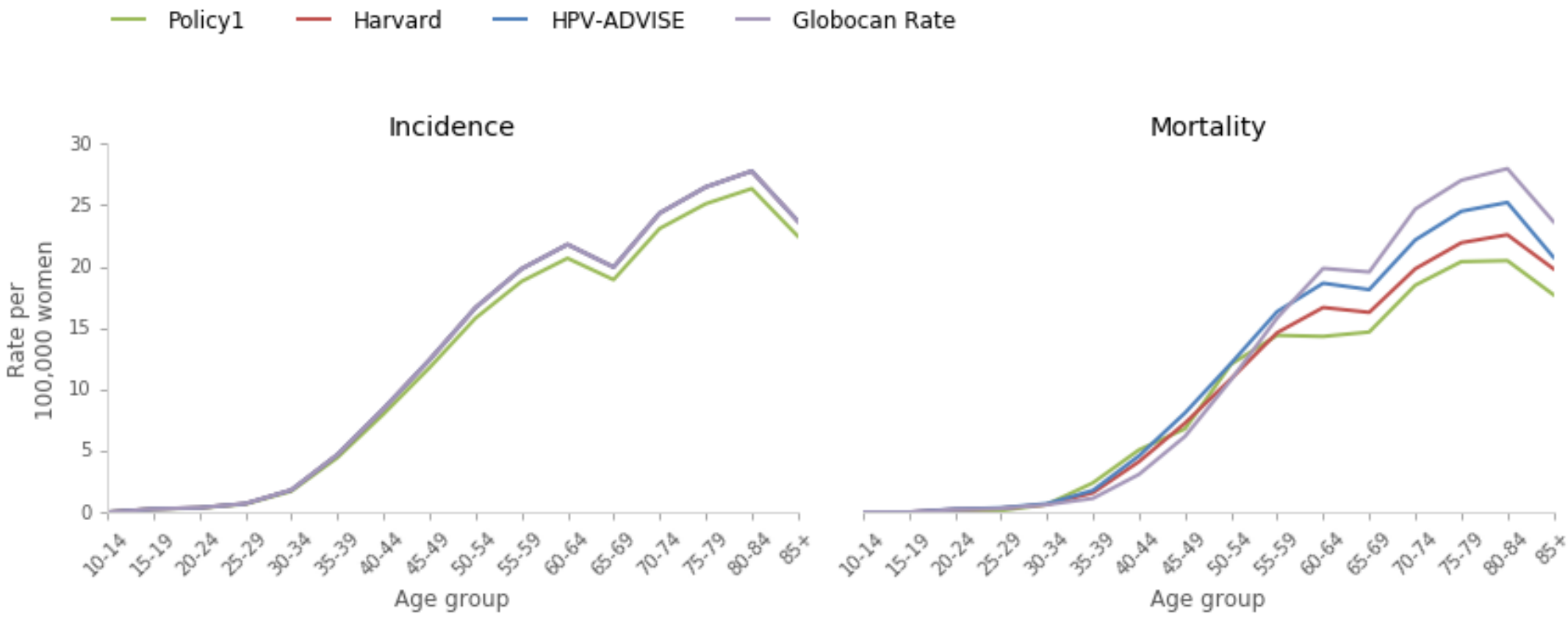
See Brisson et al and Canfell et al Lancet 2020

Policy1-Cervix: Calibration/validation in Latin America & Caribbean



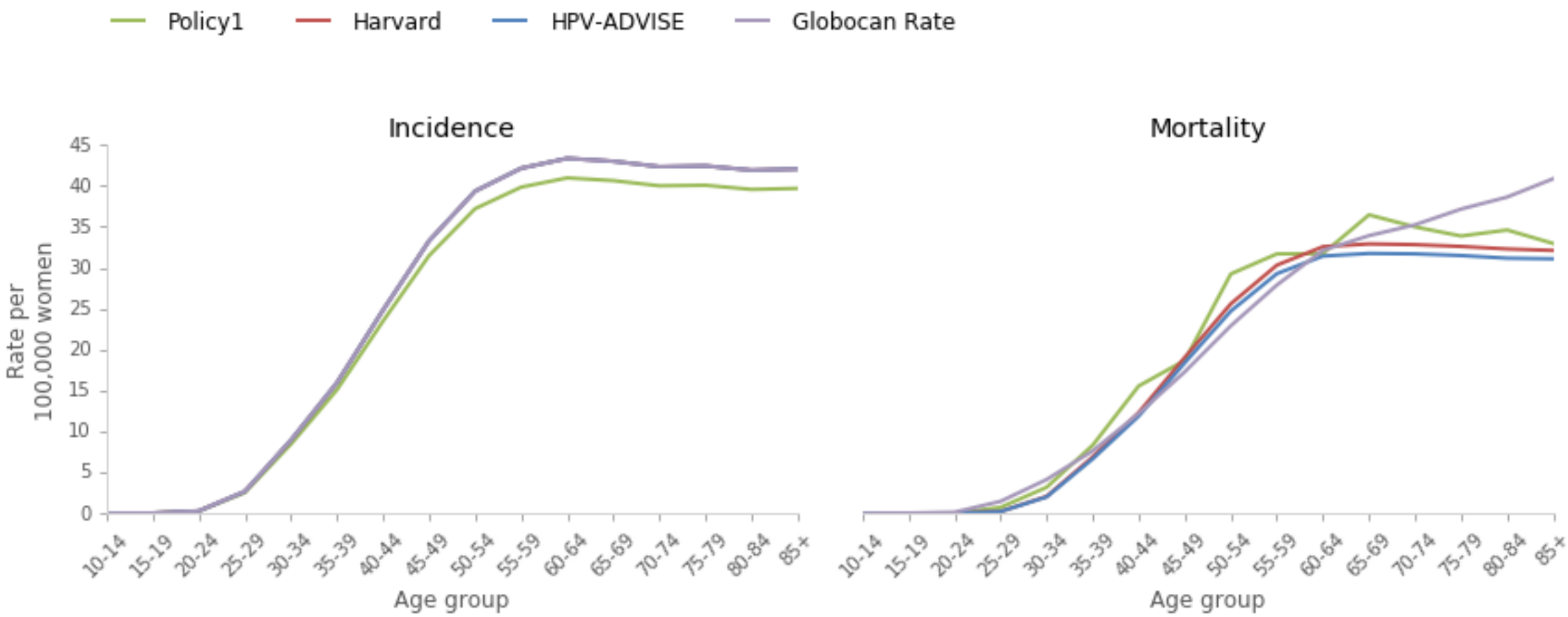
See Brisson et al and Canfell et al Lancet 2020

Policy1-Cervix: Calibration/validation in Middle East & North Africa



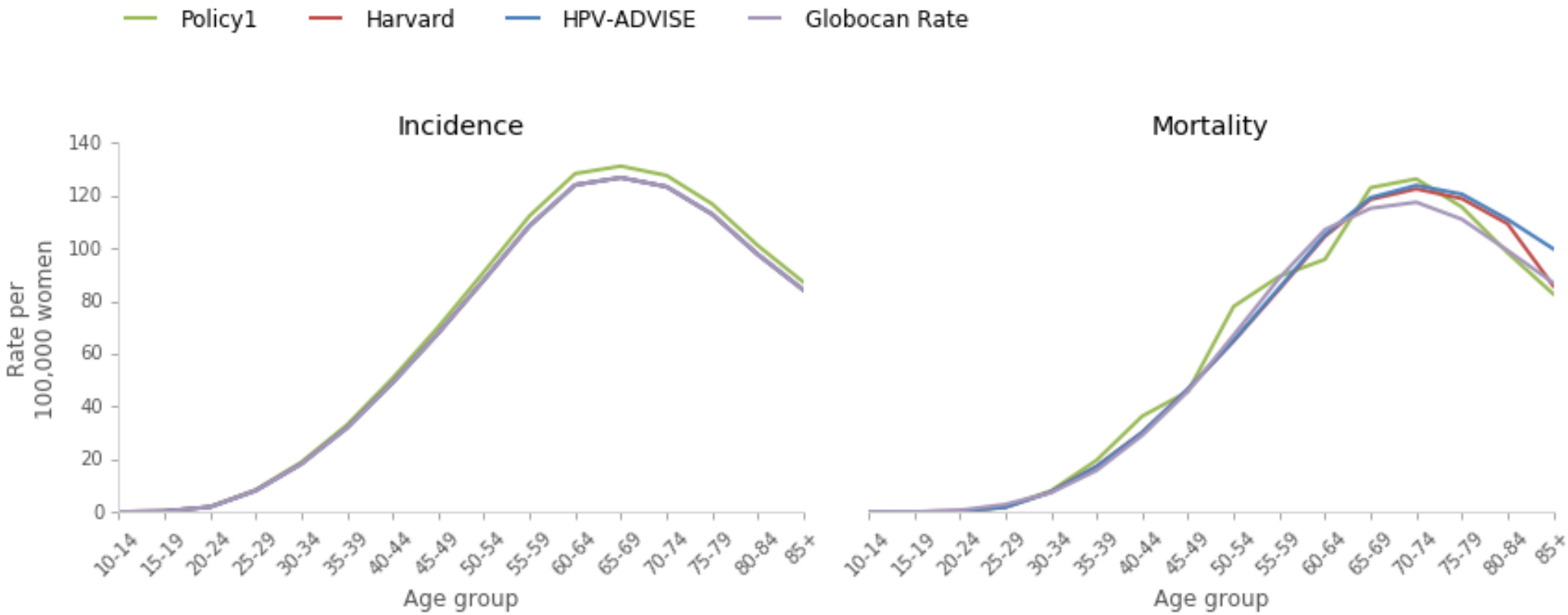
See Brisson et al and Canfell et al Lancet 2020

Policy1-Cervix: Calibration/validation in South Asia



See Brisson et al and Canfell et al Lancet 2020

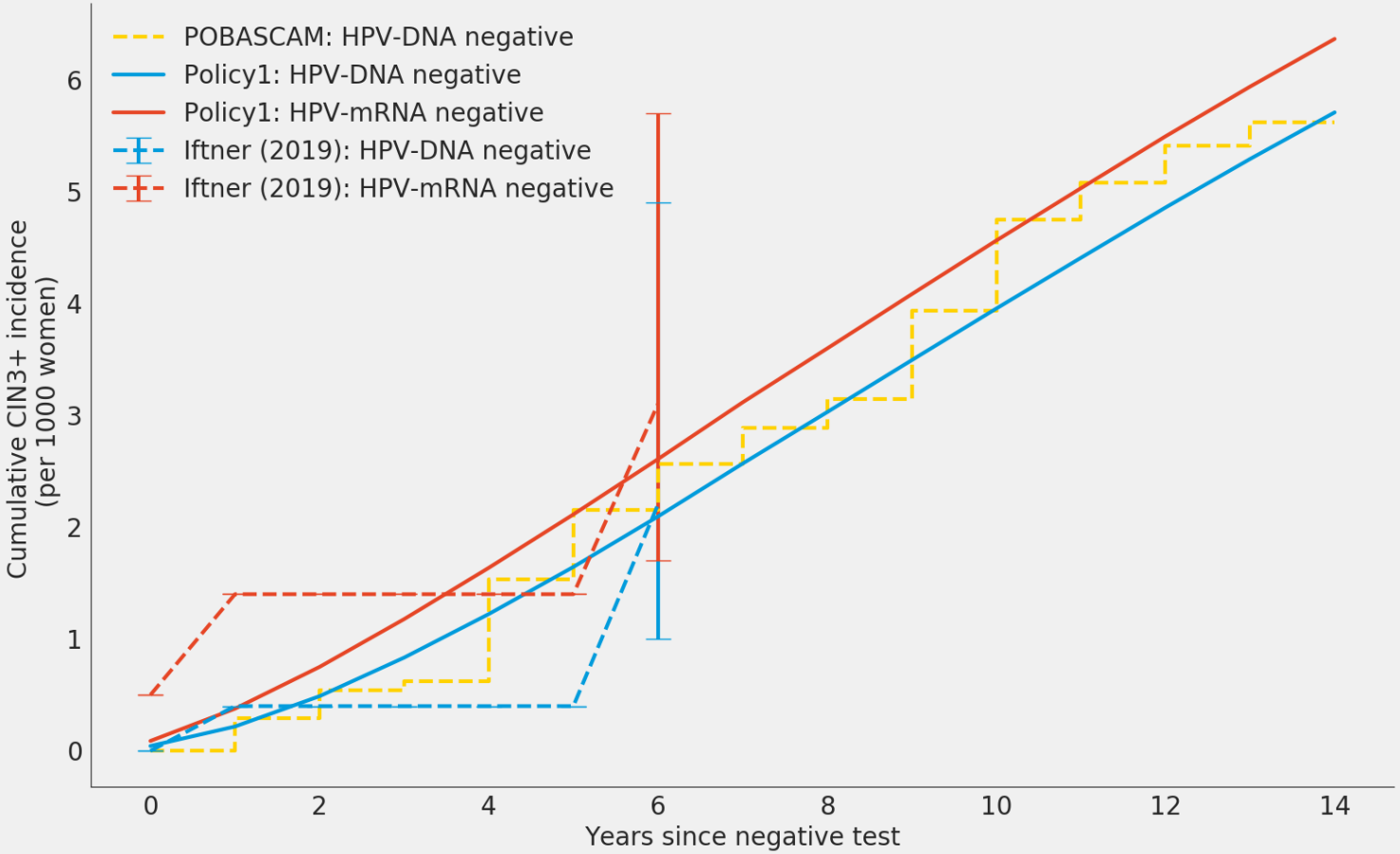
Policy1-Cervix: Calibration/validation in Sub-Saharan Africa



See Brisson et al and Canfell et al Lancet 2020

Model validation of testing technologies: mRNA and DNA

Longitudinal model outputs versus data

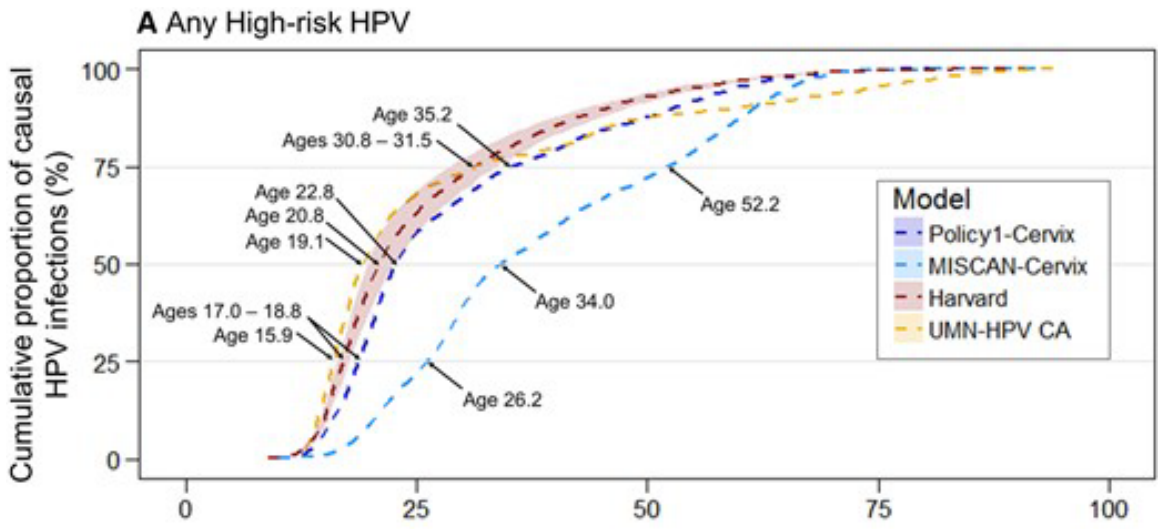


- Model predicted cumulative rates of 2.1-3.1 per 1000 CIN3+ detected with **HPV-mRNA** at 5-7 years compared to 1.6-2.6 per 1000 after **HPV-DNA** screening (consistent with the longitudinal data).

- This results from small baseline cross-sectional differences, namely:
  - 2-3% loss in relative cross-sectional sensitivity of **HPV-mRNA** compared to **HPV-DNA** for CIN2/3+
  - Higher specificity at the CIN2+ threshold

WHO 2021 Guidelines for cervical screening & treatment

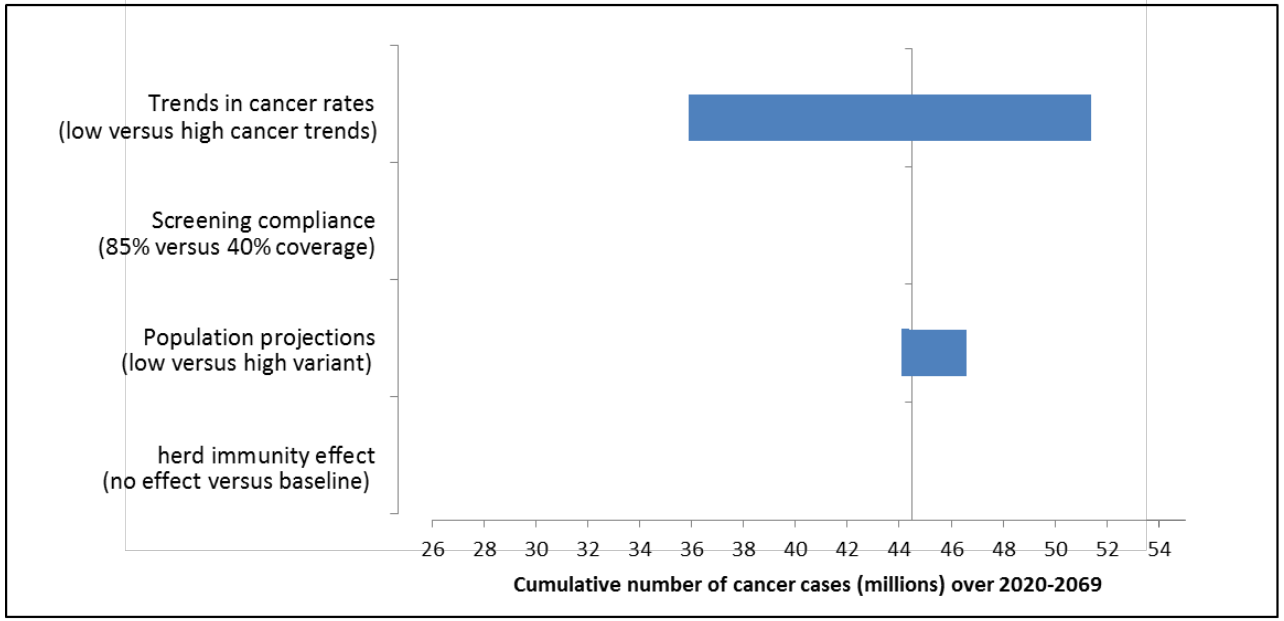
Comparative modelling of distribution of age at acquisition of a causal (i.e. cancer causing) HPV infection



- Comparative modelling between *Policy1-Cervix* and Harvard comprehensive models (a TIS model), on natural history dynamics, indicate similar conclusions about age of acquiring cancer-causing infection, and other key outcomes (see full publication[1])
- We have performed other comparative modelling analyses with other groups, such as HPV-ADVISE and our models generally compare similarly (e.g initial CCEMC modelling, Australia cost-effectiveness of HPV9)
- We have performed other comparative modelling analyses with Harvard (e.g elimination timing in USA, cost-effectiveness of adult HPV vaccination) and reach similar conclusions.[2]

1. Burger et.al. JNCI 2020
2. Burger et.al. Lancet PH 2020

Trends modelling



- Cervical cancer incidence rates in countries have undergone secular chances over the past few decades; for HIC, rates generally decrease because of screening but for other settings this could be due to a range of factors including changing exposure to co-factors, changing sexual behaviour, changing benign hysterectomy rates (a major driver in some settings).
- To account for these changes, we performed an APC trends analysis to identify the rates of change in settings with high-quality IARC-certified cervical cancer rates
- We analysed high-quality cancer registry data from IARC's Cancer Incidence in Five Continents series using data from volumes 8–11 covering the 20-year period between 1993 and 2012. The analysis included 37 registries across 20 high-density countries in eight geographical regions representing countries across four HDI categories
- Based on the trends analysis, we found that populations in Latin America and Asia have declining trends over time (except for China which is increasing by >10% per year); European and North American populations exhibited little or no changing trends, and the selected populations in sub-Saharan Africa observed increasing cancer rates over time. These results are consistent with previously published analyses for these regions.
- When performing sensitivity analysis on cervical cancer cases over time, we found that differing trends assumptions had the most substantial impact on predicted burden of cervical cancer over the next 50-years (with upper and lower trends based on the CI's from the APC modelling); conversely, doubling herd effects, or removing herd effects, from PxV had minimal impacts on predicted disease burden.

See Simms et al Lancet Onc 2019

The *Policy1-Cervix-HIV* platform (Tanzania calibration)

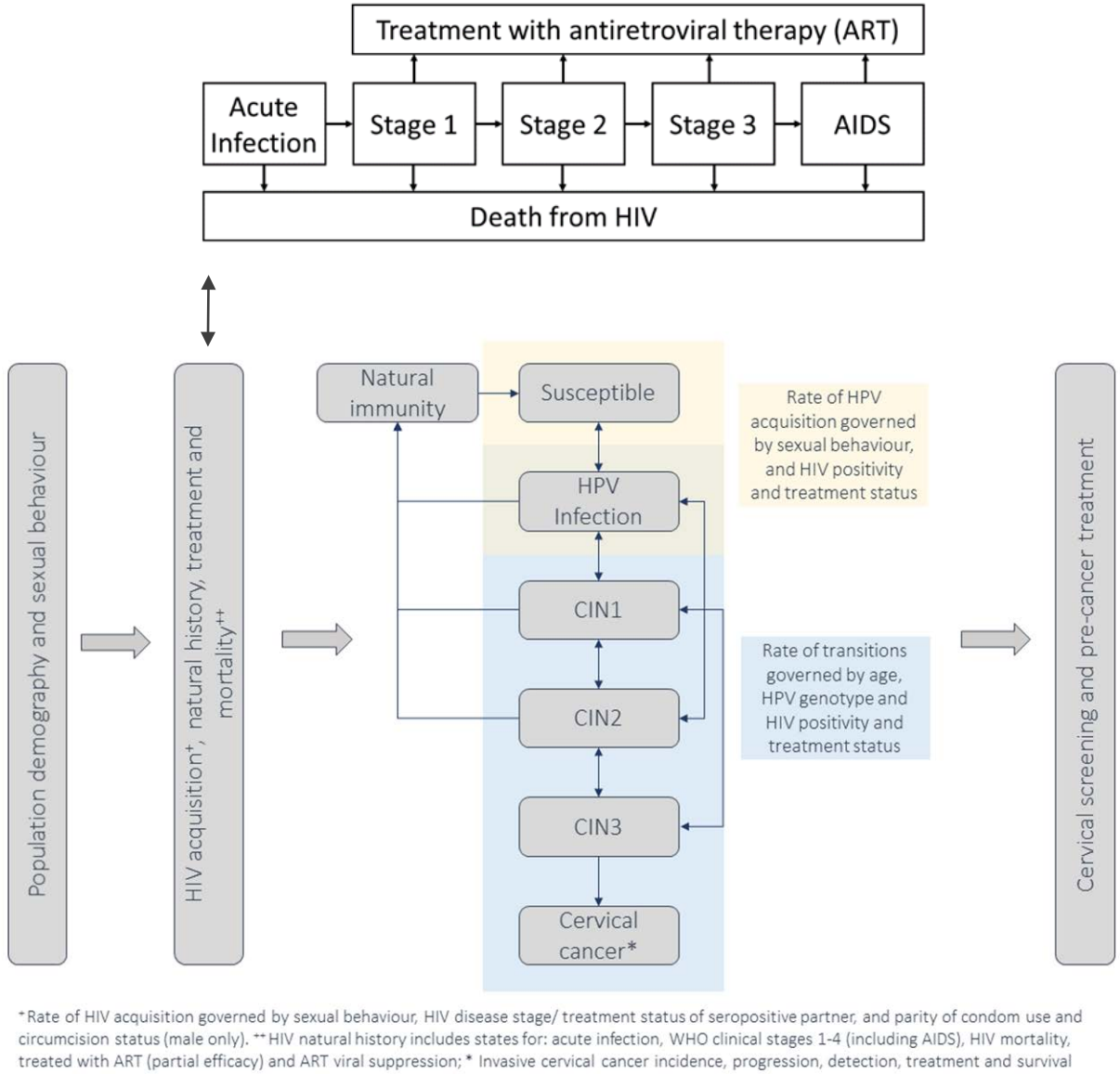
Policy1-Cervix-HIV has been used to evaluate the impact of HPV vaccination, cervical screening and cancer treatment in **the context of endemic HIV and HIV control**, including:

- Current and potential future **impact of HIV control** (including voluntary medical male circumcision, antiretroviral therapy and pre-exposure prophylaxis) on HPV prevalence and cervical cancer incidence and mortality in the United Republic of Tanzania.
- WHO triple intervention strategy (HPV vaccination, cervical screening and cancer treatment scale-up) **in all women and women living with HIV**.
- The benefits and harms of alternative test technologies, screening ages and frequencies to inform WHO updated 2021 cervical screening guidelines for women living with HIV.
- Updated to include cost-effectiveness outcomes.
- Additional implementation underway to simulate HIV and HPV at regional level.

1. Hall MT, Smith MA, Simms KT, Barnabas RV, Canfell K, Murray JM (2020) The past, present and future impact of HIV prevention and control on HPV and cervical disease in Tanzania: A modelling study. PLoS ONE 15(5): e0231388. https://doi.org/10.1371/journal.pone.0231388
2. Hall MT, Smith MA, Simms KT, Barnabas R, Murray JM, Canfell K. Elimination of cervical cancer in Tanzania: Modelled analysis of elimination in the context of endemic HIV infection and active HIV control. Int J Cancer. 2021 Jul 15;149(2):297-306. doi: 10.1002/ijc.33533. Epub 2021 Mar 24. PMID: 33634857.

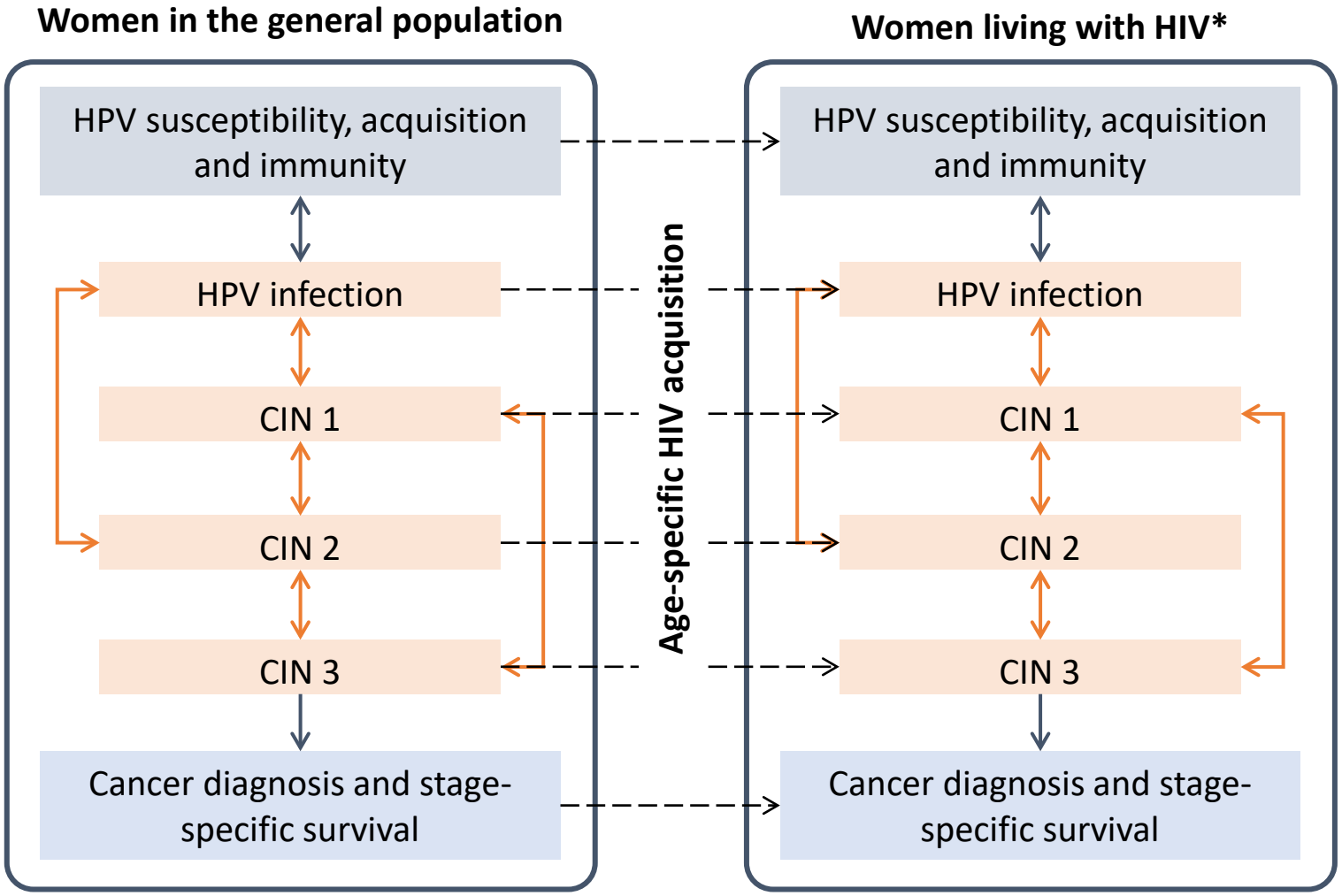
Policy1-Cervix-HIV:*

- **Demography module** captures changing population structure over time, driven by fertility and natural mortality rates
- **Sexual behaviour module** dynamically simulates HIV, HPV16/18, HPV31/33/45/52/58, and other oncogenic HPV
- **Natural history module** simulates HIV and HPV natural histories, including the impact of HIV on risk of cervical precancer and cancer
- **Intervention and control module** simulates HIV control, HPV vaccination and cervical screening



** Details of full calibration and model structure and parameters published in Hall et al 2020 PLOS ONE (https://doi.org/10.1371/journal.pone.0231388).*

Fully integrated platform: HIV infection conserves HPV natural history structure and modifies state transition rates

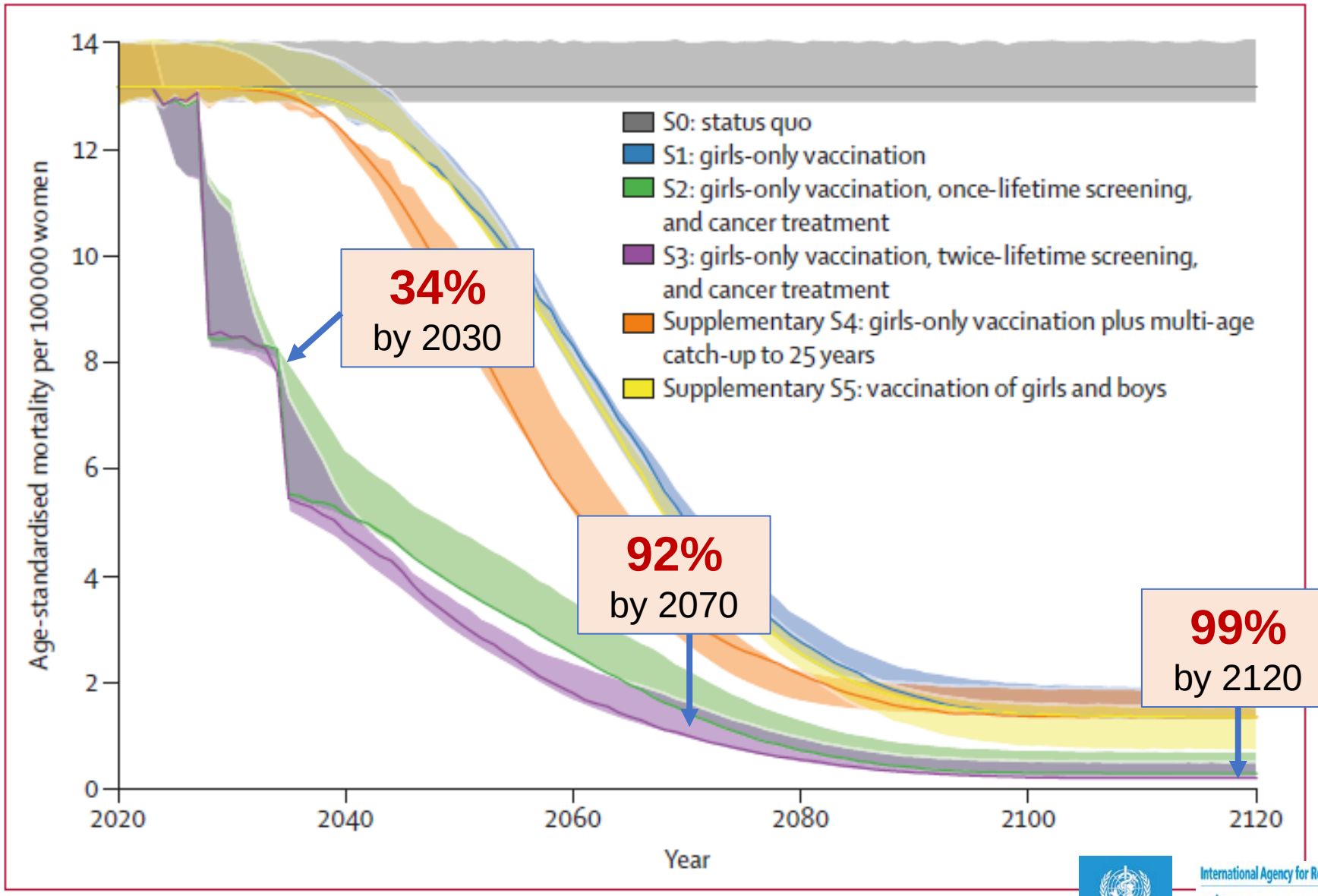


Relative increase/decrease in net transition due to HIV

HPV acquisition	2.75 (1.17-2.75)↑
HPV clearance (no CIN)	0.6↓
Progression HPV to CIN1	3.73 (2.62-3.73) ↑
Progression from HPV to CIN2	1.3 (1.1-1.33) ↑
CIN1 clearance or regression	0.7 (0.56-0.7) for HIV 16/18 and 0.67 (0.56-0.67) for all other HPV types ↓
CIN2/3 to clearance or regression	0.57 (0.26-0.57) ↓
CIN3 progression to cervical cancer	2.5 (2.3-2.5) ↑

** Viral suppression of HIV due to ART adherence returns women to near HIV-negative natural history assumptions.*

Background: Cervical cancer elimination consortium (CCEMC)

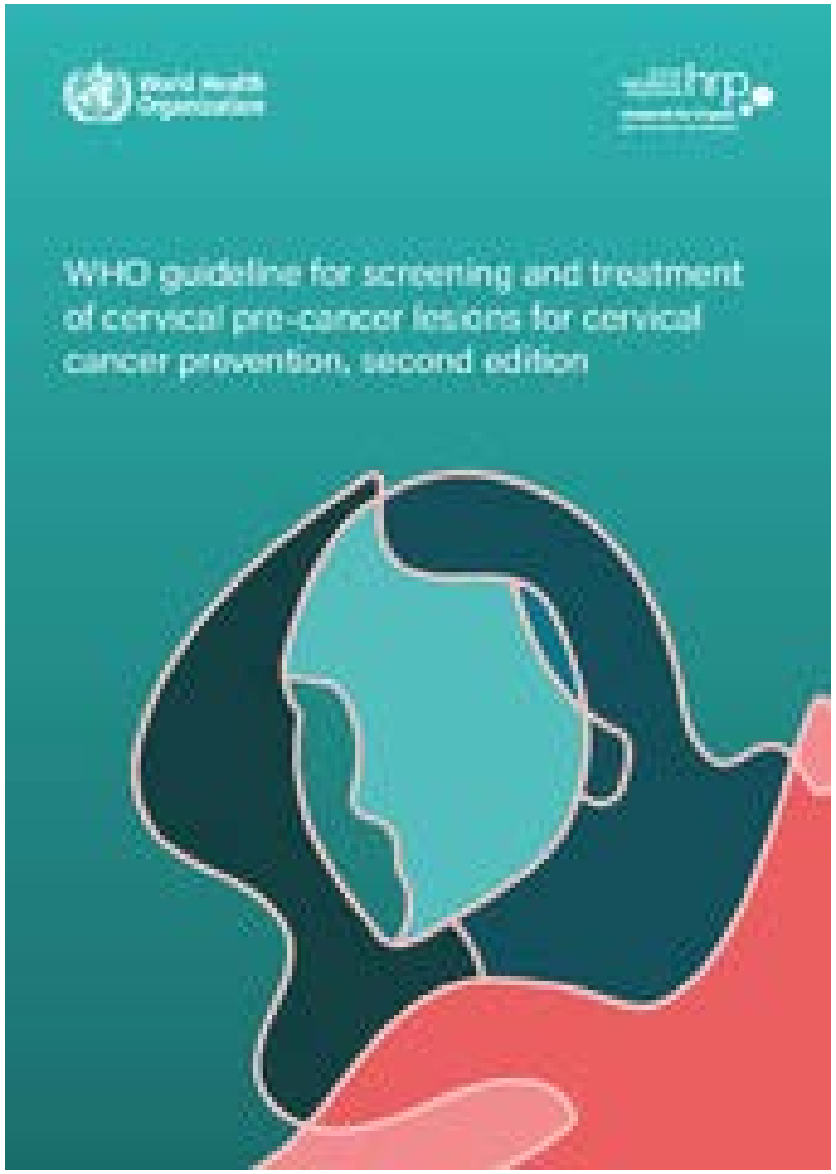


Canfell K/Kim JJ/Brisson M et al., Lancet Jan 30 2020

Three models assessed impact and cost-effectiveness of elimination scale-up across 78 low-income and lower-middle-income countries

The CCEMC models were reviewed and endorsed by IVIR-AC

2021 WHO Guidelines



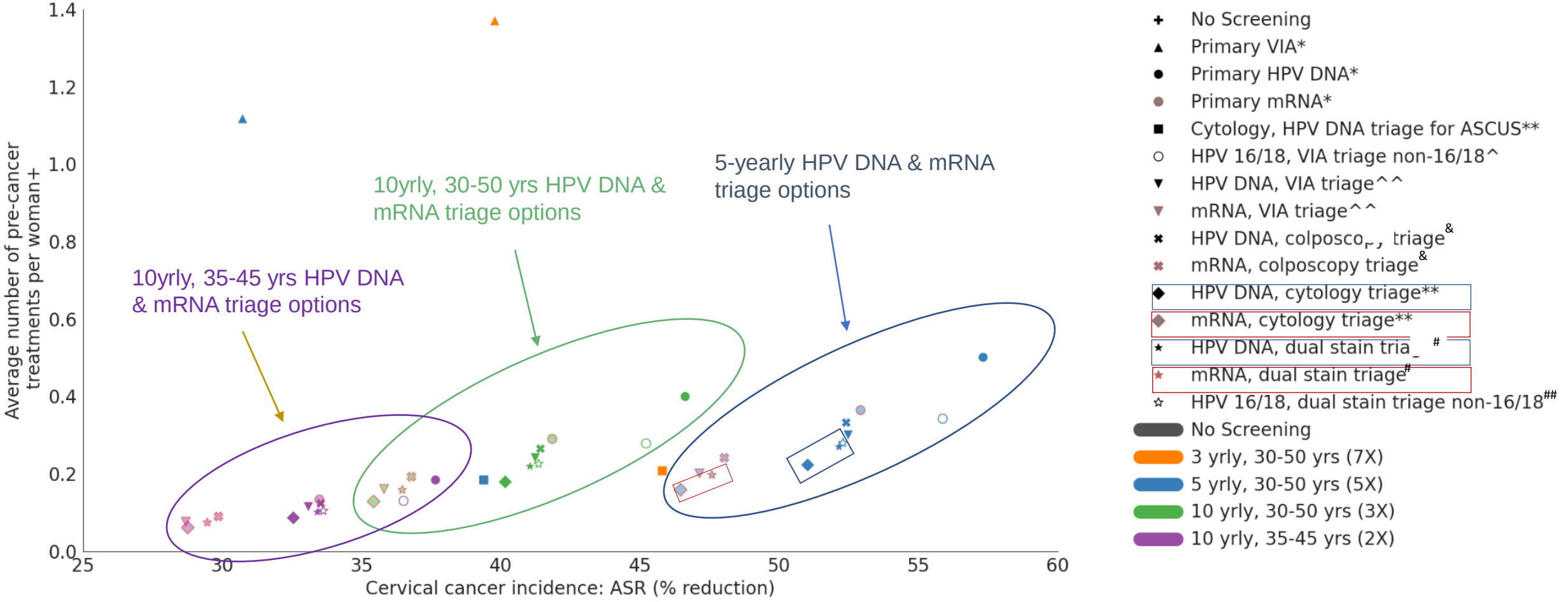
- Update of 2013 guidelines
- Drew upon work performed for updated IARC Handbook of Cervical Screening

https://www.who.int/publications/i/item/9789240030824

Summary recommendation for the general population of women	**Summary recommendation for women living with HIV**
WHO suggests using either of the following strategies for cervical cancer prevention: – HPV DNA detection in a screen-and-treat approach starting at the age of 30 years with regular screening every 5 to 10 years. – HPV DNA detection in a screen, triage and treat approach starting at the age of 30 years with regular screening every 5 to 10 years.	WHO suggests using the following strategy for cervical cancer prevention among women living with HIV: – HPV DNA detection in a screen, triage and treat approach starting at the age of 25 with regular screening every 3 to 5 years.

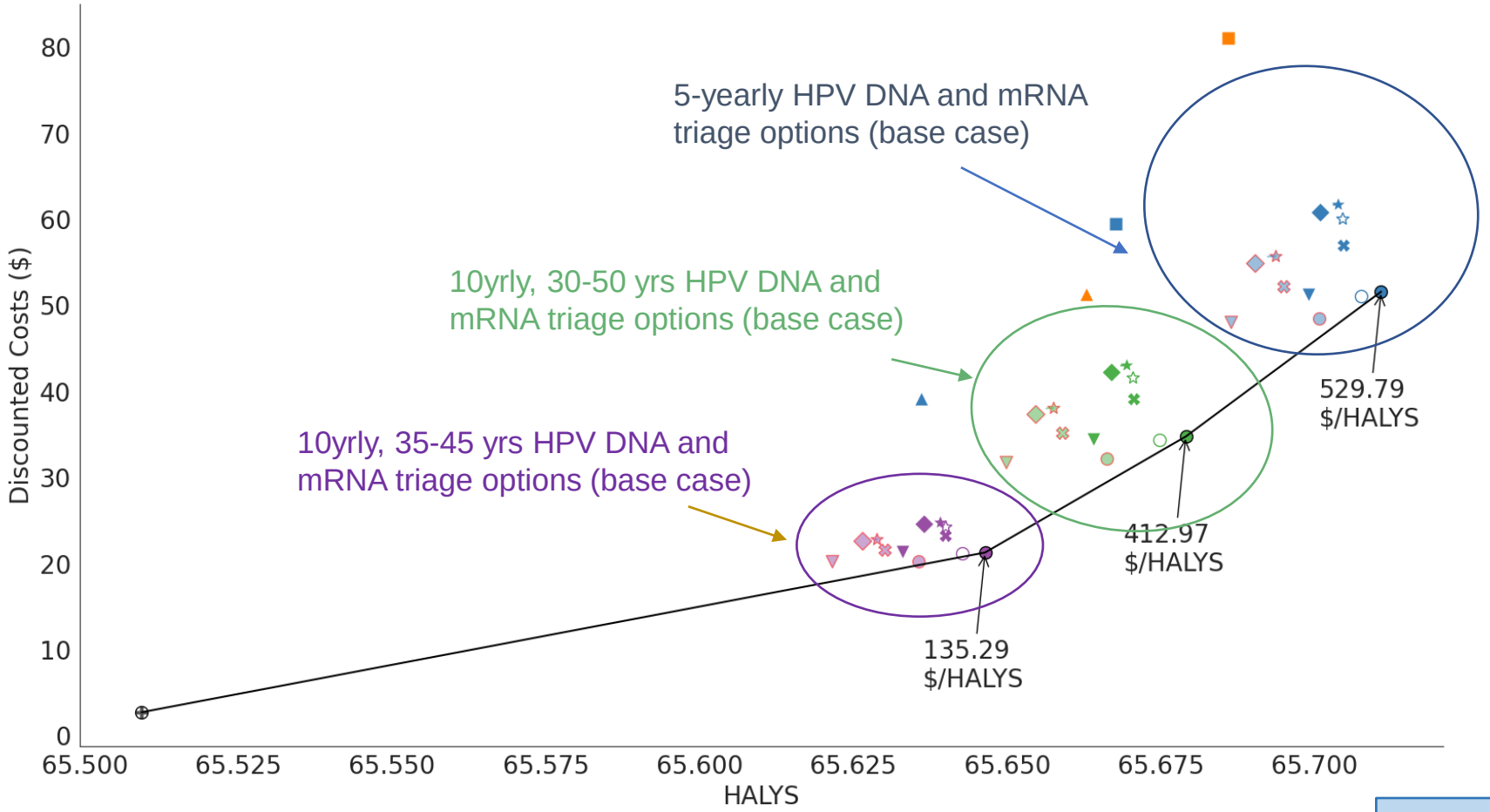
Acknowledgement: WHO Guidelines Development team; Guidelines Development Group (GDG)

Benefits (cancer incidence reduction) vs harms (pre-cancer treatments)
All scenarios including dual stain and HPV mRNA



*All positive women treated after using VIA to determine eligibility. **LSIL or worse direct to colposcopy; ASC-US + HPV triage positive referred to colposcopy. ^^ VIA triage positive women treated after using VIA to determine eligibility. ^ 16/18 positive women treated after using VIA to determine eligibility; OHR (non-16/18) positive women are treated only if VIA triage positive. & All HPV/mRNA positive go to colposcopy.
All dual stain positive go to colposcopy. ## All OHR (non-16/18) and dual stain positive or HPV16/18 positive go to colposcopy. + Note there could be multiple treatments in women who require follow-up

Cost-effectiveness (Cost/HALY) All scenarios - General population
Including Dual Stain and HPV mRNA



- No Screening
- Primary VIA*
- Primary HPV DNA*
- Primary mRNA*
- Cytology, HPV DNA triage for ASCUS**
- HPV 16/18, VIA triage non-16/18^
- HPV DNA, VIA triage^^
- mRNA, VIA triage^^
- HPV DNA, colposcopy triage&
- mRNA, colposcopy triage&
- HPV DNA, cytology triage**
- mRNA, cytology triage**
- HPV DNA, dual stain triage#
- mRNA, dual stain triage#
- HPV 16/18, dual stain triage non-16/18##
- No Screening
- 3 yrly, 30-50 yrs (7X)
- 5 yrly, 30-50 yrs (5X)
- 10 yrly, 30-50 yrs (3X)
- 10 yrly, 35-45 yrs (2X)

*All positive women treated after using VIA to determine eligibility **LSIL or worse direct to colposcopy; ASC-US + HPV triage positive referred to colposcopy ^^ VIA triage positive women treated after using VIA to determine eligibility. ^ 16/18 positive women treated after using VIA to determine eligibility; OHR (non-16/18) positive women are treated only if VIA triage positive. & All HPV/mRNA positive go to colposcopy. # All dual stain positive go to colposcopy. ## All OHR (non-16/18) and dual stain positive or HPV16/18 positive go to colposcopy.
0% discount rate for effect, 3% discount rate for cost
HALY: health-adjusted life-years

Willingness to pay threshold:
$500 (73 of the 78 LMIC (~94%) have GDP above ~$500)
Population-weighted average
1X GDP: US$2093 (29 of the 78 LMIC (~37%) have GDP ≥$2093)
0.5X GDP:US$1046 (52 of the 78 LMIC (~67%) have 0.5 GDP ≥$1046)

2. Framework and analysis plan for modelling to support determination of value case and PPCs of TxV

Modelling approach: TxV

- Using a range of scenarios reflecting TxV deployment under the two major Use Cases, and
- Varying the characteristics of the TxV and background PxV/screening,
- We will consider the potential impact of TxV across 78 LMICs, and
- Assess the benefits, harms and cost-effectiveness of each scenario.

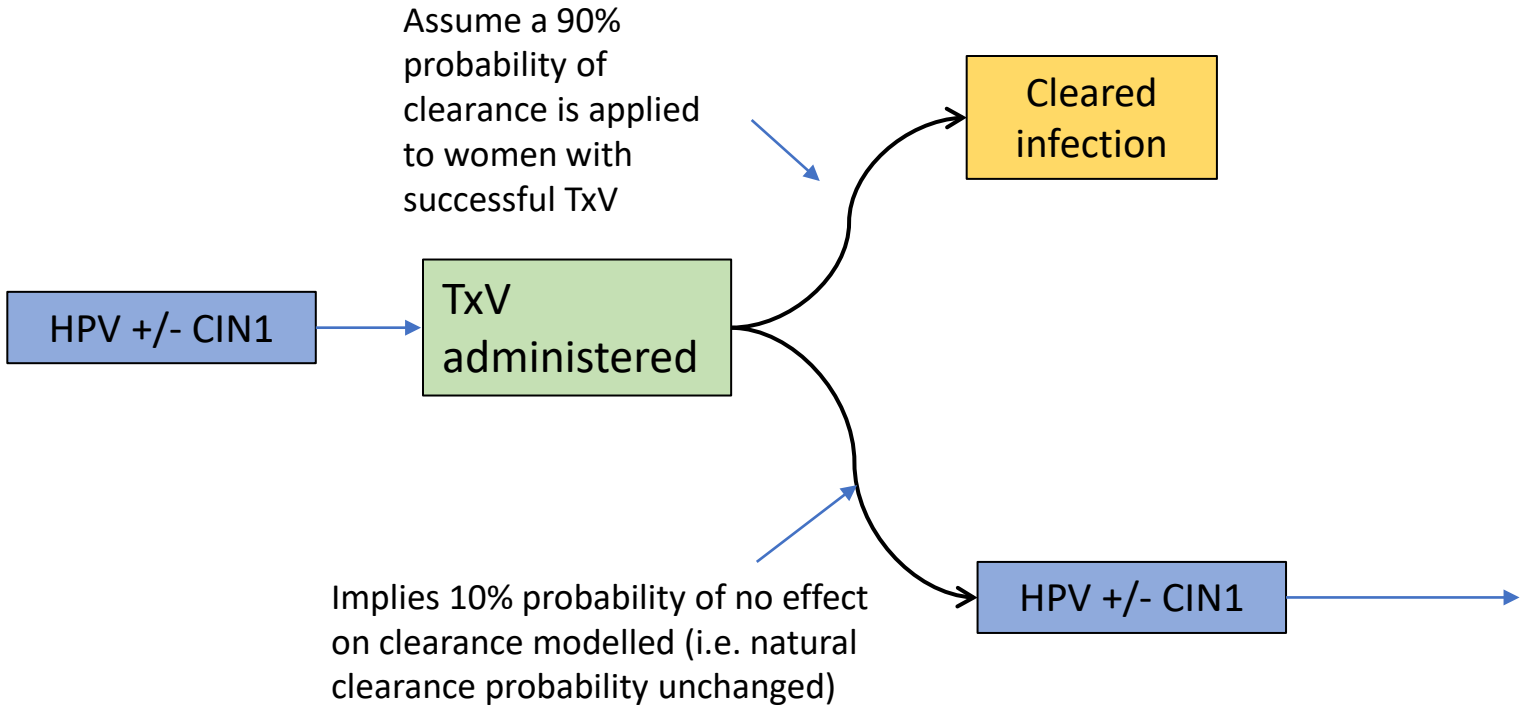
Modelling approach: TxV

- Stage 1:
  - High-level modelling of short, intermediate and long-term health impacts of TxV in large range of potential scenarios,
  - Focusing on predicted rates of CxCa incidence and mortality.
  - Limited range of assumed TxV characteristics, based on expert input.
- Stage 2:
  - 'Deep dive' health impact modelling of a relatively smaller number of the most promising and important scenarios for TxV that were identified in Stage 1.
  - Extended range of Tx characteristics will be explored.
  - Use of enhanced Policy1-Cervix platform incorporating HIV - will thus be able to consider differential efficacy effects in WLHIV.
- Stage 3:
  - Expand upon the Stage 2 impact analysis
  - Involve detailed analysis of some of the wider health benefits, cost-effectiveness and resource utilisation associated with roll-out of TxV.

Framework for modelling the Use Cases

Modelled implementation of TxV on HPV clearance: Implementation 1 - anchor on net clearance

This implementation of TxV will be evaluated against a comparator involving natural clearance



Age	HPV/CIN1_16 probability of clearance after TxV	HPV/CIN1_16 Natural probability of clearance (applied to those who did not clear after TxV)
10	0.9	0.38403
15	0.9	0.38403
20	0.9	0.38403
25	0.9	0.31216
30	0.9	0.31216
35	0.9	0.31216
40	0.9	0.289659
45	0.9	0.267728
50	0.9	0.246304
55	0.9	0.225333
60	0.9	0.204773
65	0.9	0.204773
70	0.9	0.204773
75	0.9	0.204773
80	0.9	0.204773

Implied vaccine efficacy (VE) is approx.

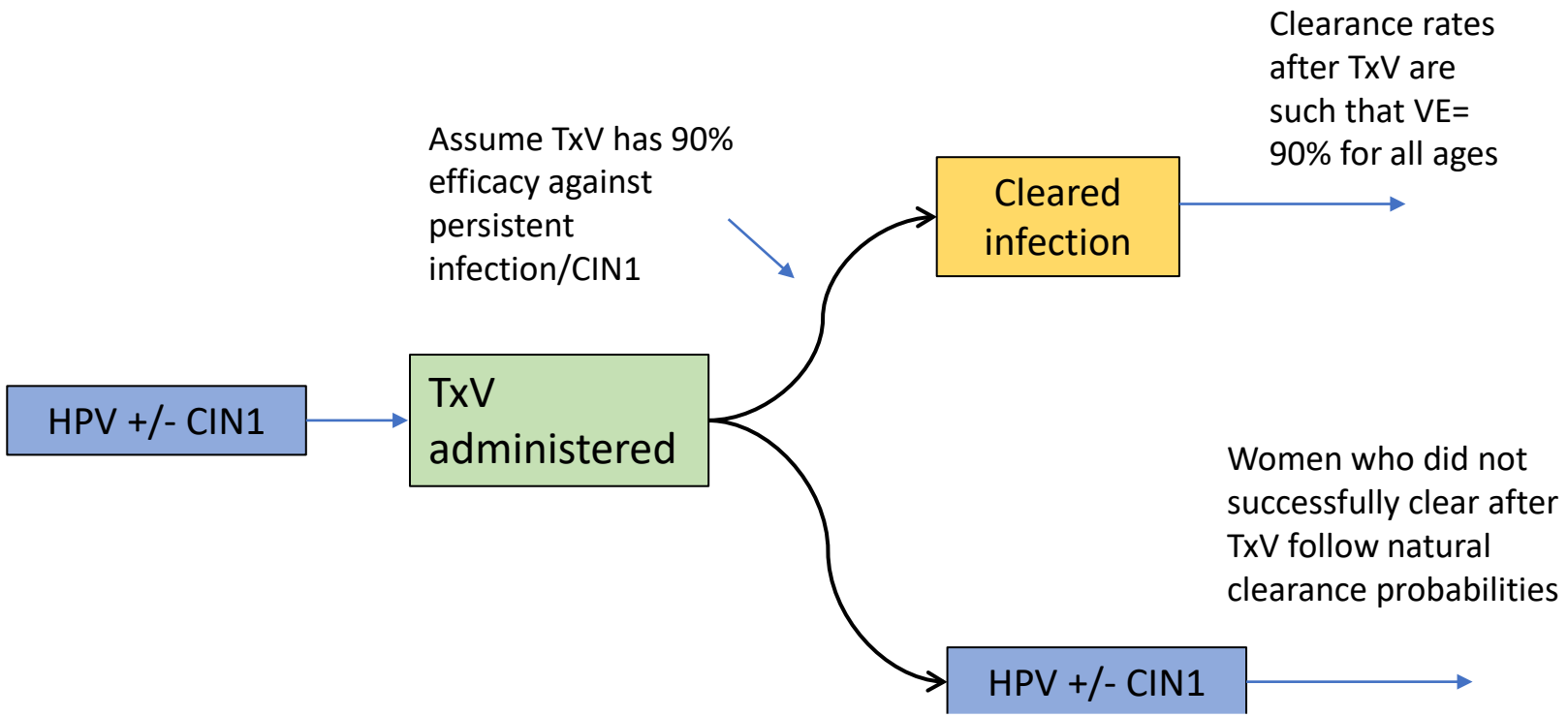
$$= \frac{\text{(Prob persistence placebo [i.e. natural history] – prob persistence in TxV group)}}{\text{Prob persistence placebo (natural history)}}$$

At age 30 years = (69%-10%)/69% = 86%
At age 60 years = (80%-10%)/80% = 88%

We will consider different, some based on net clearance (where VE thus varies across ages) and some based on VE being a fixed number (e.g. 90%) across all ages

Modelled implementation of TxV on HPV clearance:
Implementation 2 – anchor on VE

This implementation of TxV will be evaluated against a comparator involving natural clearance



Age	HPV/CIN1_16 probability of clearance after TxV	HPV/CIN1_16 Natural probability of clearance (applied to those who did not clear after TxV)
10	0.938403	0.38403
15	0.938403	0.38403
20	0.938403	0.38403
25	0.931216	0.31216
30	0.931216	0.31216
35	0.931216	0.31216
40	0.9289659	0.289659
45	0.9267728	0.267728
50	0.9246304	0.246304
55	0.9225333	0.225333
60	0.9204773	0.204773
65	0.9204773	0.204773
70	0.9204773	0.204773
75	0.9204773	0.204773
80	0.9204773	0.204773

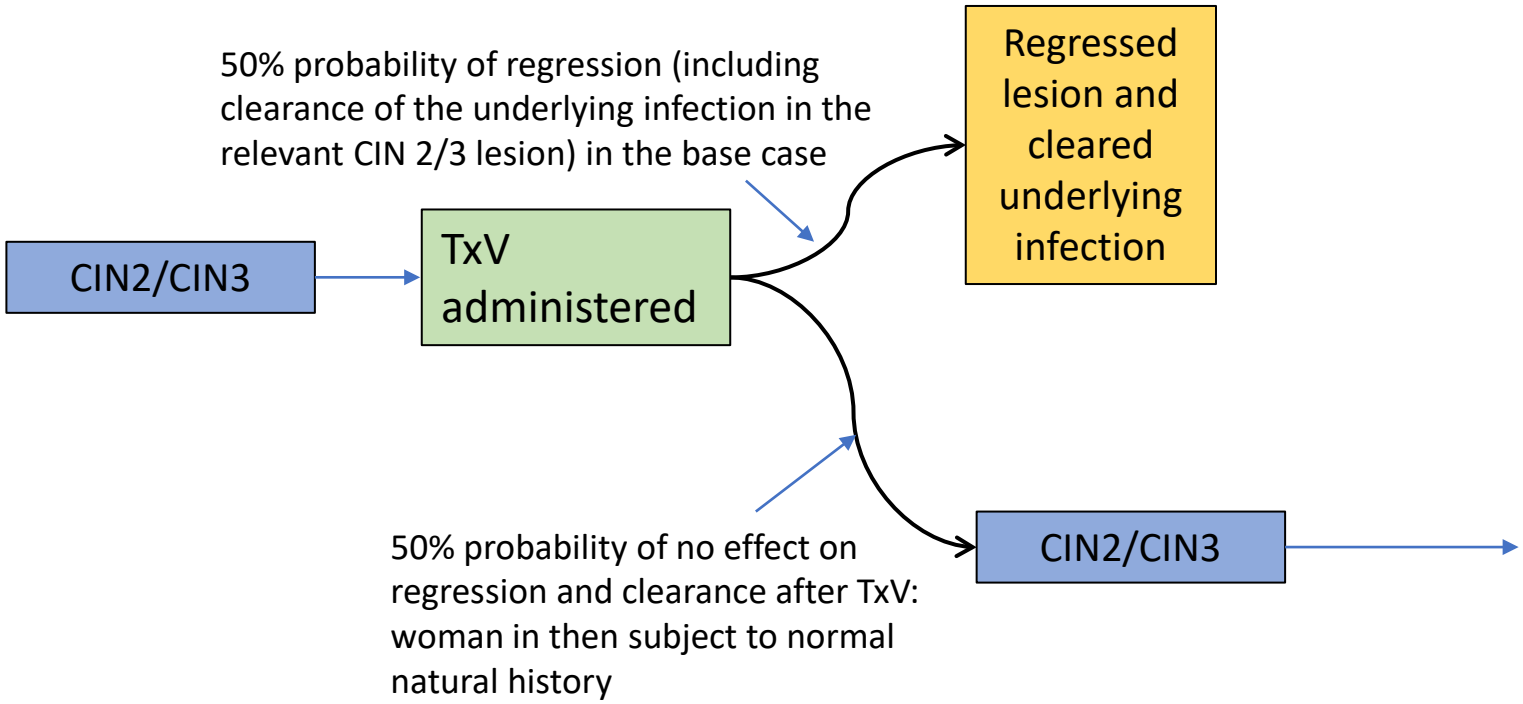
Vaccine efficacy (VE) is approx.

$$= \frac{\text{(Prob persistence placebo [i.e. natural history] – prob persistence in TxV group)}}{\text{Prob persistence placebo (natural history)}}$$

At age 30 years = (69%-7%)/69% = 90%
At age 60 years = (80%-8%)/80% = 90%

We will consider different, some based on net clearance (where VE thus varies across ages) and some based on VE being a fixed number (e.g. 90%) across all ages

Modelled implementation of TxV on CIN regression



Vaccine efficacy difficult to interpret because rate of natural clearance + regression in women with underlying CIN3 is negligible

For CIN3, we assume a 50% probability of complete clearance and regression in women with successfully administered TxV

This implementation of TxV will be evaluated against a comparator involving natural regression and clearance

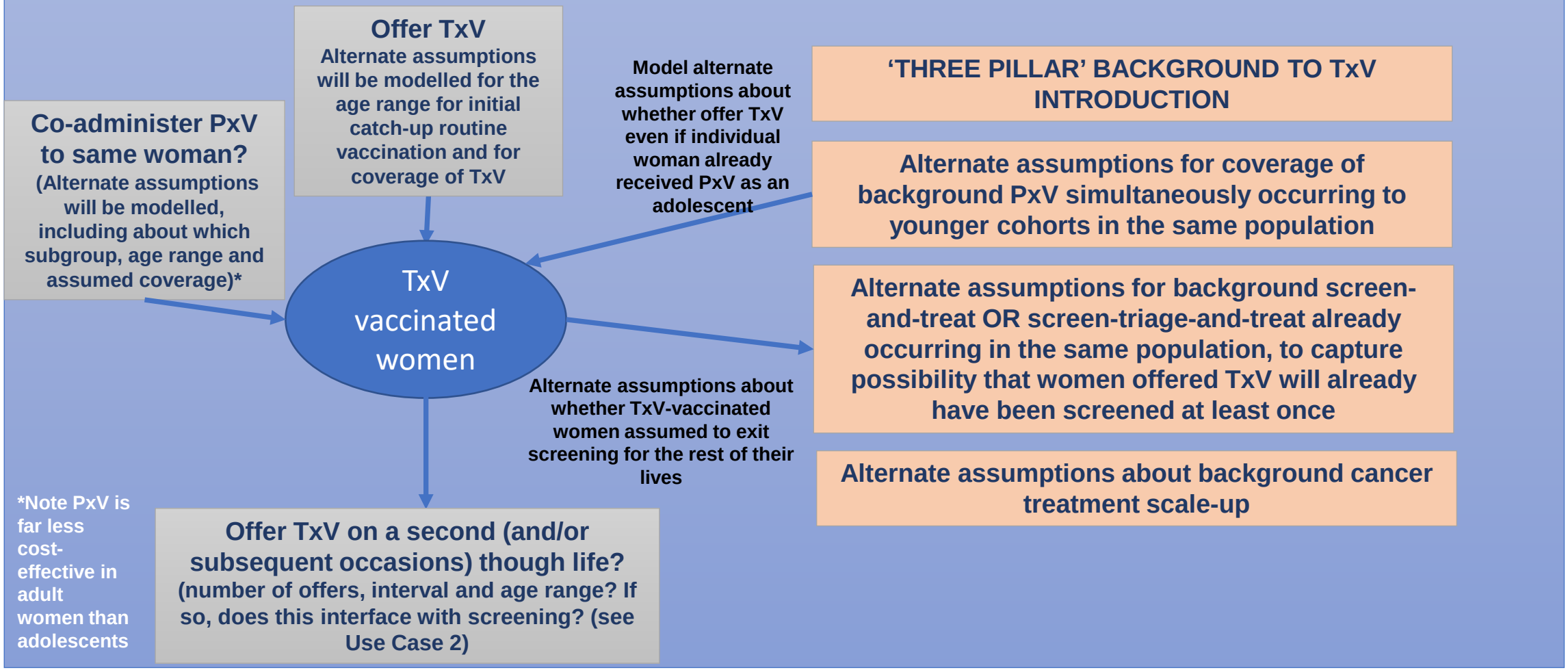
Age	CIN3_16 to uninfected after TxV	CIN3_16 to uninfected	CIN3_16 to HPV/CIN1_16	CIN3_16 to CIN2_16
10	0.5	0	0.052526	0.037418
15	0.5	0	0.052526	0.037418
20	0.5	0	0.052526	0.037418
25	0.5	0	0.052526	0.037418
30	0.5	0	0.052526	0.037418
35	0.5	0	0.022392	0.037418
40	0.5	0	0.022392	0.014908
45	0.5	0	0.022392	0.014908
50	0.5	0	0.022392	0.011174
55	0.5	0	0.022392	0.011174
60	0.5	0	0.007445	0.007445
65	0.5	0	0.007445	0.007445
70	0.5	0	0.007445	0.007445
75	0.5	0	0.007445	0.00372
80	0.5	0	0.007445	0.00372

USE CASE ALGORITHMS

This high level summary shows the many possible variations on the Use Cases which will be considered and modelled

Use Case 1: Population-level vaccination of all adult females in a given age range

Alternate assumptions about timing of TxV availability will be modelled. Direct efficacy will be assumed against HPV 16/18 (with some cross-protection against related HPV types)



USE CASE ALGORITHMS

This high level summary shows the many possible variations on the Use Cases which will be considered and modelled

Use Case 2A: Targeted usage of TxV within an HPV screening program, for women with positive oncogenic HPV status.

Alternate assumptions about timing of TxV availability will be modelled. Direct efficacy will be assumed against HPV 16/18 (with some cross-protection against related HPV types)

HPV screened woman

Alternate assumptions about background screen-and-treat OR screen-triage-and-treat coverage

HPV negative

HPV positive

Offer PxV?
Alternate assumptions will be modelled, including about which subgroup, age range and assumed coverage*

Offer TxV
Alternate assumptions will be modelled for the age range

ALTERNATE ASSUMPTIONS FOR

- Coverage of TxV
- Distinguish between HPV16/18 vs any oncogenic HPV in TxV offe (WHO 2021 Guidelines include partial genotyping algorithms for HPV 16/18 which will allow this distinction to be made)
- Offer TxV even if individual woman already received PxV as an adolescent

Note that with HPV self-collection, both HPV and TxV could potentially occur outside clinical settings, potentially without pelvic exams

TxV vaccinated women

Alternate assumptions about whether TxV-vaccinated women assumed to exit any established screening program

OTHER BACKGROUND TO TxV INTRODUCTION

Alternate assumptions around underlying coverage of prior PxV vaccination

Alternate assumptions for background cancer treatment scale-up coverage

Refer for diagnostic evaluation and/or ablation/LLETZ treatment of existing CIN
(Assume management according to WHO 2021 screen-and-tret guidelines)

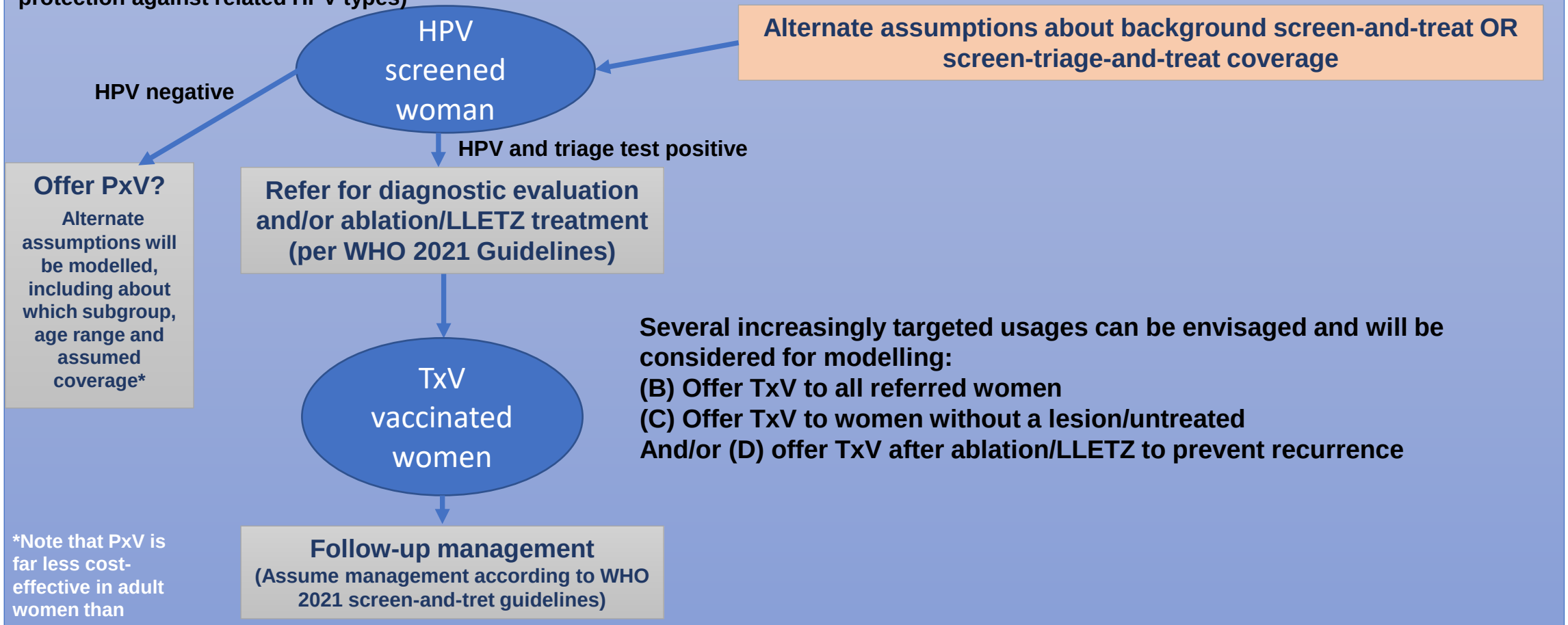
*Note PxV is far less cost-effective in adult women than adolescents

USE CASE ALGORITHMS

This high level summary shows the many possible variations on the Use Cases which will be considered and modelled

Use Case 2B,2C,2D: Targeted usage of TxV within an HPV screening program, for those B) either referred to diagnostic evaluation, C) Without confirmed lesion; D) After ablation/LLETZ

Alternate assumptions about timing of TxV availability will be modelled. Direct efficacy will be assumed against HPV 16/18 (with some cross-protection against related HPV types)



Several increasingly targeted usages can be envisaged and will be considered for modelling:
(B) Offer TxV to all referred women
(C) Offer TxV to women without a lesion/untreated
And/or (D) offer TxV after ablation/LLETZ to prevent recurrence

3. Summary of main outcomes from recent targeted consultation workshops

Summary of some key insights from vaccine development workshop (1)

- **An interactive workshop was held on Feb 4 with three experts: Margaret Stanley, John Schiller and Peter Dull.**
- **A range of questions were posed related to future feasible ('target') therapeutic vaccine (TxV) characteristics.**
- **Although discussions are ongoing, some key insights to date include:**

(1) Future TxV may be assumed to increase net clearance of prevalent HPV +/- CIN1 infection substantially, e.g. to 90% over a year. Net regression of prevalent CIN2/3 can potentially be assumed to increase to ~50% over a year. No survival benefit (or clearance) assumed to be experienced in women with prevalent underlying invasive cervical cancer.

(Note, the model will capture TxV efficacy as additional clearance/regression beyond that which is experienced without TxV i.e. will capture additional effects beyond natural-immunity mediated clearance).

Summary of some key insights from vaccine development workshop (2)

(2) In successfully treated women with infection, TxV will immediately clear the infection. Assumptions about the degree of immune memory were extensively discussed.
Although in the base case we will consider no immune memory, one scenario to be considered is that any subsequent HPV re-infection would be swiftly resolved due to memory effects i.e. that there would be some degree of ongoing 'prophylactic' protection against new persisting infection.

(3) TxV incorporating HPV types 16/18 will be assumed in baseline analysis, with 50% (relative) cross-type efficacy assumed against 16/18-closely related types.

(4) Population-level introduction and scale-up of TxV could be assumed to start from 2030 (realistic best-case), but with assessment of the impact of delay to 2040. After this workshop, the internal team deliberated further and determined that a roll-out date of 2027 should also be modelled.

(5) Mode of delivery – potentially simple IM injection OR IM prime/intravaginal boost.

Summary of some key insights from screening workshop (1)

- **An interactive workshop was held on Feb 9 with six experts: Partha Basu, Rolando Herrero, Raul Murillo, Linda Eckert, Mike Chirenje and Nico Wentzensen.**
- **A range of questions were posed related to defining scenarios with different background assumptions for the three elimination pillars, discussing what should be assumed for any concomitant screening and treatment, and considering variations on whether prophylactic vaccine is co-administered**
- **Some key insights from the first group included that:**

(1) We should consider a wide range of assumptions around the successful implementation of the three pillars by 2030, including (in the best case) having reached the 90-70-90 targets, and (in the worst case) assuming no additional increase in coverage from today's access rates (which could be considered as approximately and in effect 0-0-33% for LMICs).*

*Recognizing that although some women in LMICs have access to vaccination and screening, penetration of organized and effective screening programs with optimal QC, monitoring and evaluation is still very limited, especially considering Covi-19 impacts,

Summary of some key insights from screening workshop (2)

(2) It was discussed that concomitant PxV for adult women was unlikely to be cost-effective. Therefore this would not be considered in the main scenario. However, it was recognised that demonstrating lack of cost-effectiveness of adult PxV in this context would potentially be an important outcome of the modelling.

(3) Target age for TxV – starting at 20 years could be considered since it is assumed that TxV considerably increases clearance of HPV infections and this could have a population level long term impact on reducing risk. General agreement that starting at 20 or 30 years could both be evaluated.
(It should be borne in mind that starting at age 30 years is likely to be shown in the modelling to be more efficient/cost-effective since HPV infection and CIN in young women both have very high probabilities of natural regression).

(4) It would be useful to model the impact of TxV in women who test HPV16/18 positive only, and a separate scenario in which we model TxV in women who test any HR-HPV positive, taking into account in the modelling, projected cross-efficacy against other HPV types (assumed cross-efficacy per vaccine experts opinion).

(5) There was extensive discussion about whether there could be a scenario considered where women who test HPV positive and are offered TxV, are not followed-up from that point. Benefits/public health benefit and cost-effectiveness, as well as missed disease in this scenario, would be quantified by the modelling exercise.

Summary of some key insights from Implementation workshop (1)

- **An interactive workshop was held on Feb 15-16 with seven experts: Marion Saville, Patty Garcia, Sinead Delany-Moretlwe, Mamadou Diop, Hiro Akaba and Paul Bloem.**
- **A range of questions were related to defining realistic scenarios for background assumptions for the three elimination pillars, the current data sources on uptake of prophylactic vaccination and screening.**
- **Some key insights from this group included that:**

1) As in the screening workshop, there was considerable uncertainty that the three pillar targets (90-70-90) could be reached across all countries by 2030, and that realistic scale-up assumptions would be important to consider.

Summary of some key insights from implementation workshop (2)

2) Up-to-date information on current coverage across the three pillars will be important background context

- Vaccination coverage from WHO/ICO can provide current information; for projections of coverage, we should be cautious about assuming similar trajectories to other vaccines and should consider the strength of the immunisation implementation system of countries. Utilisation of metrics such as ‘DTP minus 10%’ (as used by Gavi) to inform such projections is a possible option.
- There are some studies by ICO and others on screening coverage in the AFRO region, stratified by HIV status. However, we should be cautious when using data on screening coverage for a number of reasons (e.g. different primary tests are used including VIA, follow-up compliance may be limited, coverage may be reported as ‘ever screened’ versus routine attendance, lack of full organised approach including QA and monitoring)
- Using radiotherapy access as a surrogate for all treatment (as used for WHO CCEMC elimination modelling) will inform the best available estimates of current cancer treatment access, although again, there are issues with the data.

Summary of some key insights from implementation workshop (3)

3) There was some interest in considering the wider impact of TxV including on other cancers or considering males. However, overall, the group felt that targeting the vaccine to the highest-risk groups, including LMIC was of highest priority initially.

4) Considering a start-age of 20 years for TxV was thought unlikely to be cost-effective, but the group agreed it was worth including in the modelling to quantify the impact and cost-effectiveness.

Focused discussion at Advisory Group meeting

An interactive workshop was held on March 2 with the wider Advisory Group (AG), including all those involved in the interactive workshops. We brought the group together for further multidisciplinary, focused discussion on three key unresolved topics.

TOPIC 1. We asked about characteristics and delivery of therapeutic vaccine for WLHIV:

- Bearing in mind that the modelling will inform the future impact assessment as we go forward, how might WLHIV benefit from and potentially access the therapeutic vaccine?
- Unfortunately, there is an expectation from the vaccine development experts that, if anything, efficacy in WLHIV will be lower than in the general population.
- What are some of the public health issues that should be borne in mind as a result?

Some key insights from the discussion:

- Starting with the same efficacy assumptions as general population is reasonable, assuming those accessing TxV would have well-controlled HIV infection
- Higher TxV coverage rates in WLHIV could be considered than in the general population, since these women could be offered TxV when returning for ART/refills.

Focused discussion at Advisory Group meeting

***TOPIC 2. We asked about delivery of therapeutic vaccine within cervical screening programs* (Use Case 2).**

- Bearing in mind that the modelling will inform the future impact assessment as we go forward, could a scenario be considered where women with HPV infection and/or CIN receive the therapeutic vaccine and are not followed up further?
- Note that there would likely be considerable public health benefits overall which will be quantified in the modelling, but that in this situation women with undiagnosed invasive cancer would not receive any health benefits and potentially women would derive false reassurance from vaccination, if communications are not carefully managed.

Some key insights from this discussion:

- Without appropriate follow-up, diagnosis of CaCx in a proportion of TxV women would be inevitable. Even if communication was carefully managed, this might result in catastrophic loss of confidence in TxV and thus a scenario of rapidly collapsing TxV coverage could be considered
- However, the group reached consensus that use in HPV positive women should only be in situations where follow-up was recommended. Different levels of compliance with follow-up recommendations (from 0% to a realistic level as used in WHO screening guidelines e.g.70%) should be considered.

Focused discussion at Advisory Group meeting

TOPIC 3. We asked about communicating uncertainty about potential wider population benefits.

A therapeutic vaccine may also protect against other HPV-related cancers and thus could provide further benefits to females as well as benefits to males.

Quantifying these effects is out of scope for the current exercise because:

- the framing is CaCx elimination
- we have not accounted for the additional development time and/or clinical trials
- we have not considered delivery of vaccine to adult males, and
- modelling of Use Cases involving males introduces unwieldy degree of complexity to the current exercise.

How do the group think that we can best convey and communicate this issue to all stakeholders when it comes to dissemination of results?

Some key insights from the discussion:

- Natural history of other HPV-cancers is more uncertain
- Life cycle/development analogy can be made with prophylactic vaccines (first trialled and effectiveness established against CIN2/3; later extended to outcomes for other cancers)
- Communication about the scope of the current exercise is key.

Summary of key insights

Decisions from vaccine development workshop

- TxV targets 16/18 infections and lesions
- 90% net clearance of HPV +/- CIN1 *
- 50% regression + clearance of CIN2/3
- 50% cross-protection against 16/18 related types
- No effect on invasive cervical cancer
- Population-level scale-up of TxV in LMIC to start from 2030 (base case) 2027 (best case); 2040 (worst case)
- Vaccine delivered IM OR IM+ prime/intravaginal boost

*Later, in the AG meeting, we also proposed and it was agreed that we would also model VE=90% at all ages in Stage 1.

Decisions from Screening workshop

Elimination targets

- 90-70-90 reached by 2030 (best case)
- No change from current rates (worst case)

Co-administering of PxV and TxV

- No co-administering of PxV and TxV (base case)
- Co-administering explored (sensitivity)

TxV administered from

- age 20 years (use case 1 only)
- age 30 years

For Use Case 2, we assume TxV administered in women who receive an HPV test and

- Screen 16/18 positive (genotyping only)
- Screen any HR-HPV positive (any primary HPV)

For Use case 2, after TxV in HPV-positive women we assume

- Women are not followed-up;
- Women are followed-up for missed disease

Relative benefits and cost-effectiveness assessed

Decisions from Implementation workshop

Vaccination coverage

- Most up-to-date coverage from WHO/ICO
- Realistic projections 2020-2030 informed by metrics such as ‘DTP-10%’ (used by Gavi)

Screening and precancer treatment coverage

- Published data along with studies on screening coverage in AFRO region stratified by HIV-status will be obtained
- Data should be interpreted cautiously, due to differences in screening tests used, lack of formal QA and monitoring, ect.

Cancer treatment coverage

- Radiotherapy as a surrogate access

Focus should be on optimising outcomes in groups at highest-risk in the first instance, (i.e women in LMIC at risk of cervical cancer)

Questions and discussion

Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries

Marc Brisson, Jane J Kim*, Karen Canfell*, Mélanie Drolet, Guillaume Gingras, Emily A Burger, Dave Martin, Kate T Simms, Élodie Bénard, Marie-Claude Boily, Stephen Sy, Catherine Regan, Adam Keane, Michael Caruana, Diep T N Nguyen, Megan A Smith, Jean-François Laprise, Mark Jit, Michel Alary, Freddie Bray, Elena Fidarova, Fayad Elsheikh, Paul J N Bloem, Nathalie Broutet, Raymond Hutubessy*

Summary

Background The WHO Director-General has issued a call for action to eliminate cervical cancer as a public health problem. To help inform global efforts, we modelled potential human papillomavirus (HPV) vaccination and cervical screening scenarios in low-income and lower-middle-income countries (LMICs) to examine the feasibility and timing of elimination at different thresholds, and to estimate the number of cervical cancer cases averted on the path to elimination.

Methods The WHO Cervical Cancer Elimination Modelling Consortium (CCEMC), which consists of three independent transmission-dynamic models identified by WHO according to predefined criteria, projected reductions in cervical cancer incidence over time in 78 LMICs for three standardised base-case scenarios: girls-only vaccination; girls-only vaccination and once-lifetime screening; and girls-only vaccination and twice-lifetime screening. Girls were vaccinated at age 9 years (with a catch-up to age 14 years), assuming 90% coverage and 100% lifetime protection against HPV types 16, 18, 31, 33, 45, 52, and 58. Cervical screening involved HPV testing once or twice per lifetime at ages 35 years and 45 years, with uptake increasing from 45% (2023) to 90% (2045 onwards). The elimination thresholds examined were an average age-standardised cervical cancer incidence of four or fewer cases per 100 000 women-years and ten or fewer cases per 100 000 women-years, and an 85% or greater reduction in incidence. Sensitivity analyses were done, varying vaccination and screening strategies and assumptions. We summarised results using the median (range) of model predictions.

Findings Girls-only HPV vaccination was predicted to reduce the median age-standardised cervical cancer incidence in LMICs from 19·8 (range 19·4–19·8) to 2·1 (2·0–2·6) cases per 100 000 women-years over the next century (89·4% [86·2–90·1] reduction), and to avert 61·0 million (60·5–63·0) cases during this period. Adding twice-lifetime screening reduced the incidence to 0·7 (0·6–1·6) cases per 100 000 women-years (96·7% [91·3–96·7] reduction) and averted an extra 12·1 million (9·5–13·7) cases. Girls-only vaccination was predicted to result in elimination in 60% (58–65) of LMICs based on the threshold of four or fewer cases per 100 000 women-years, in 99% (89–100) of LMICs based on the threshold of ten or fewer cases per 100 000 women-years, and in 87% (37–99) of LMICs based on the 85% or greater reduction threshold. When adding twice-lifetime screening, 100% (71–100) of LMICs reached elimination for all three thresholds. In regions in which all countries can achieve cervical cancer elimination with girls-only vaccination, elimination could occur between 2059 and 2102, depending on the threshold and region. Introducing twice-lifetime screening accelerated elimination by 11–31 years. Long-term vaccine protection was required for elimination.

Interpretation Predictions were consistent across our three models and suggest that high HPV vaccination coverage of girls can lead to cervical cancer elimination in most LMICs by the end of the century. Screening with high uptake will expedite reductions and will be necessary to eliminate cervical cancer in countries with the highest burden.

Funding WHO, UNDP, UN Population Fund, UNICEF–WHO–World Bank Special Program of Research, Development and Research Training in Human Reproduction, Canadian Institute of Health Research, Fonds de recherche du Québec–Santé, Compute Canada, National Health and Medical Research Council Australia Centre for Research Excellence in Cervical Cancer Control.

Introduction

Cervical cancer is the second most frequent cancer among women in low-income and lower-middle-income countries (LMICs).[1] In 2018, 290 000 (51%) of the 570 000 new cervical cancer cases worldwide occurred in women living in LMICs (500 000 [88%] when including upper-middle-income countries).[1] Without further intervention, these inequalities in the burden of cervical cancer are expected to grow, because recent increases in the uptake of human papillomavirus (HPV) vaccination and cervical

Lancet 2020; 395: 575–90

Published **Online** January 30, 2020 https://doi.org/10.1016/S0140-6736(20)30068-4

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*Joint first authors

Centre de recherche du CHU de Québec - Universite Laval, Québec, QC, Canada (Prof M Brisson PhD, M Drolet PhD, G Gingras PhD, D Martin PhD, É Bénard MSc, Prof M-C Boily PhD, J-F Laprise PhD, Prof M Alary MD); **Department of Social and Preventive Medicine, Universite Laval, Québec, QC, Canada** (Prof M Brisson, Prof M-C Boily, Prof M Alary); **MRC Centre for Global Infectious Disease Analysis, Department of Infectious Disease Epidemiology, Imperial College London, London, UK** (Prof M Brisson, Prof M-C Boily); **Center for Health Decision Science, Harvard T.H. Chan School of Public Health, Boston, MA, USA** (Prof J J Kim PhD, E A Burger PhD, S Sy MS, C Regan BA); **Cancer Research Division, Cancer Council NSW, Sydney, NSW, Australia** (K Canfell DPhil, K T Simms PhD, A Keane PhD, M Caruana DPhil, D T N Nguyen PhD, M A Smith PhD); **School of Public Health, Sydney Medical School, University of Sydney, Sydney, NSW, Australia** (K Canfell, K T Simms, A Keane, M Caruana, D T N Nguyen, M A Smith); **Prince of Wales Clinical School, University of New South Wales, Sydney, NSW, Australia** (K Canfell); **Department of Health Management and Health Economics, University of Oslo, Oslo, Norway** (E A Burger); **Centre for Mathematical Modelling of Infectious Disease, London School of**

Hygiene and Tropical Medicine, London, UK (Prof M Jit PhD); **Modelling and Economics Unit, Public Health England, London, UK** (Prof M Jit); **School of Public Health, University of Hong Kong, Hong Kong, China** (Prof M Jit); **Institut national de santé publique du Québec, Québec, QC, Canada** (Prof M Alary); **Section of Cancer Surveillance, International Agency for Research on Cancer, Lyon, France** (F Bray PhD); **and Department for the Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention** (E Fidarova MD), **Department of Immunization, Vaccines and Biologicals** (F Elsheikh MPH, P J N Bloem MBA, R Hutubessy PhD), **and Department of Reproductive Health and Research** (N Broutet MD), **World Health Organization, Geneva, Switzerland**

Correspondence to: Prof Marc Brisson, Centre de recherche du CHU de Québec, Universite Laval, Axe Santé des populations et pratiques optimales en santé, Québec, QC G1S 4L8, Canada
marc.brisson@crchudequebec.ulaval.ca

Research in context

Evidence before this study

In May, 2018, WHO issued a global call to eliminate cervical cancer as a public health problem. To inform its global strategy to accelerate cervical cancer elimination, WHO created the Cervical Cancer Elimination Modelling Consortium (CCEMC) to examine the following key questions: what elimination threshold should be used; what prevention strategies can lead to elimination; when could elimination be reached for different countries; and how many cancers could be averted. The current working definition of elimination is an age-standardised cervical cancer incidence of four or fewer cases per 100 000 women-years. Alternative definitions, such as an incidence of ten or fewer cases per 100 000 women-years and an 80–90% reduction in incidence, have also been suggested. The only previous multicountry modelling study of cervical cancer elimination suggests that global elimination is possible through girls-only human papillomavirus (HPV) vaccination at 80–100% coverage with a perfectly effective 9-valent vaccine and twice-lifetime HPV-based screening. Given that models necessarily include simplifying assumptions, the goal of the consortium is to use multiple models, taking into account their respective strengths and limitations, to illustrate the robustness of predictions. A systematic comparative modelling approach was used. To form the CCEMC, WHO selected three models that met the predefined eligibility criteria: HPV-ADVISE, Harvard, and Policy1-Cervix. The models projected reductions in cervical cancer incidence over time based on standardised HPV vaccination and cervical screening scenarios determined after consultations at various WHO technical expert, advisory group, and global stakeholder meetings. Three elimination thresholds were examined (cervical cancer incidence of four or fewer cases per 100 000 women-years, ten or fewer cases per 100 000 women-years, and ≥85% reduction in incidence).

Added value of this study

This comparative modelling analysis, which includes projections from three independent transmission-dynamic models, provides consistent results suggesting that 90% HPV vaccination coverage of girls can lead to cervical cancer elimination in most low-income and lower-middle-income countries (LMICs) within the next century. However, countries with the highest cervical cancer incidence (>25 cases per 100 000 women-years) might not reach elimination at the threshold of four or fewer cases per 100 000 women-years by vaccination alone, although these countries are predicted to have the greatest absolute reductions. More than 90% of these LMICs are in sub-Saharan Africa. Screening would accelerate elimination by 11–31 years and will be necessary to eliminate cervical cancer in countries with the highest incidence. Profound health benefits are predicted on the path to elimination. Intensive scale-up of girls-only vaccination with twice-lifetime screening is predicted to halve the age-standardised cervical cancer incidence by 2048 (and by 2061 with vaccination only), and to avert more than 74 million cervical cancer cases (61 million with vaccination only) in LMICs over the next century.

Implications of all the available evidence

The results of the CCEMC suggest that cervical cancer elimination as a public health problem is possible by the end of the century. However, to achieve elimination across all LMICs under the most ambitious threshold (four or fewer cases per 100 000 women-years), both high HPV vaccination coverage and screening uptake will be necessary, which will require considerable international commitment. These results have directly informed WHO's target of 90% HPV vaccination coverage, 70% screening coverage, and 90% of cervical lesions treated by 2030, as well as the WHO global strategy to accelerate cervical cancer elimination, which will be presented at the World Health Assembly in May, 2020.

cancer screening have mainly occurred in high-income countries. Less than 30% of LMICs have introduced HPV vaccination compared with more than 85% of high-income countries.[2,3] Additionally, only about 20% of women in LMICs have ever been screened for cervical cancer compared with more than 60% in high-income countries.[4,5]

Inequalities in HPV vaccination and screening uptake persist, despite the large body of evidence demonstrating that these interventions are highly effective and cost-effective. Large international randomised control clinical trials have shown that HPV vaccines are safe and highly effective against vaccine-type persistent infection and cervical precancerous lesions in women (with vaccine efficacy ≥93%).[6–8] These vaccines target high-risk HPV types that cause about 70% (bivalent and quadrivalent vaccines: HPV types 16 and 18) and 90% (9-valent vaccine: HPV types 16, 18, 31, 33, 45, 52, and 58) of cervical cancers.[9,10] Countries that have achieved high vaccination coverage have observed declines of 73–85% in vaccine-type HPV prevalence, and declines of 41–57% in high grade lesions (cervical intraepithelial neoplasia, grade 2 or worse) among young women, less than 10 years after implementation of HPV vaccination.[11] The effectiveness of population-based cervical cancer screening has also been shown, through the sharp declines in age-standardised cervical cancer incidence in high-income countries following the implementation of cytology-based screening.[12,13] Randomised controlled trials have shown that HPV-based tests are highly effective at detecting precancerous lesions and are likely to be more effective at preventing cervical cancer than visual inspection with acetic acid or

cytology.[14–16] Finally, mathematical modelling studies have consistently shown that girls-only HPV vaccination and cervical cancer screen-and-treat programmes are cost-effective in LMICs.[17–22]

Given the substantial global burden of cervical cancer, the increasing inequalities, and opportunities for effective and cost-effective primary and secondary prevention, the WHO Director-General made a global call in May, 2018, for action towards the elimination of cervical cancer as a public health problem.[23] To achieve this goal, WHO is developing, with its partners, a global strategy towards the elimination of cervical cancer.[24] Fundamental questions that must be addressed in the global strategy include: what elimination definition and threshold should be used, what prevention strategies can lead to elimination, when could elimination be reached, how many cervical cancers and deaths can be averted on the path to elimination, and what are the most efficient and cost-effective strategies to reach elimination? These important questions can only be addressed through mathematical modelling, which integrates our understanding of HPV transmission, cervical carcinogenesis, vaccine efficacy, and cervical screening and treatment performance to project the long-term health consequences of alternative cancer control policies. Hence, to inform its global strategy to accelerate cervical cancer elimination, WHO assembled the Cervical Cancer Elimination Modelling Consortium (CCEMC).[25,26]

In this Article, we describe the comparative modelling approach used by the CCEMC to inform WHO's global strategy towards the elimination of cervical cancer,[24] and present the CCEMC's predictions of the impact of various HPV vaccination and screening elimination strategies on cervical cancer incidence in 78 LMICs. The specific objectives of this analysis were to identify prevention strategies that lead to elimination, estimate the timing of elimination, and predict the number of cervical cancer cases averted on the path to elimination, for different elimination thresholds and country characteristics. In an accompanying Article,[27] we present the CCEMC's predictions of the impact of HPV vaccination, screening, and treatment scale-up on cervical cancer mortality.

Methods

Comparative modelling approach

This comparative modelling analysis adhered to recently published guidelines for multi-model comparisons[28] and for reporting model-based analyses of HPV vaccination and cervical screening[29] (appendix pp 26–28). A three-step systematic comparative modelling approach was used.

The aim of the first step was to identify and select the mathematical models. To minimise selection bias, WHO selected models that met the following predefined eligibility criteria: the models explicitly included the dynamic transmission of HPV infection, were capable of projecting the impact of HPV vaccination and cervical screening for all 78 LMICs, were independently developed and had been previously peer reviewed and published, and were able to provide predictions in a short timeframe to inform the WHO global strategy.[24] Four independent models were identified: HPV-ADVISE,[30,31] Harvard,[32,33] Policy1-Cervix,[34–36] and Spectrum.[37,38]

The aim of the second step was to identify HPV vaccination and screening strategies that can lead to cervical cancer elimination and examine between-model variability. The four models were used to predict the change in cervical cancer incidence over time for 40 standardised HPV vaccination and screening scenarios, with a subset of ten LMICs (appendix pp 14–15). Impact predictions were done without harmonising the basic structure of the models or parameters governing the setting and disease. The results were presented at various WHO technical expert, advisory group, and global stakeholder meetings, and ultimately three HPV vaccination and screening scenarios were identified to proceed in a larger number of countries (78 LMICs).[39] The three final scenarios that were selected for the global analysis (see scenario descriptions below and in the appendix p 16) were chosen as they showed potential for cervical cancer elimination in LMICs and follow WHO recommendations for HPV vaccination and cervical screening.[40,41]

Finally, the aim of the third step was to produce predictions of the population-level impact of the three HPV vaccination and cervical screening scenarios for all 78 LMICs. Three of the four models (HPV-ADVISE, Harvard, and Policy1-Cervix) were able to provide predictions for all 78 LMICs within the required timelines, and thus form the core models of the CCEMC. The structure of the models and the comparative modelling approach were presented and reviewed by the WHO Advisory Committee on Immunization and Vaccines related Research (IVIR).[39]

Model description

The three CCEMC models (HPV-ADVISE, Harvard, and Policy1-Cervix) have been used extensively to inform recommendations on cervical screening and HPV vaccination in Australia, Canada, the UK, the USA, and at a global level.[30–36] Although developed independently, the models have common features. First, they are transmission-dynamic models of HPV infection and the natural history of cervical cancer. Second, they include the following components: sexual behaviour and HPV transmission, natural history of cervical cancer, vaccination, and screening, diagnosis, management, and treatment of cervical lesions and cancer. HPV transmission and cervical carcinogenesis are modelled for the HPV types in the 9-valent vaccine (HPV types 16, 18, 31, 33, 45, 52, 58) and other high-risk types. The models simulate type-specific HPV transmission through sexual activity, based on different risk groups and sexual mixing. The models reproduce the type-specific natural history of cervical cancer, from persistent HPV infection to cervical

See Online for appendix

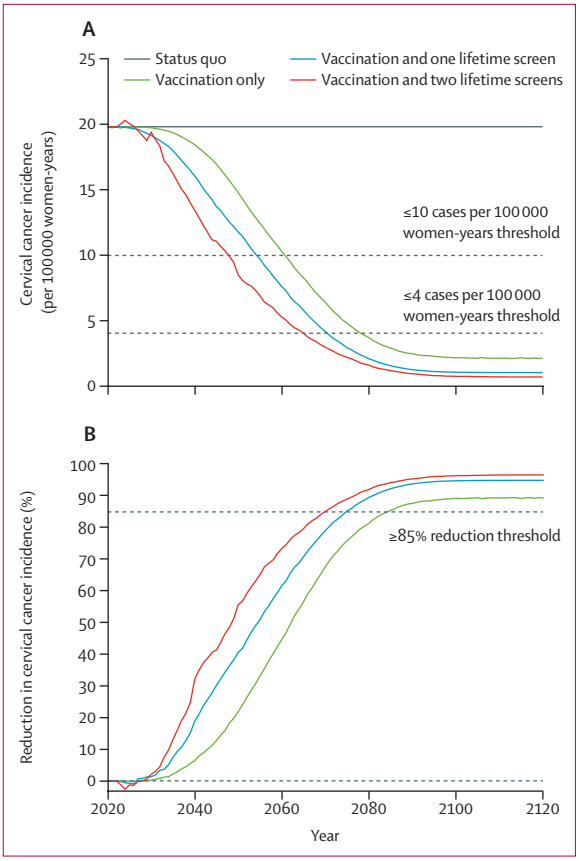

Figure 1: **Dynamics of cervical cancer incidence after HPV vaccination and cervical screening**
Average age-standardised cervical cancer incidence per 100 000 women-years (A) and relative reduction in incidence (B) after HPV vaccination and screening ramp-up in low-income and lower-middle-income countries. Median prediction from the three models. Vaccination coverage=90% at age 9 years (and at ages 10–14 years in 2020). Vaccine efficacy=100% against HPV16, 18, 31, 33, 45, 52, and 58. Vaccine duration=lifetime. Screening=HPV testing. Screening uptake=45% (2023–29), 70% (2030–44), and 90% (2045 onwards). Screen and treat efficacy=100%. Loss to follow-up=10%. Equilibrium occurs 90–100 years after the introduction of HPV vaccination only (and earlier for the screening scenarios). HPV=human papillomavirus.

cancer via precancerous cervical lesions (cervical intraepithelial neoplasia grade 1 to 3). All models assume that HPV vaccines are prophylactic and capture post-vaccination herd effects. They can also simulate complex cervical screening and treatment algorithms at the individual level, by tracking and simulating each woman's screening history. Finally, all models were calibrated to highly stratified sexual behaviour and epidemiological data, validated to clinical trials or post-vaccination data, or both, and reproduce the age-specific cervical cancer incidence estimates from the Global Cancer Observatory (GLOBOCAN) 2018 for all 78 LMICs[42] (see the appendix pp 18–23 for further details of the CCEMC models).

Vaccination and screening scenarios

Three standardised base-case HPV vaccination and cervical screening scenarios were examined. The first was vaccination only: routine vaccination of girls aged 9 years (with a 1-year multi-age cohort catch-up to age 14 years) reaching 90% coverage in the first year (2020). The second was vaccination and once-lifetime screening: scenario 1 plus one lifetime screen at age 35 years, assuming screening uptake ramp-up over time (45% in 2023, 70% in 2030, and 90% in 2045). The third was vaccination and twice-lifetime screening: scenario 1 plus two lifetime screens at ages 35 years and 45 years, assuming screening uptake ramp-up over time (45% in 2023, 70% in 2030, and 90% in 2045).

For the base-case scenarios, HPV vaccination was assumed to provide 100% efficacy against HPV types 16, 18, 31, 33, 45, 52, and 58, and lifelong duration of protection. Cervical screening was assumed to involve primary HPV screen-and-treat testing, with 100% pre-cancer treatment efficacy and 10% of individuals lost to follow-up (due to treatment non-compliance). To estimate the population-level impact of the base-case scenarios, we also modelled a status quo scenario, which assumes no further scale-up of preventive interventions (see appendix p 16 for more details). The 40 HPV vaccination and cervical screening scenarios from step 2 of the comparative modelling approach were used to understand the impact of model assumptions on predictions. The sensitivity analysis included varying HPV vaccination coverage, the targeted population (girls only *vs* girls and boys), ages at vaccination, screening frequency, the HPV types targeted by the vaccine, and the duration of vaccine protection. Results of the sensitivity analysis are shown for two example countries, representing one low-income country in sub-Saharan Africa (Uganda) and one lower-middle-income country in east Asia (Vietnam).

Outcomes

Population-level impact was measured with three main outcomes: age-standardised cervical cancer incidence, relative reductions in age-standardised cervical cancer incidence (*vs* status quo), and number of cases averted (*vs* status quo). The time horizon of the analysis was from 2020 to 2120. The age-standardised cervical cancer incidence and relative reductions in incidence over time were used to assess the feasibility and timing of cervical cancer elimination at different thresholds. We used the CCEMC models to independently estimate the outcomes for each of the 78 countries. Results were also aggregated by World Bank income level and region (see appendix p 17 for a description of country characteristics). Outcomes are presented with the median (range) of the predictions of the three models to represent between-model uncertainty.[28]

The age-standardised cervical cancer incidence over time was estimated for each CCEMC model, vaccination, and screening scenario, and for each country using the predictions of age-specific cervical cancer incidence over time and applying the age structure of the 2015 global female population aged 0–99 years.[43] Reductions (absolute

	Incidence per 100 000 women-years			Reduction in incidence (%)		Base-case elimination threshold: ≤4 cases per 100 000		Alternative elimination threshold: ≤10 cases per 100 000		Alternative elimination threshold: ≥85% reduction	
	2020	2045	Equilibrium	2045	Equilibrium	Countries (%)	Year of elimination	Countries (%)	Year of elimination	Countries (%)	Year of elimination
All low-income and lower-middle-income countries (n=78)											
Vaccination only	19·8 (19·4–19·8)	16·9 (16·2–17·5)	2·1 (2·0–2·6)	12·9 (11·6–14·4)	89·4 (86·2–90·1)	60·3 (57·7–65·4)	X (X–X)	98·7 (88·5–100·0)	X (2096–X)	87·2 (37·2–98·7)	X (X–X)
Vaccination and one lifetime screen	19·8 (19·4–19·8)	13·7 (13·3–13·8)	1·0 (0·9–2·0)	30·3 (28·6–30·8)	95·0 (89·0–95·3)	96·2 (60·3–97·4)	X (X–X)	100·0 (94·9–100·0)	2090 (2082–X)	100·0 (100·0–100·0)	2085 (2080–2100)
Vaccination and two lifetime screens	19·8 (19·3–19·9)	11·0 (10·7–11·6)	0·7 (0·6–1·6)	41·5 (40·6–46·1)	96·7 (91·3–96·7)	100·0 (70·5–100·0)	2098 (2097–X)	100·0 (98·7–100·0)	2085 (2078–X)	100·0 (100·0–100·0)	2081 (2077–2094)
World Bank income levels											
Low-income countries (n=34)											
Vaccination only	32·7 (32·7–33·6)	28·6 (28·0–31·1)	3·9 (3·4–5·7)	13·4 (12·7–14·3)	88·1 (84·1–89·5)	44·1 (41·2–50·0)	X (X–X)	100·0 (82·4–100·0)	2093 (2090–X)	82·4 (14·7–100·0)	X (2091–X)
Vaccination and one lifetime screen	32·7 (32·7–33·6)	22·6 (22·6–25·7)	1·8 (1·7–4·6)	31·1 (28·4–31·1)	94·7 (87·1–94·9)	97·1 (44·1–97·1)	X (X–X)	100·0 (94·1–100·0)	2082 (2079–X)	100·0 (100·0–100·0)	2083 (2079–2098)
Vaccination and two lifetime screens	32·8 (32·7–33·7)	19·0 (17·5–21·8)	1·2 (1·2–3·8)	41·9 (39·3–46·6)	96·4 (89·5–96·5)	100·0 (52·9–100·0)	2089 (2088–X)	100·0 (100·0–100·0)	2076 (2074–2099)	100·0 (100·0–100·0)	2079 (2073–2092)
Low-income and lower-middle-income countries (n=44)											
Vaccination only	17·8 (17·2–17·8)	15·3 (14·0–15·9)	1·8 (1·8–2·1)	12·3 (11·0–14·1)	89·7 (87·0–90·2)	72·7 (70·5–77·3)	X (X–X)	97·7 (93·2–100·0)	X (2096–X)	90·9 (54·5–97·7)	X (X–X)
Vaccination and one lifetime screen	17·8 (17·2–17·9)	12·4 (11·5–12·5)	0·9 (0·8–1·6)	29·8 (28·3–30·4)	95·1 (89·8–95·4)	95·5 (72·7–97·7)	X (X–X)	100·0 (95·5–100·0)	2090 (2082–X)	100·0 (100·0–100·0)	2085 (2080–2100)
Vaccination and two lifetime screens	17·8 (17·2–17·9)	9·7 (9·5–10·5)	0·6 (0·6–1·3)	41·1 (40·8–45·7)	96·8 (92·0–96·8)	100·0 (84·1–100·0)	2098 (2097–X)	100·0 (97·7–100·0)	2085 (2078–X)	100·0 (100·0–100·0)	2081 (2077–2094)
World Bank regions											
East Asia and Pacific (n=12)											
Vaccination only	19·9 (19·3–19·9)	17·0 (15·0–17·5)	2·2 (2·2–2·5)	13·7 (12·0–14·5)	87·3 (87·2–89·2)	100·0 (91·7–100·0)	2102 (2087–X)	100·0 (100·0–100·0)	2067 (2066–2069)	100·0 (91·7–100·0)	2091 (2087–X)
Vaccination and one lifetime screen	19·9 (19·2–19·9)	13·4 (12·0–13·7)	1·2 (0·9–1·7)	31·4 (30·8–32·5)	93·8 (90·3–95·3)	100·0 (100·0–100·0)	2079 (2075–2091)	100·0 (100·0–100·0)	2061 (2060–2061)	100·0 (100·0–100·0)	2078 (2078–2087)
Vaccination and two lifetime screens	19·9 (19·1–20·1)	10·3 (9·6–11·4)	0·8 (0·7–1·3)	44·7 (42·8–48·5)	96·0 (92·4–96·7)	100·0 (100·0–100·0)	2071 (2069–2085)	100·0 (100·0–100·0)	2052 (2050–2054)	100·0 (100·0–100·0)	2073 (2073–2081)
Europe and central Asia (n=6)											
Vaccination only	15·7 (15·6–15·7)	11·8 (11·6–12·3)	1·4 (1·2–1·7)	22·9 (21·7–25·0)	90·9 (88·5–92·7)	100·0 (100·0–100·0)	2080 (2078–2080)	100·0 (100·0–100·0)	2059 (2059–2060)	100·0 (100·0–100·0)	2085 (2081–2088)
Vaccination and one lifetime screen	15·7 (15·6–15·8)	8·9 (8·8–9·0)	0·7 (0·7–1·3)	43·2 (40·1–44·2)	95·6 (91·1–95·8)	100·0 (100·0–100·0)	2070 (2069–2075)	100·0 (100·0–100·0)	2052 (2052–2053)	100·0 (100·0–100·0)	2073 (2078–2079)
Vaccination and two lifetime screens	15·7 (15·5–15·7)	7·6 (6·8–7·7)	0·5 (0·5–1·1)	51·0 (49·6–56·7)	96·7 (92·5–96·8)	100·0 (100·0–100·0)	2065 (2063–2069)	100·0 (100·0–100·0)	2048 (2046–2049)	100·0 (100·0–100·0)	2068 (2066–2074)

(Table continues on next page)

	Incidence per 100 000 women-years			Reduction in incidence (%)		Base-case elimination threshold: ≤4 cases per 100 000		Alternative elimination threshold: ≤10 cases per 100 000		Alternative elimination threshold: ≥85% reduction	
	2020	2045	Equilibrium	2045	Equilibrium	Countries (%)	Year of elimination	Countries (%)	Year of elimination	Countries (%)	Year of elimination
(Continued from previous page)											
Latin America and Caribbean (n=5)											
Vaccination only	26·8 (25·6–27·0)	21·4 (18·9–21·9)	3·0 (2·7–3·7)	18·3 (18·2–20·3)	88·8 (84·1–90·1)	80·0 (80·0–80·0)	X (X–X)	100·0 (100·0–100·0)	2070 (2070–2071)	100·0 (X-100·0)	2091 (2086- X)
Vaccination and one lifetime screen	26·8 (25·8–27·0)	16·5 (15·3–16·7)	1·5 (1·3–3·0)	37·8 (33·7–38·5)	94·5 (87·0–95·2)	100·0 (80·0–100·0)	2079 (2074–X)	100·0 (100·0–100·0)	2065 (2061–2066)	100·0 (100·0–100·0)	2079 (2077–2099)
Vaccination and two lifetime screens	26·8 (25·7–26·8)	13·3 (13·2–14·3)	1·1 (1·0–2·6)	46·6 (43·1–50·3)	96·0 (88·9–96·4)	100·0 (100·0–100·0)	2073 (2069–2089)	100·0 (100·0–100·0)	2057 (2056–2058)	100·0 (100·0–100·0)	2076 (2072–2094)
North Africa and Middle East (n=7)											
Vaccination only	6·8 (6·5–6·8)	6·1 (5·2–6·4)	0·8 (0·5–0·9)	8·2 (6·9–10·5)	88·5 (84·9–92·9)	100·0 (100·0–100·0)	2081 (2076–2081)	100·0 (100·0–100·0)	2062 (2061–2066)	100·0 (71·4–100·0)	2090 (2085- X)
Vaccination and one lifetime screen	6·8 (6·5–6·9)	5·2 (4·5–5·2)	0·3 (0·3–0·7)	23·8 (21·3–23·9)	95·0 (87·5–95·9)	100·0 (100·0–100·0)	2073 (2073–2078)	100·0 (100·0–100·0)	2058 (2057–2058)	100·0 (100·0–100·0)	2081 (2080–2097)
Vaccination and two lifetime screens	6·8 (6·5–6·9)	4·1 (3·8–4·4)	0·2 (0·2–0·6)	35·7 (34·1–39·6)	96·6 (90·1–97·2)	100·0 (100·0–100·0)	2068 (2068–2074)	100·0 (100·0–100·0)	2050 (2048–2051)	100·0 (100·0–100·0)	2079 (2077–2094)
South Asia (n=7)											
Vaccination only	15·5 (14·6–15·5)	13·3 (11·3–13·8)	1·4 (1·1–1·5)	12·3 (10·9–14·6)	91·3 (88·3–92·8)	100·0 (100·0–100·0)	2074 (2072–2077)	100·0 (100·0–100·0)	2060 (2058–2061)	100·0 (100·0–100·0)	2087 (2082–2092)
Vaccination and one lifetime screen	15·5 (14·6–15·6)	10·8 (9·2–11·0)	0·7 (0·6–1·2)	28·9 (28·3–30·7)	95·8 (90·8–96·2)	100·0 (100·0–100·0)	2070 (2069–2071)	100·0 (100·0–100·0)	2053 (2053–2054)	100·0 (100·0–100·0)	2079 (2079–2087)
Vaccination and two lifetime screens	15·5 (14·6–15·6)	8·6 (7·6–9·3)	0·4 (0·4–0·9)	40·6 (40·4–44·6)	97·1 (92·9–97·3)	100·0 (100·0–100·0)	2063 (2063–2065)	100·0 (100·0–100·0)	2046 (2046–2049)	100·0 (100·0–100·0)	2074 (2074–2082)
Sub-Saharan Africa (n=41)											
Vaccination only	37·4 (37·4–38·7)	33·6 (33·0–37·5)	4·9 (4·5–6·7)	10·7 (10·0–11·7)	87·0 (84·1–87·9)	26·8 (24·4–36·6)	X (X–X)	97·6 (78·0–100·0)	X (2096–X)	75·6 (X-97·6)	X (X–X)
Vaccination and one lifetime screen	37·4 (37·4–38·6)	27·2 (27·1–31·5)	2·2 (2·0–5·5)	27·4 (25·0–27·5)	94·1 (87·0–94·7)	92·7 (26·8–95·1)	X (X–X)	100·0 (90·2–100·0)	2090 (2082–X)	100·0 (100·0–100·0)	2085 (2079–2100)
Vaccination and two lifetime screens	37·5 (37·4–38·8)	22·7 (21·0–26·7)	1·4 (1·4–4·4)	39·4 (36·5–43·9)	96·3 (89·6–96·4)	100·0 (43·9–100·0)	2098 (2097–X)	100·0 (97·6–100·0)	2085 (2078–X)	100·0 (100·0–100·0)	2081 (2073–2094)

Data are median (range) predictions from three dynamic models. Equilibrium occurs 90–100 years after the introduction of human papillomavirus (HPV) vaccination only (and earlier for the screening scenarios). X=elimination not reached in all countries in the income or regional group. Girls-only vaccination refers to vaccination coverage of 90% at age 9 years (and at ages 10–14 years in 2020). Vaccine efficacy=100% against HPV16, 18, 31, 33, 45, 52, and 58. Vaccine duration=lifetime cervical screening. Screening=HPV testing. Screening uptake=45% (2023–29), 70% (2030–44), and 90% (2045 onwards). Screen and treat efficacy=100%. Loss to follow-up=10%.

***Table*: Change in age-standardised cervical cancer incidence over time, percentage of countries reaching elimination for different thresholds, and year of elimination, by World Bank income level and region**

and relative) in age-standardised cervical cancer incidence over time were estimated compared to the status quo. Finally, the cumulative number of cases averted over time was estimated with a three-step process. First, for each CCEMC model, vaccination, and screening scenario, and country, we estimated the number of cervical cancers by year and age group by multiplying the predicted age-specific cervical cancer incidence and the age-specific UN population growth projections.[43] Second, we estimated the number of cervical cancers in each year by summing the cases predicted in each age group. Third, the number of cases averted in each year was estimated by subtracting the number of cases predicted under each vaccination and screening scenario from those predicted under the status quo. The number of cancer cases averted in each World Bank income level or region was estimated by aggregating the country-specific results. The model predictions were done independently by each group and collated by the study's coordinating centre (Laval University, Québec, QC, Canada). See the appendix (pp 18–25) for more methodological details.

Elimination thresholds

Our base-case definition of elimination is an age-standardised (2015 world standard) cervical cancer incidence of four or fewer cases per 100 000 women-years, which is the current working definition used by WHO and the proposed WHO global strategy towards elimination of cervical cancer.[24] The threshold was determined following multiple WHO technical expert meetings and global stakeholder consultations held between March and September, 2018.[24] Alternative definitions, such as a higher incidence threshold (ten cases per 100 000 women-years) and a percentage reduction in incidence (85–90%), were also discussed.[39] Thus, as a sensitivity analysis, two alternative definitions were explored: age-standardised cervical cancer incidence of ten or fewer cases per 100 000 women-years and a reduction in age-standardised cervical cancer incidence of ≥85% (*vs* status quo). Elimination was predicted to occur the first year in which a country reached the threshold definition. Elimination within a region or income level was predicted to occur the year in which all countries within the region or income level reached elimination.

Role of the funding source

This study was partly funded by WHO. WHO contributed to study design, data analysis, data interpretation, and writing of the report. The other funding sources had no role in this work. MB, JJK, and KC had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The CCEMC models predicted that girls-only HPV vaccination with 90% coverage will reduce the median age-standardised cervical cancer incidence in LMICs from 19·8 (range 19·4–19·8) to 2·1 (2·0–2·6) cases per 100 000 women-years over the next century, which represents an 89·4% (86·2–90·1) reduction in cervical cancer (*vs* the status quo; figure 1, table). The addition of screening was predicted to substantially accelerate declines in cervical cancer and to lead to lower cervical cancer incidence at equilibrium. HPV vaccination and once-lifetime screening was predicted to reduce the average age-standardised cervical cancer incidence in LMICs to 1·0 (0·9–2·0) cases per 100 000 women-years over the next century (95·0% [89·0–95·3] reduction), whereas HPV vaccination and twice-lifetime screening was predicted to reduce the average age-standardised cervical cancer incidence to 0·7 (0·6–1·6) cases per 100 000 women-years at equilibrium (96·7% [91·3–96·7] reduction). Additionally, the models predicted that cervical cancer incidence will be halved in LMICs by 2061 (2060–63) with HPV vaccination alone, by 2055 (2055–56) when adding once-lifetime screening, and by 2048 (2047–49) when adding twice-lifetime screening. Notably, the models predicted that HPV vaccination with or without screening will reduce age-standardised cervical cancer incidence in women of childbearing age (<45 years) by more than 85% before 2050 (appendix p 5).

The predicted dynamics of cervical cancer incidence following HPV vaccination only, and for HPV vaccination with once-lifetime or twice-lifetime screening, were very similar for the three models (figure 2). Additionally, although the age-standardised cervical cancer incidence in 2020 varied widely by country income level and region (figure 2; appendix p 5), the models predicted that the post-intervention dynamics and percentage reduction in cervical cancer incidence will be similar (figure 2, table). For example, the predicted percentage reduction in cervical cancer following HPV vaccination only varied from 87% (range 84–88) in sub-Saharan Africa to 91% (88–93) in South Asia, and percentage reductions following HPV vaccination with twice-lifetime screening varied from 96% (90–96) in sub-Saharan Africa to 97% (93–97) in South Asia. However, the models predicted that age-standardised cervical cancer incidence following HPV vaccination with or without screening will vary greatly between regions and countries because of the large heterogeneity in the starting incidence (figure 2, table), which contributed to variability between countries in the potential for and timing of elimination.

With the base-case elimination threshold (four or fewer cases per 100 000 women-years), the CCEMC models predicted that girls-only HPV vaccination could lead to cervical cancer elimination in 60% (range 58–65) of LMICs, HPV vaccination with once-lifetime screening could lead to elimination in 96% (60–97) of LMICs, and HPV vaccination with twice-lifetime screening could lead to elimination in 100% (71–100) of LMICs (figure 3, table). HPV vaccination alone was predicted to result in elimination in all regions in the world, except for sub-Saharan Africa, where 27% (range 24–37) of

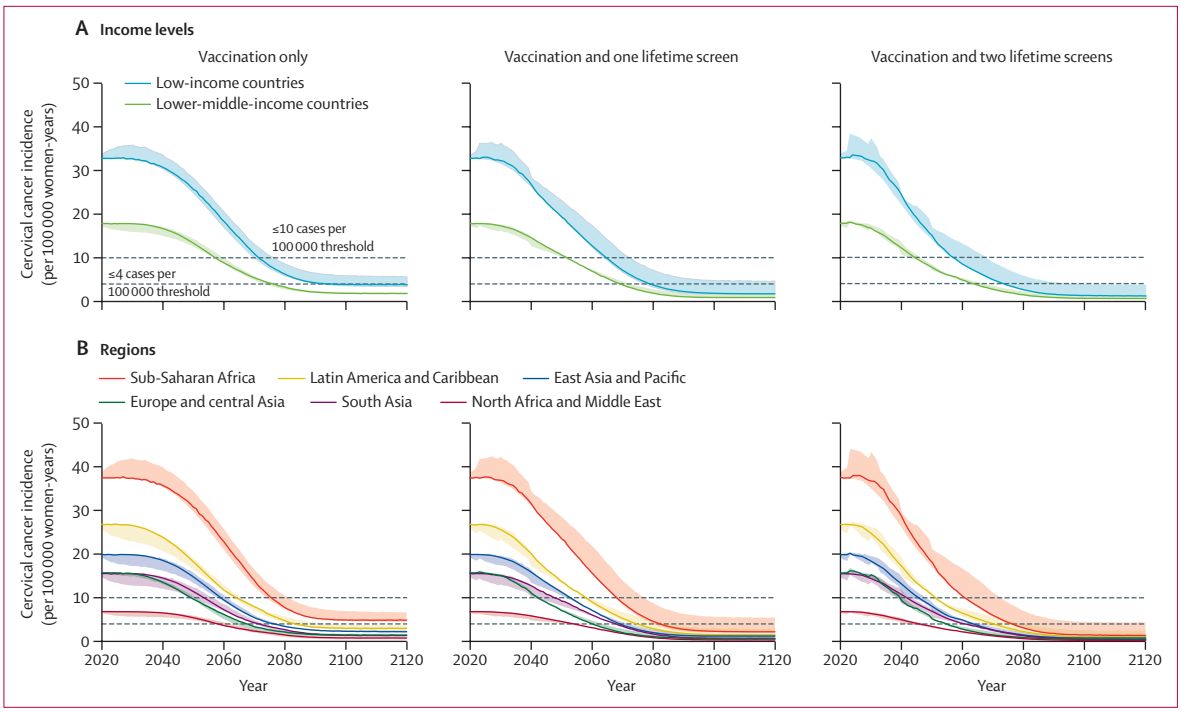

Figure 2: **Variability in model predictions of the impact of HPV vaccination and screening strategies**
The average age-standardised cervical cancer incidence per 100 000 women-years over time in low-income countries and lower-middle-income countries, by World Bank income level (A) and region (B). The solid line represents the median prediction and shaded area represents the minimum and maximum predictions of the three models. Vaccination coverage=90% at age 9 years (and at ages 10–14 years in 2020). Vaccine efficacy=100% against HPV types 16, 18, 31, 33, 45, 52, and 58. Vaccine duration=lifetime. Screening=HPV testing. Screening uptake=45% (2023–29), 70% (2030–44), and 90% (2045 onwards). Screen and treat efficacy=100%. Loss to follow-up=10%. Equilibrium occurs 90–100 years after the introduction of HPV vaccination only (and earlier for the screening scenarios). HPV=human papillomavirus.

countries would reach elimination, and Latin America and Caribbean, where 80% (80–80) of countries would reach elimination. The countries that were not predicted to reach elimination through HPV vaccination alone were those with an age-standardised cervical cancer incidence of more than 25 cases per 100 000 women-years in 2020 (figure 4, appendix p 7). These same countries were predicted to have the greatest absolute reductions in cervical cancer incidence following HPV vaccination (figure 4). Importantly, for these countries, mainly in sub-Saharan Africa, once-lifetime or twice-lifetime screening was required to achieve elimination. Country-specific and model-specific predictions of elimination and the age-specific cervical cancer incidence at equilibrium are shown in the appendix (p 7).

The models predicted that among the regions that can achieve elimination (four or fewer cases per 100 000 women-years) with girls-only HPV vaccination alone, elimination will occur between 2074 and 2102 (table). Adding twice-lifetime screening was predicted to accelerate elimination by 11–31 years. In sub-Saharan Africa, where both HPV vaccination and twice-lifetime screening are required to achieve elimination, elimination is predicted to occur slightly before 2100 (table). Country-specific and model-specific predictions of the year of elimination are provided in the appendix (p 8).

The CCEMC models predicted that girls-only HPV vaccination could lead to cervical cancer elimination in 99% (range 89–100) of LMICs based on a threshold of ten or fewer cases per 100 000 women-years, and in 87% (37–99) of LMICs based on a threshold of an 85% or greater reduction (table; figure 3; figure 4). Adding once or twice-lifetime screening was predicted to result in cervical cancer elimination for 100% of LMICs under both thresholds. Elimination was also predicted to occur faster with these thresholds (table).

The CCEMC models predicted that 21·3 million (range 20·7–21·3) cervical cancer cases will occur in LMICs between 2020 and 2060 without further interventions (status quo). During the same period, including girls-only HPV vaccination with 90% coverage was predicted to avert 3·2 million (3·0–3·6) cervical cancer cases; adding once-lifetime screening to vaccination was predicted to avert an extra 2·2 million (1·8–2·7) cases, and adding twice-lifetime screening was predicted to avert an extra 4·6 million (3·9–4·8) cancer cases (figure 5; appendix pp 2–4). Hence, in the short to medium term (<40 years), adding screening could more than double the number of cervical cancer cases averted in LMICs (*vs* HPV vaccination alone). In the longer term, the models predicted that 93·5 million (93·5–95·3) cervical cancer cases will occur in LMICs

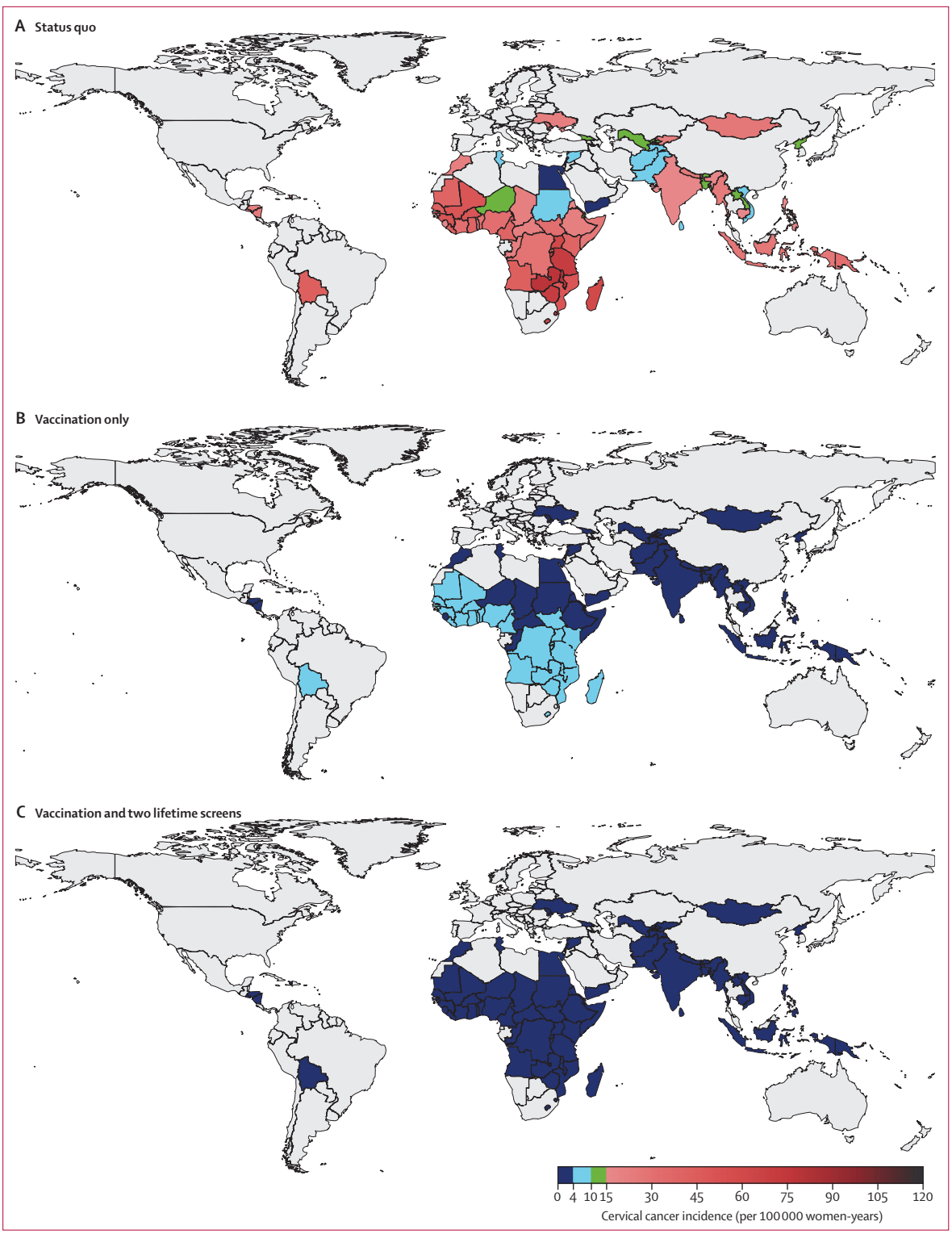

Figure 3: **Global map of cervical cancer elimination in 78 low-income and lower-middle-income countries**
Age-standardised incidence of cervical cancer at equilibrium (2100–20), assuming status quo (A), girls-only vaccination (B), and girls-only vaccination and two lifetime screens (C). Median prediction from the three models. Vaccination coverage=90% at age 9 years (and at ages 10–14 years in 2020). Vaccine efficacy=100% against HPV16, 18, 31, 33, 45, 52, and 58.Vaccine duration=lifetime. Screening=HPV testing. Screening uptake=45% (2023–29), 70% (2030–44), and 90% (2045 onwards). Screen and treat efficacy=100%. Loss to follow-up=10%. See videos 1–3 for the global maps of cervical cancer elimination over time and the appendix (p 6) for the change in the distribution of the country-specific age-standardised cervical cancer incidence over time. HPV=human papillomavirus.

See **Online** for videos 1, 2, and 3

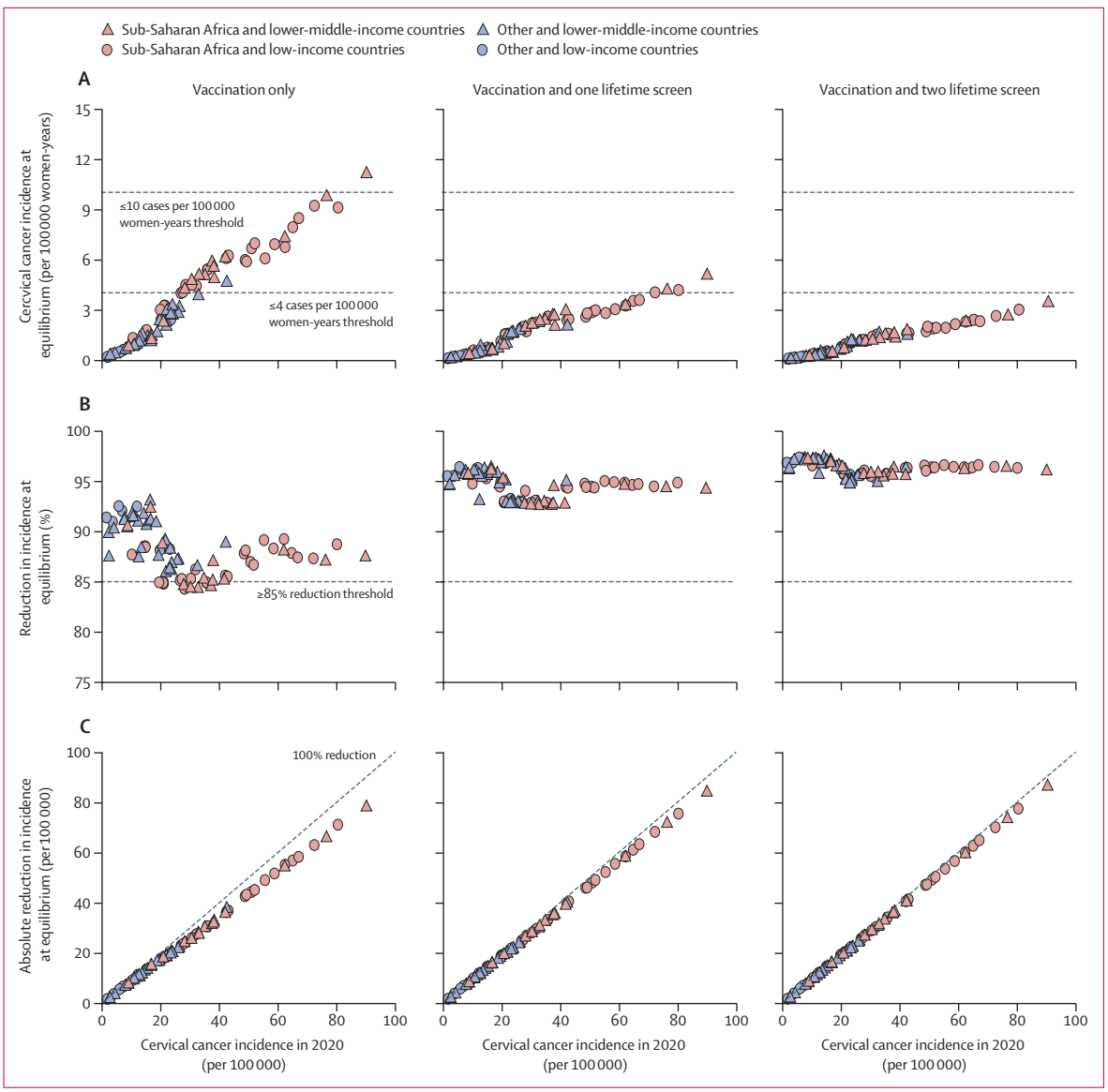

Figure 4: **Impact of current cervical cancer incidence on elimination predictions**
The age-standardised incidence of cervical cancer (A) and relative (B) and absolute (C) reduction in incidence at equilibrium (2100–20) following vaccination and screening, as a function of initial age-standardised incidence of cervical cancer for each low-income and lower-middle-income country. Median prediction from the three models. Vaccination coverage=90% at age 9 years (and at ages 10–14 years in 2020). Vaccine efficacy=100% against HPV16, 18, 31, 33, 45, 52, and 58. Vaccine duration=lifetime. Screening=HPV testing. Screening uptake=45% (2023–29), 70% (2030–44), and 90% (2045 onwards). Screen and treat efficacy=100%. Loss to follow-up=10%. HPV=human papillomavirus.

between 2020 and 2120 without further scale-up of HPV vaccination or cervical screening (ie, the status quo scenario). During this period, including girls-only HPV vaccination with 90% coverage was predicted to avert 61·0 million (60·5–63·0) cervical cancer cases; adding once-lifetime screening to vaccination was predicted to avert an extra 6·8 million (4·3–9·4) cases and adding twice-lifetime screening was predicted to avert an extra 12·1 million (9·5–13·7) cervical cancer cases (figure 5; appendix pp 2–4). Overall, an estimated 74·1 million (70·4–75·1) cases would be averted by 2120 through intensive scale-up of girls-only HPV vaccination with twice-lifetime screening. Predictions of the number of cervical cancer cases averted over time were similar for the three models, at the global and regional levels (appendix p 9).

Most cervical cancer cases averted through HPV vaccination and screening in LMICs were predicted to be among women living in sub-Saharan Africa (figure 5; appendix pp 2–4). For example, our models predicted that HPV vaccination and twice-lifetime screening will avert 49·9 million (range 49·5–50·9) cases in sub-Saharan

Africa over the next century, which represents about 70% of all cases averted in LMICs.

The sensitivity analysis suggests that a small reduction in HPV vaccination coverage from 90% to 80% would have little impact on the decline in cervical cancer incidence in the first 30 years following girls-only HPV vaccination (without screening), but would lead to slightly higher long-term incidence (appendix pp 10–11). Hence, some LMICs that can eliminate cervical cancer with 90% vaccination coverage (using the threshold of four or fewer cases per 100 000 women-years) might not with 80% coverage (eg, countries with current age-standardised cervical cancer incidence of 20–25 cases per 100 000 women-years). In general, if HPV vaccination coverage was high among girls, vaccinating boys was predicted to produce very small incremental gains in cervical cancer prevention (appendix pp 10–11). For example, the CCEMC models predicted that girls-only HPV vaccination with 90% coverage would produce the same reduction in cervical cancer incidence as vaccinating both girls and boys at 80% coverage. Hence, vaccinating boys in addition to girls would not be sufficient to help countries with the highest age-standardised cervical cancer incidence (eg, Uganda) reach the elimination threshold of four or fewer cases per 100 000 women-years. Finally, the models predicted that multi-age cohort vaccination up to age 25 years would substantially accelerate the declines in cervical cancer incidence, but would not change cervical cancer incidence at equilibrium (appendix pp 10–11). Thus, vaccinating older cohorts of girls or women would not ultimately change the potential for elimination.

A sensitivity analysis examining the impact of screening suggests that although twice-lifetime screening without HPV vaccination would substantially reduce cervical cancer incidence, the age-standardised cervical cancer incidence would remain higher than four cases per 100 000 women-years in the countries examined (appendix pp 10–11). Hence, HPV vaccination is required for most LMICs to reach cervical cancer elimination. In the context of high-coverage girls-only vaccination, adding a third lifetime screen (to HPV vaccination and twice-lifetime screening) was predicted to provide very small additional gains in cervical cancer prevention, and only slightly accelerated time to elimination.

Finally, our sensitivity analysis showed that the duration of protection and the number of types included in the HPV vaccine can affect whether girls-only HPV vaccination with twice-lifetime screening leads to cervical cancer elimination (appendix pp 10–11). When assuming 20 years of vaccine protection (instead of lifelong), the models predicted that the age-standardised cervical cancer incidence would be higher than four cases per 100 000 women-years in the countries examined. Thus, a long-term duration of vaccine protection (>20 years) is required to reach elimination in LMICs.

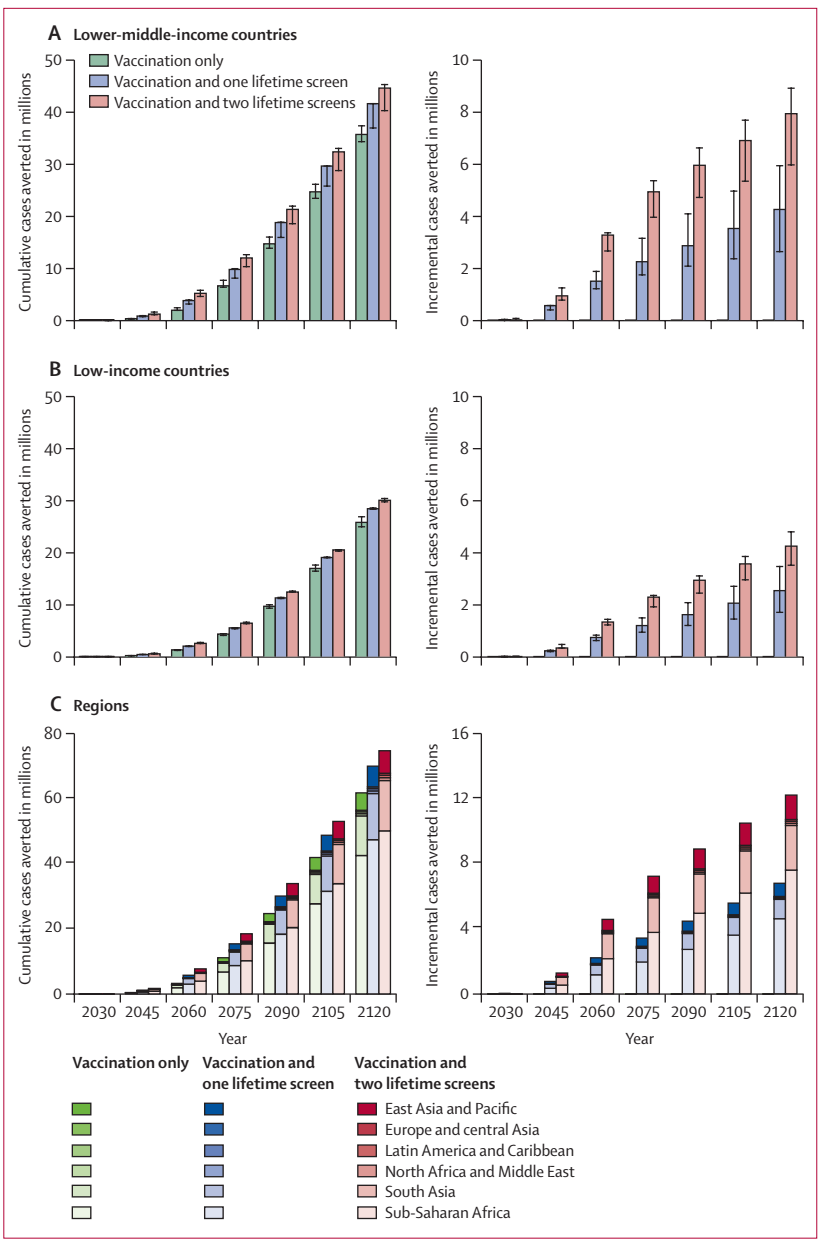

Figure 5: **Cervical cancer cases averted**
Cumulative cases averted by girls-only vaccination or girls-only vaccination plus screening, and incremental cases averted by screening in addition to vaccination over time, for lower-middle-income countries (A), low-income countries (B), and by region (C). Median prediction from the three models. Error bars represent the minimum and maximum estimates from the three models. Vaccination coverage=90% at age 9 years (and at ages 10–14 years in 2020). Vaccine efficacy=100% against HPV types 16, 18, 31, 33, 45, 52, and 58. Vaccine duration=lifetime. Screening=HPV testing. Screening uptake=45% (2023–29), 70% (2030–44), and 90% (2045 onwards). Screen and treat efficacy=100%. Loss to follow-up=10%. HPV=human papillomavirus.

The models predicted that cervical cancer elimination might be possible in LMICs with an age-standardised incidence of fewer than 25 cases per 100 000 women-years (eg, Vietnam) by use of a vaccine that includes only HPV types 16 and 18. However, for LMICs with the highest cervical cancer incidence (eg, Uganda), broad-spectrum protection against HPV types 16, 18, 31, 33, 45,

52, and 58 was predicted to be required for these countries to reach elimination.

Elimination was generally easier to achieve under the different scenarios examined in the sensitivity analysis with the thresholds of fewer than ten cases per 100 000 women-years and 85% or greater reduction. The models predicted that all vaccination strategies will achieve elimination, except for girls-only vaccination with 80% coverage. Twice-lifetime screening (without vaccination) could also potentially lead to elimination with these thresholds in LMICs that have an age-standardised cervical cancer incidence of less than 25 cases per 100 000 women-years (eg, Vietnam).

Discussion

Our comparative modelling analysis, which includes projections from three independent transmission-dynamic models, provides consistent results predicting that cervical cancer can be eliminated as a public health problem by the end of the century, based on WHO's proposed elimination threshold (ie, cervical cancer incidence of four or fewer cases per 100 000 women-years). Our modelling study shows that girls-only HPV vaccination would lead to cervical cancer elimination in most LMICs, if high coverage is reached (>90% coverage) and the vaccine provides long-term protection. However, countries with the highest cervical cancer incidence at present (>25 cases per 100 000 women-years), more than 90% of which are in sub-Saharan Africa, would not reach elimination by vaccination alone. To achieve cervical cancer elimination in all 78 LMICs, our models predict that scale-up of both girls-only HPV vaccination and twice-lifetime screening is necessary, with 90% HPV vaccination coverage, 90% screening uptake, and long-term protection against HPV types 16, 18, 31, 33, 45, 52, and 58. If this global elimination strategy of combined intensive scale-up of HPV vaccination and cervical screening can be achieved, our results suggest that cervical cancer elimination could be achieved in all countries by 2100. In doing so, cervical cancer incidence would be reduced by 97% and more than 74 million cases would be averted over the next century.

In January, 2019, the Executive Board of WHO requested the Director-General to lead the development of a draft global strategy to accelerate cervical cancer elimination, with clear targets for 2030.[24] The draft global strategy will be presented for consideration at the World Health Assembly in May, 2020. The results presented in this study were used to help inform the following key elements of the global strategy: the cervical cancer elimination threshold, the intervention strategies needed to achieve global elimination, and the 2030 targets towards global elimination.

Elimination of cervical cancer requires a clear and commonly agreed upon threshold, under which cervical cancer would no longer be considered a public health problem.[24] Establishment of this threshold thus requires a careful and informed process, as it is more complex than the definition of elimination (or eradication) of an infectious disease, which is simply reduction to zero incidence. The proposed threshold of four or fewer cases per 100 000 women-years was established on the basis of the definition of a rare cancer,[44] on the global distribution of cervical cancer incidence showing that this threshold is currently reached in only a few countries (compared with many countries reaching ten or fewer cases per 100 000),[42] as well as on our modelling results (and those of Simms and colleagues[34]) showing that cervical cancer elimination can be achieved in every country with this threshold. In this study, we examined the consequences of using alternative thresholds (ten or fewer cases per 100 000 women-years and ≥85% reduction), which were proposed during various WHO meetings and consultations,[24] on the achievability and timing of elimination in LMICs for different prevention strategies and country characteristics. Our results show that intensive scale-up of both HPV vaccination and twice-lifetime screening would eliminate cervical cancer in all LMICs for all thresholds investigated.

However, the choice of threshold can produce disparities in the effort required by countries to achieve elimination. For example, based on the threshold or ten or fewer cases per 100 000 women-years, only 1% of LMICs were unable to achieve elimination through HPV vaccination alone. By contrast, based on the proposed threshold of four or fewer cases per 100 000 women-years, 40% of LMICs were unable to achieve elimination through vaccination alone. These countries have the highest burden of cervical cancer (incidence >25 per 100 000 women-years) and are mostly in sub-Saharan Africa. For these countries, up to 90% uptake of twice-lifetime screening is required, in addition to vaccination, to reach the proposed elimination threshold. More generally, our results indicate that elimination will be hardest to achieve in countries with the highest burden of cervical cancer and lowest income level. Considerable financial and political international commitment is needed so that HPV vaccination and cervical screening resources can be prioritised for these countries, not only to achieve global elimination but also to reduce the enormous disparities in the worldwide cervical cancer burden. This is particularly important since current HPV vaccination and cervical screening uptake is very low in most low-income and sub-Saharan African countries.[2–5]

Partly based on the CCEMC projections presented here and the considerations described above, WHO has proposed the following triple-intervention global cervical cancer elimination strategy: intensive scale-up of girls-only HPV vaccination, twice-lifetime screening, and treatment of cancer and precancers.[24] The 2030 targets for this strategy are for 90% of girls to be fully vaccinated, for 70% of women to be screened at 35 years and 45 years of age, and for 90% of women diagnosed with cervical precancer or cancer to receive treatment or care. Our

findings suggest that to achieve global elimination by the end of the century, these targets need to be met in the countries with the highest burden of cervical cancer, and these countries also need to be supported to scale up twice-lifetime screening from 70% to 90% by 2045. Although we show that many LMICs could achieve elimination with HPV vaccination alone, the triple-intervention strategy was chosen as the global elimination strategy as it would accelerate elimination by 11–31 years and prevent an additional 12 million cervical cancer cases over the next century (compared with vaccination alone). Furthermore, combining cervical screening with HPV vaccination has been predicted to be cost-effective across several LMICs.[20–22] The CCEMC is currently examining the incremental cost-effectiveness of the triple-intervention cervical cancer elimination strategy at the global level. Importantly, the proposed global cervical cancer elimination strategy provides general direction about the country-specific strategies that should be used, which should be customised to country-specific epidemiological, economic, and social contexts. For example, countries might want to scale up vaccination and screening at different ages than those modelled, because of logistical issues or to maximise uptake.

The base-case vaccination-only strategy examined in the comparative-model analysis was routine girls-only HPV vaccination at age 9 years with a 1-year multi-age cohort catch-up for girls aged 10–14 years. This strategy was chosen as it is the recommended strategy by the WHO Strategic Advisory Group of Experts on Immunization (SAGE)[41] and a large body of evidence shows that it is highly cost-effective in LMICs and high-income countries.[17,19,31,32] However, given the recent worldwide shortage of vaccine supply, SAGE recommended in October, 2019, that multi-age cohort catch-up vaccination for girls aged 10–14 years should be postponed to alleviate the demand for vaccine doses in the coming years. The recommended WHO alternative strategies are variants of our base-case vaccination-only strategy: routine vaccination of girls aged 14 years, with a later switch to routine vaccination at an earlier age (eg, 9 years); and routine vaccination at age 9 years, with an extended interval of 3–5 years between doses.[45] The recommendations were partly based on results from HPV-ADVISE showing that these strategies would produce similar benefits to girls-only vaccination at age 9 years with a 1-year catch-up for girls aged 10–14 years.[46] Implementation of these alternative strategies would alleviate vaccine supply to allow sufficient doses for all LMICs to reach 90% coverage within the next few years.[45] Hence, assuming countries follow SAGE recommendations, the HPV vaccine shortage should have little long-term impact on our projections of time to elimination provided supply constraints are relieved over the next decade. In our sensitivity analysis, we examined the impact of gender-neutral and multi-age cohort vaccination up to 25 years of age on cervical cancer incidence over time. Because our models predict that 90% girls-only vaccination can almost eliminate HPV vaccine types, the incremental benefits of vaccinating boys on cervical cancer incidence were predicted to be small. Multi-age cohort vaccination up to 25 years of age was predicted to substantially accelerate elimination and avert additional cervical cancer cases but would have no effect on whether a country reaches elimination, which is only determined by long-term routine vaccination coverage. Given their low incremental impact in relation to the number of doses required, WHO recommended that countries should temporarily postpone the implementation of gender-neutral and multi-age cohort HPV vaccination strategies, to maximise the number of countries that can introduce vaccination.[45]

The two base-case screening strategies examined, primary HPV screen-and-treat testing with once-lifetime and twice-lifetime screening, were chosen as they are the recommended strategies by WHO.[40] These screening scenarios were meant to represent a wide range of validated HPV tests and future screening tests, given their high sensitivity and specificity (see Canfell, Kim, Brisson and colleagues[27] for an in-depth discussion of the screening strategies). Our results suggest that including screening in addition to HPV vaccination would substantially increase the number of cervical cancer cases averted and would accelerate elimination, mainly by preventing cases in older, unvaccinated women. Additionally, cervical cancer elimination can be achieved in all but three LMICs (in sub-Saharan Africa) with once-lifetime screening and in all LMICs with twice-lifetime screening. This is because even if HPV vaccination were to eradicate HPV types 16, 18, 31, 33, 45, 52, and 58, a proportion of LMICs (mainly in sub-Saharan Africa) would still have cervical cancer incidence greater than the threshold of four cases per 100 000 women-years; about 10% of cervical cancers are due to HPV types that are not in the currently available HPV vaccines[10] and many countries have cervical cancer incidence higher than 40 cases per 100 000 women-years.[1] For these countries, high cervical screening uptake will have to be sustained for elimination to be maintained (or additional types would have to be included in future HPV vaccines). Finally, in the sensitivity analysis, we predicted relatively small additional gains in cervical cancer prevention by including a third lifetime screen.

Our study has two major strengths. First, we used a comparative modelling approach including three models that have been extensively peer reviewed and validated with post-vaccination surveillance data.[30–36] Without harmonising the model structure or parameters, the three models produced very similar results in terms of absolute and relative reductions in cervical cancer incidence and cancer cases averted over time following HPV vaccination and cervical screening by country, income level, and region. Our results are consistent in part because the key drivers of our predictions (eg, achievability and timing of

elimination) are country-specific baseline cervical cancer incidence and percentage of cancers due to the HPV vaccine types, which were based on the same data sources.[1,10] However, the results were not sensitive to the main differences between our models, which were the sexual behaviour components. At high HPV vaccination coverage and vaccine efficacy, our models predicted similar dynamics and herd effects across the different LMICs, even though sexual behaviour varies substantially. Although we could not directly compare our results to other HPV transmission-dynamic models in LMICs because of the scarcity of such models and their incompatibility in intervention scenarios, a previous systematic comparison of 16 HPV models in high-income countries (including the three CCEMC models) showed consistent predictions of the population-level impact of HPV vaccination when coverage is high.[47] Second, key knowledge users from WHO were involved in all aspects of the study, from its design to interpretations of findings. Additionally, the modelling results were presented and discussed at multiple WHO advisory group and global stakeholder meetings.[24,39,48] This process has ensured that the study was responsive to the needs of global policy decisions and, importantly, that those using the findings are aware of both its strengths and limitations.

Our study has four main limitations. First, our projections are for more than 100 years, a period over which substantial demographic and behavioural changes and technological development are anticipated that can have an impact on cervical cancer incidence.[43,49] Population growth and changes in life expectancy can have an important impact on our predictions of cervical cancer cases averted. When producing projections with low population predictions from the UN,[43] we estimated that 62 million cervical cancer cases would be averted with the triple-intervention global elimination strategy, and that 88 million cases would be averted with the UN's high population predictions, versus 74 million cases with base-case projections (appendix p 12). However, given that the definition of elimination is based on age-standardised cervical cancer incidence, demographic changes are expected to have minimal impact on our predictions of the achievability and timing of elimination. Sexual behaviour has been changing in many LMICs, from a more traditional pattern of sexual behaviour, with a lower reported number of lifetime partners and wider age gaps between partners, to a more sex-similar pattern of behaviour, where both sexes have a similar and higher number of partners and narrow age gaps. In these countries (mainly in Asia), age-adjusted HPV infection and cervical cancer rates might be increasing,[49] and thus time to elimination might be slightly longer than predicted. Technological developments should not have major implications for our predictions, as we assumed 100% vaccine efficacy, high screening test sensitivity and specificity, and 100% treatment efficacy. Second, we assumed intensive scale-up and 90% uptake of HPV vaccination and cervical screening. These assumptions are based on data suggesting that worldwide coverage of measles, poliomyelitis, hepatitis B, and diphtheria-tetanus-pertussis vaccines have reached 84–90% (≥90% in many LMICs)[50] and that more than 90% of women in high-income countries are screened for cervical cancer at least once in their lifetime.[4] If scale-up is slower than modelled, this would delay the predicted timing of elimination and reduce the number of cancer cases averted, but it would not affect whether or not elimination can be achieved. Thirdly, our models do not include plausible biological interactions between HIV and HPV (eg, HPV acquisition and disease progression might be increased among people living with HIV).[51] By not capturing such interactions, our models might overestimate the impact of HPV vaccination in high HIV prevalence settings (five of 78 LMICs have HIV prevalence ≥10%[52]). Specific prevention strategies might be required for people living with HIV to accelerate cervical cancer elimination in high HIV prevalence settings. Modelling work is ongoing as part of the CCEMC to examine these issues. Finally, our country-specific cervical cancer incidence data are based on GLOBOCAN estimates,[42,53] which, where possible, are derived from extrapolation of recent trends in incidence obtained from national or subnational population-based cancer registries. If cervical cancer incidence is underestimated because of underreporting in these countries, elimination might take longer than predicted. There is an overwhelming need to strengthen population-based cancer surveillance in many LMICs to improve the accuracy of GLOBOCAN estimates, to inform local cancer control strategies, and to monitor whether elimination targets are being met.

In conclusion, our comparative modelling analysis suggests that cervical cancer elimination as a public health problem is possible by the end of the century, resulting in a 97% reduction in cervical cancer incidence in LMICs. To achieve elimination across all LMICs under the proposed threshold (four or fewer cases per 100 000 women-years), both high HPV vaccination coverage and screening uptake will be necessary, particularly in countries with the highest burden. Considerable international commitment will be required to achieve WHO's triple-intervention targets, particularly in countries with the highest burden of cervical cancer, where scale-up of vaccination and screening resources are most urgently needed. Our results are being used by WHO to inform its global strategy to accelerate cervical cancer elimination, which will be presented at the World Health Assembly in May, 2020.

Contributors

MB, JJK, and KC co-designed the study and co-led overall data interpretation. MB led the HPV-ADVISE analysis, JJK led the Harvard analysis, and KC led the Policy1-Cervix analysis. NB and RH also participated in study design. MD, EAB, EB, CR, KTS, and AK did the literature searches. MB, MD, GG, KTS, EB, CR, AK, M-CB, MA, FB, EF, PJNB, NB, RH, and DTNN participated in data collection and MB, JJK,

KC, GG, KTS, AK, EAB, EB, DM, SS, CR, J-FL, MC, RH, FB, and NB participated in data analysis. MB, GG, MD, and EB produced the tables and figures. MB, JJK, and KC drafted the Article and RH coordinated the CCEMC. All authors interpreted the results and critically revised the manuscript for scientific content. All authors approved the final version of the Article.

Declaration of interests

MB, MD, GG, DM, EB, J-FL, JJK, EAB, SS, CR, and DTNN report grants from WHO during the conduct of the study. KC, AK, KTS, MC, and MAS report grants from the National Health and Medical Research Council Australia during the conduct of the study. KC and MC are investigators of an investigator-initiated trial of cervical screening in Australia (Compass; ACTRN12613001207707 and NCT02328872), which is conducted and funded by the VCS Foundation, a government-funded health promotion charity; the VCS Foundation received equipment and a funding contribution from Roche Molecular Systems and Ventana USA but KC and MC (or their institution on their behalf) do not receive direct funding from industry for this trial or any other project. MAS also reports grants from Cancer Institute NSW during the conduct of the study. M-CB, MJ, MA, FB, EF, FE, PJNB, NB, and RH declare no competing interests.

Acknowledgments

Where authors are identified as personnel of the International Agency for Research on Cancer or WHO, the authors alone are responsible for the views expressed in this Article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer or WHO. M-CB acknowledges Centre funding from the MRC Centre for Global Infectious Disease Analysis (MRC-GIDA). This award is jointly funded by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement and is also part of the European and Developing Countries Clinical Trials Partnership (EDCTP2) programme supported by the European Union (MR/R015600/1).

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Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries

Karen Canfell, Jane J Kim*, Marc Brisson*, Adam Keane, Kate T Simms, Michael Caruana, Emily A Burger, Dave Martin, Diep T N Nguyen, Élodie Bénard, Stephen Sy, Catherine Regan, Mélanie Drolet, Guillaume Gingras, Jean-Francois Laprise, Julie Torode, Megan A Smith, Elena Fidarova, Dario Trapani, Freddie Bray, Andre Ilbawi, Nathalie Broutet, Raymond Hutubessy*

Summary

Background WHO is developing a global strategy towards eliminating cervical cancer as a public health problem, which proposes an elimination threshold of four cases per 100 000 women and includes 2030 triple-intervention coverage targets for scale-up of human papillomavirus (HPV) vaccination to 90%, twice-lifetime cervical screening to 70%, and treatment of pre-invasive lesions and invasive cancer to 90%. We assessed the impact of achieving the 90–70–90 triple-intervention targets on cervical cancer mortality and deaths averted over the next century. We also assessed the potential for the elimination initiative to support target 3.4 of the UN Sustainable Development Goals (SDGs)—a one-third reduction in premature mortality from non-communicable diseases by 2030.

Methods The WHO Cervical Cancer Elimination Modelling Consortium (CCEMC) involves three independent, dynamic models of HPV infection, cervical carcinogenesis, screening, and precancer and invasive cancer treatment. Reductions in age-standardised rates of cervical cancer mortality in 78 low-income and lower-middle-income countries (LMICs) were estimated for three core scenarios: girls-only vaccination at age 9 years with catch-up for girls aged 10–14 years; girls-only vaccination plus once-lifetime screening and cancer treatment scale-up; and girls-only vaccination plus twice-lifetime screening and cancer treatment scale-up. Vaccination was assumed to provide 100% lifetime protection against infections with HPV types 16, 18, 31, 33, 45, 52, and 58, and to scale up to 90% coverage in 2020. Cervical screening involved HPV testing at age 35 years, or at ages 35 years and 45 years, with scale-up to 45% coverage by 2023, 70% by 2030, and 90% by 2045, and we assumed that 50% of women with invasive cervical cancer would receive appropriate surgery, radiotherapy, and chemotherapy by 2023, which would increase to 90% by 2030. We summarised results using the median (range) of model predictions.

Findings In 2020, the estimated cervical cancer mortality rate across all 78 LMICs was 13·2 (range 12·9–14·1) per 100 000 women. Compared to the status quo, by 2030, vaccination alone would have minimal impact on cervical cancer mortality, leading to a 0·1% (0·1–0·5) reduction, but additionally scaling up twice-lifetime screening and cancer treatment would reduce mortality by 34·2% (23·3–37·8), averting 300 000 (300 000–400 000) deaths by 2030 (with similar results for once-lifetime screening). By 2070, scaling up vaccination alone would reduce mortality by 61·7% (61·4–66·1), averting 4·8 million (4·1–4·8) deaths. By 2070, additionally scaling up screening and cancer treatment would reduce mortality by 88·9% (84·0–89·3), averting 13·3 million (13·1–13·6) deaths (with once-lifetime screening), or by 92·3% (88·4–93·0), averting 14·6 million (14·1–14·6) deaths (with twice-lifetime screening). By 2120, vaccination alone would reduce mortality by 89·5% (86·6–89·9), averting 45·8 million (44·7–46·4) deaths. By 2120, additionally scaling up screening and cancer treatment would reduce mortality by 97·9% (95·0–98·0), averting 60·8 million (60·2–61·2) deaths (with once-lifetime screening), or by 98·6% (96·5–98·6), averting 62·6 million (62·1–62·8) deaths (with twice-lifetime screening). With the WHO triple-intervention strategy, over the next 10 years, about half (48% [45–55]) of deaths averted would be in sub-Saharan Africa and almost a third (32% [29–34]) would be in South Asia; over the next 100 years, almost 90% of deaths averted would be in these regions. For premature deaths (age 30–69 years), the WHO triple-intervention strategy would result in rate reductions of 33·9% (24·4–37·9) by 2030, 96·2% (94·3–96·8) by 2070, and 98·6% (96·9–98·8) by 2120.

Interpretation These findings emphasise the importance of acting immediately on three fronts to scale up vaccination, screening, and treatment for pre-invasive and invasive cervical cancer. In the next 10 years, a one-third reduction in the rate of premature mortality from cervical cancer in LMICs is possible, contributing to the realisation of the 2030 UN SDGs. Over the next century, successful implementation of the WHO elimination strategy would reduce cervical cancer mortality by almost 99% and save more than 62 million women's lives.

Funding WHO, UNDP, UN Population Fund, UNICEF–WHO–World Bank Special Program of Research, Development and Research Training in Human Reproduction, Germany Federal Ministry of Health, National Health and Medical Research Council Australia, Centre for Research Excellence in Cervical Cancer Control, Canadian Institute of Health Research, Compute Canada, and Fonds de recherche du Québec–Santé.

Lancet 2020; 395: 591–603

Published Online January 30, 2020 https://doi.org/10.1016/S0140-6736(20)30157-4

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*Joint first authors

Cancer Research Division, Cancer Council NSW, Sydney, NSW, Australia (K Canfell DPhil, A Keane PhD, K T Simms PhD, M Caruana DPhil, D T N Nguyen PhD, M A Smith PhD); **School of Public Health, Sydney Medical School, University of Sydney, Sydney, NSW, Australia** (K Canfell, A Keane, K T Simms, M Caruana, D T N Nguyen, M A Smith); **Prince of Wales Clinical School, University of New South Wales, Sydney, NSW, Australia** (K Canfell); **Center for Health Decision Science, Harvard TH Chan School of Public Health, Boston, MA, USA** (Prof J J Kim PhD, E A Burger PhD, S Sy MS, C Regan BA); **Centre de recherche du CHU de Québec - Université Laval, Québec, QC, Canada** (Prof M Brisson PhD, D Martin PhD, É Bénard MSc, M Drolet PhD, G Gingras PhD, J-F Laprise PhD); **Département de médecine sociale et préventive, Université Laval, Québec, QC, Canada** (Prof M Brisson); **MRC Centre for Global Infectious Disease Analysis, Department of Infectious Disease Epidemiology, Imperial College, London, UK** (Prof M Brisson); **Department of Health Management and Health Economics, University of Oslo, Oslo, Norway** (E A Burger); **Union for International Cancer Control, Geneva, Switzerland** (J Torode PhD); **Department for the Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention, World Health Organization, Geneva,**

Switzerland (E Fidarova MD, D Trapani MD, A Ilbawi MD); **Section of Cancer Surveillance, International Agency for Research on Cancer, Lyon, France** (F Bray PhD); **and Department of Reproductive Health and Research** (N Broutet MD) **and Department of Immunization, Vaccines and Biologicals** (R Hutubessy PhD), **World Health Organization, Geneva, Switzerland**

Correspondence to: Dr Karen Canfell, Cancer Research Division, Cancer Council NSW, Woolloomooloo, Sydney 2011, NSW, Australia
karen.canfell@nswcc.org.au

Introduction

In 2018, an estimated 570 000 cases of cervical cancer were diagnosed, and 311 000 women died from the disease.[1] Although cervical cancer has been relatively well controlled for several decades in many high-income countries, mainly because of cervical screening initiatives and effective cancer treatment services, it remains the most common cause of cancer-related death among women in 42 countries, most of which are low-income and lower-middle-income countries (LMICs).[2]

Prophylactic vaccines against oncogenic human papillomavirus (HPV) have been available in most high-income countries from 2006 onwards. First-generation vaccines directly protect against oncogenic HPV types 16 and 18 in individuals naive for those types, and these HPV types are responsible for approximately 70% of invasive cervical cancers.[3,4] More recently, broader-spectrum protection against the types responsible for up to 90% of cervical cancers has been shown either via direct protection against a larger proportion of types (second-generation 9-valent vaccine) or via cross-protection against non-vaccine included types (bivalent vaccine).[5,6] However, because vaccines are primarily targeted at pre-adolescents or young adolescents, it is expected to take several decades after deployment in a population before their full benefits in terms of cancer prevention are realised, and a substantial impact of vaccines on cervical cancer incidence or mortality outcomes is yet to be observed. To date, vaccine coverage in LMICs has been low overall, with an estimated 3% of the primary targeted population of young girls in less developed regions vaccinated by 2014.[7] By 2016, only 14% of LMICs had established vaccination programmes.[8]

Many high-income countries are transitioning, or considering transitioning, from cervical cytology to primary HPV testing for cervical screening, which is generally a

Research in context

Evidence before this study

Most low-income and lower-middle-income countries (LMICs) do not have access to human papillomavirus (HPV) vaccination, cervical screening programmes are unavailable or poorly implemented, and population-level access to cancer treatment services is variable. WHO, with its partners, is developing a global strategy towards the elimination of cervical cancer as a public health problem. The draft strategy involves triple-intervention targets for scale-up of vaccination, screening, and precancer treatment and invasive cancer treatment and palliative care in all countries; these targets, known as the 90–70–90 WHO triple-intervention strategy, specify 90% coverage of HPV vaccination, 70% coverage of twice-lifetime screening with HPV testing (or a similarly high sensitivity test), and 90% of women having access to cervical precancer and cancer treatment and palliative care services, by 2030. In the accompanying Article published in *The Lancet*, the WHO Cervical Cancer Elimination Modelling Consortium (CCEMC) predicted the impact of various HPV vaccination and screening and precancer treatment strategies on cervical cancer incidence in 78 LMICs. The analysis found that cervical cancer elimination by 2120 at a threshold of four cases per 100 000 women-years was possible in all 78 LMICs if girls-only vaccination was combined with twice-lifetime screening. The results suggested that elimination was consistently achievable, and the number of cervical cancer cases averted maximised, only if vaccination was combined with twice-lifetime cervical screening and with appropriate treatment for women found to have cervical precancer. The CCEMC harnesses three independent, extensively peer-reviewed models: Policy1-Cervix (Cancer Council NSW, Sydney, NSW Australia), Harvard (Harvard University, Boston, MA, USA), and HPV-ADVISE (Laval University, Quebec, QC, Canada). In this analysis, the models projected the reductions in cervical cancer mortality over time by use of standardised scenarios determined via consultations at various WHO technical expert, advisory group, and global stakeholder meetings.

Added value of this study

This analysis of the impact of the WHO triple-intervention cervical cancer elimination strategy on mortality outcomes shows that, in the next 10 years, achieving substantial reductions in mortality will require successful scale-up of cancer diagnostic and treatment services in LMICs, including pathology, surgery, radiotherapy, and chemotherapy; supportive and palliative care services will also need to be scaled up. If this is done, the 2030 UN Sustainable Development Goal of achieving a greater than one-third reduction in premature mortality from non-communicable diseases could be realised for cervical cancer. In the next 50 years, cervical screening and vaccination will both have an important role. The triple-intervention strategy would result in mortality rate reductions of 92% by 2070, increasing to almost 99% over the course of the next century as the full benefits of vaccination of young cohorts are realised over time.

Implications of all the available evidence

Implementing the 90–70–90 WHO triple-intervention strategy to achieve cervical cancer elimination will result in more than 74 million cervical cancer cases averted and more than 62 million women's lives saved over the course of the next century. These findings have informed the draft WHO global strategy for cervical cancer elimination, which will be presented to the WHO Executive Board in February, 2020, and thereafter considered at the World Health Assembly in May, 2020.

more effective and cost-effective approach to screening.[9–11] Initiatives for both HPV vaccination and screening have been introduced in the context of broad access to diagnostic, precancer treatment, cancer treatment, and supportive and palliative care services in high-income countries, and the combination of early detection via screening and effective treatment with surgery, chemotherapy, and radiotherapy has meant that net 5-year survival for cervical cancer is around 60–70% or greater in several high-income countries.[12] However, in LMICs, uptake of cervical screening has been low and inconsistent, and population-level access to cancer care is generally poor. As a consequence of these differentials in access to cervical screening and treatment, the majority of deaths (91%) from cervical cancer currently occur in LMICs and upper-middle-income countries, and 60% of deaths are in LMICs.[1] Access to supportive and palliative care services for people in LMICs is poor,[13] and thus the majority of women dying from cervical cancer do so with little or no supportive care or pain relief.

In May, 2018, the Director-General of WHO announced a call to action to eliminate cervical cancer as a public health problem, and in January, 2019, the WHO Executive Board requested that a draft global strategy to achieve elimination be developed. The draft global strategy being developed by WHO, with its partners, includes triple-intervention targets for scale-up of vaccination, screening, precancer treatment, and invasive cancer treatment in all countries; these targets specify 90% coverage of HPV vaccination, 70% coverage of twice-lifetime screening, and 90% access to cervical precancer and cancer treatment services and palliative care, by 2030.[14] To inform the strategic planning process, the WHO Cervical Cancer Elimination Modelling Consortium (CCEMC) was formed and has done comparative modelling of potential intervention scenarios in all 78 LMICs. In the accompanying Article published in *The Lancet*,[15] CCEMC predictions of the impact of HPV vaccination, screening, and precancer treatment strategies on cervical cancer incidence and cases averted are presented; the analysis found that elimination by 2120 at a threshold of four cases per 100 000 women was possible in all 78 LMICs if girls-only vaccination was combined with twice-lifetime screening. This strategy was predicted to reduce age-standardised incidence across 78 LMICs by 97% and to avert more than 74 million cervical cancer cases over the next century.[15] The analysis concluded that adding screening with high uptake to vaccination will expedite reductions in cervical cancer incidence and the number of cases averted, and will be necessary to eliminate cervical cancer in countries with the highest burden.

The aims of the current analysis were to model cancer treatment scale-up in addition to HPV vaccination and cervical screening and to assess the impact of achieving the 90–70–90 triple-intervention targets on cervical cancer mortality and deaths averted over the next century on the path to elimination. The cervical cancer elimination initiative has been framed within the context of the UN Sustainable Development Goals (SDGs) to support the realisation of SDG target 3.4—a one-third reduction in premature mortality from non-communicable diseases by 2030.[16] Therefore, we also assessed the potential for the cervical cancer elimination strategy to deliver a one-third reduction in premature mortality from cervical cancer by 2030.

For more on the **UN Sustainable Development Goals** see https://sustainabledevelopment.un.org/?menu=1300

Methods

Countries included in the analysis

The 78 LMICs considered were located in six regions according to World Bank definitions: east Asia and Pacific, Europe and central Asia, Latin America and Caribbean, north Africa and the Middle East, South Asia, and sub-Saharan Africa (see the appendix pp 44–45 for the full list of countries within each region and the grouping of countries by income level).

See **Online** for appendix

Description of the WHO CCEMC models

The WHO CCEMC comprised three modelling groups collaborating with WHO and the International Agency for Research on Cancer (IARC). The platforms were independent dynamic models, identified by WHO by use of predefined criteria. The modelling methods have been previously described.[15] In brief, the selected models for the analysis explicitly considered the dynamic transmission of HPV infection (and could thus capture the effects of herd immunity); were capable of projecting the impact of HPV vaccination, cervical screening, and precancer treatment and clinical and screen-detected cancer treatment scale-up at a country level for all 78 LMICs considered; and were independently developed and have been extensively validated and peer reviewed. Three models were selected: Policy1-Cervix (Cancer Council NSW, Sydney, NSW, Australia), Harvard (Harvard University, Boston, MA, USA), and HPV-ADVISE (Laval University, Quebec, QC, Canada). The individual CCEMC models have been previously used to inform national policy on cervical screening and HPV vaccination in Australia, Canada, the UK, and the USA, and at the global level.[10,17–22] The structure of the CCEMC models and the comparative modelling approach were endorsed by the WHO Advisory Committee on Immunization and Vaccines related Implementation Research (IVIR-AC).[23]

HPV transmission and cervical carcinogenesis are modelled for the oncogenic HPV types included in second-generation vaccines (HPV types 16, 18, 31, 33, 45, 52, and 58) and other oncogenic types, and each model simulates the type-specific natural history of cervical cancer from persistent HPV infection to cervical cancer via high-grade precancerous cervical lesions (cervical intraepithelial neoplasia grades 2 [CIN2] and 3 [CIN3]). All models can simulate complex cervical screening and treatment algorithms, and for the current analysis these models were adapted to incorporate country-level assumptions

about the proportion of women receiving cervical cancer treatment and the consequent survival outcomes. Reporting was done according to a consensus-based framework for modelled evaluations of HPV prevention and cervical cancer control: HPV-FRAME.[24] See the appendix (pp 50–56, 74–76) for a detailed description of the model platforms and HPV-FRAME reporting.

Status quo assumptions

The comparator (status quo) S0 scenario assumed no scale-up of vaccination, cervical screening, or cancer treatment. Under the status quo, it was assumed that none of the 78 LMICs had achieved substantial vaccination coverage by 2020, although in practice a few countries, such as Rwanda, have initiated high-coverage vaccination initiatives within the past few years. Thus, our analysis only captures the effect of scaled-up vaccination from 2020 onwards. For cervical screening, modelling groups made different assumptions about whether the impact of limited existing screening coverage was considered in the status quo (see the appendix pp 50–56 for further details).

Treatment for cervical cancer involves stage-appropriate multimodality therapies with radiotherapy and chemotherapy, with surgery (partial or total hysterectomy) being an important option for early-stage disease. Cervical cancer clinical staging was based on the International Federation of Gynaecology and Obstetrics (FIGO) system. Institute for Health Metrics and Evaluation (IHME) sub-regional-level estimates for the stage distribution of invasive cervical cancer at diagnosis, and data on 5-year and 10-year survival rates were derived from systematic reviews done by WHO based on peer-reviewed publications and national reports including cancer control plans, cross-referenced to data from IARC cancer registries. Radiotherapy access, estimated as machine density per 1000 patients with cancer, was used as a surrogate for multimodal treatment delivery. We used 2018 data for radiotherapy access and availability of external beam radiation therapy and personnel (radiation oncologists, medical physicists, and radiation therapy technologists) provided by the International Atomic Energy Agency's Directory of Radiotherapy Centres (DIRAC). Ranges of treatment access rates in each World Bank region encompassed the lowest and the highest treatment access rates of the countries in each region and represented the percentage of the population that could potentially be served with the equipment and workforce available (table 1). These data were then used to derive initial estimates of country-level current status quo stage distributions, treatment access rates, and survival rates (appendix pp 63–70). We used these data as an initial (pre-calibration) input to the models.

Calibration to GLOBOCAN 2018

Global Cancer Observatory (GLOBOCAN) 2018 estimates are based on IARC-certified cancer registry information where available in a country, or on a series of estimation methods if verified registry data are not available.[1,2] Each group incorporated initial country-level stage-specific 5-year and 10-year survival rates, and models were then calibrated to country-specific and age-specific mortality rates from GLOBOCAN 2018 by incorporating a quality factor into the final estimated country-specific and stage-specific survival assumptions. This approach encompasses limitations in the available data on staging, treatment access, uncertainties in actual delivery of treatment, variations in treatment delivery from established protocols and recommendations, equipment and infrastructure maintenance and logistics, and treatment abandonment. The calibrated results for incidence and

	Stage distribution at diagnosis				Overall 5-year (and 10-year) survival rates				Treatment access rate (range)*
	Stage 1	Stage 2	Stage 3–4A	Stage 4B	Stage 1	Stage 2	Stage 3–4A	Stage 4B	
East Asia and Pacific	23%	39%	27%	11%	65% (15%)	51% (13%)	15% (10%)	2% (2%)	17% (0–37)
Europe and central Asia	34%	19%	28%	19%	74% (42%)	62% (37%)	34% (28%)	6% (4%)	48% (18–100)
Latin America and Caribbean	23%	26%	46%	5%	73% (39%)	61% (34%)	32% (26%)	6% (4%)	44% (0–77)
North Africa and Middle East	13%	43%	31%	13%	80% (59%)	69% (52%)	46% (39%)	9% (6%)	67% (0–100)
South Asia	13%	36%	40%	11%	74% (42%)	62% (37%)	34% (28%)	6% (4%)	48% (0–55)
Sub-Saharan Africa	8%	36%	48%	8%	62% (6%)	47% (5%)	9% (4%)	1% (1%)	7% (0–37)

This table provides a regional summary of the data used as an initial (pre-calibration) input to the models; however, each modelling group also applied a quality factor to further adjust survival in the status quo to fit to Global Cancer Observatory (GLOBOCAN) 2018 estimates for cervical cancer mortality by 5-year age group (appendix pp 3–7, 63–70). Detailed country-specific estimates for status quo treatment access rates are provided in the appendix (pp 63–70). Staging is according to International Federation of Gynaecology and Obstetrics (FIGO) staging for carcinoma of cervix (2009 version) and TNM, 7th edition. Data based on a systematic review done by WHO, which obtained information from 43 countries, prioritising countries with population-based cancer registries. Results were derived by the Institute for Health Metrics and Evaluation (IHME) subregions. Regional results shown are weighted on the basis of each country's cancer case burden. *Treatment access rates were estimated on the basis of radiotherapy access and on the most recent availability of external beam radiation therapy and personnel (radiation oncologists, medical physicists, and radiation therapy technologists), which were provided by the Directory of Radiotherapy Centres (DIRAC). Ranges of treatment access rates in each region encompass the lowest and the highest treatment access rates of the countries in each region and represent the percentage of the population that could potentially be serviced on the basis of the equipment and workforce available.

Table 1: **Summary of treatment assumptions by region for status quo scenario: FIGO stage distributions, stage-specific survival rates, and treatment access rates**

mortality are shown for each model in the appendix (pp 3–7), summarised as the results across all 78 LMICs and at the regional level. Calibration results were comparable for all three models and generally demonstrated good fit with GLOBOCAN 2018.

Modelled scenarios

Models projected age-standardised cervical cancer mortality and deaths over time in 78 LMICs for standardised scenarios. The selection of core scenarios was determined after consultation at several WHO technical expert, advisory group, and global stakeholder meetings in 2018 and was based on a multi-step process, as previously described.[15,23] The scenarios were aligned with the scale-up targets articulated in the WHO draft global strategy for elimination.[14] The final fully articulated core scenarios for the mortality impact analysis were ongoing girls-only vaccination at age 9 years with multi-age cohort catch-up in the first year for ages 10–14 years (S1); girls-only vaccination, once-lifetime screening at around age 35 years with precancer treatment, and invasive cancer treatment scale-up (S2); and girls-only vaccination, twice-lifetime screening at around ages 35 years and 45 years with precancer treatment, and invasive cancer treatment scale-up (S3; the WHO triple-intervention strategy). We also considered two supplementary vaccination scenarios: girls-only vaccination with initial extended multi-age cohort catch-up to age 25 years (S4), and vaccination of girls and boys at age 9 years with multi-age cohort catch-up at ages 10–14 years (S5; appendix 57–59).

Vaccination was assumed to scale up to 90% coverage from 2020 with 100% lifetime broad spectrum protection against HPV oncogenic types 16, 18, 31, 33, 45, 52, and 58 in individuals susceptible to the relevant type; the analysis thus applies to a broad-spectrum vaccine that protects against these types either by direct protection (as per a second-generation 9-valent vaccine) or via cross-protection for non-vaccine-included types. We assumed that full efficacy against vaccine types was achieved with two doses for vaccine recipients aged younger than 15 years, and with three doses for older vaccine recipients (although dose delivery was not explicitly modelled). Cervical screening was assumed to involve HPV testing once or twice per lifetime at age 35 years, or at ages 35 years and 45 years, with increasing uptake from 45% in 2023, 70% in 2030, to 90% in 2045 onwards. Sensitivity of HPV testing was assumed to be 90% for CIN2 and 94% for CIN3 or worse, independent of age. We assumed that 90% of HPV screen-positive women received visual assessment and appropriate treatment as required for precancer or cancer (triaging was not explicitly modelled). For successfully delivered precancer treatment, treatment success was assumed to be 100%; CCEMC groups differed in their modelling of post-treatment natural history for whether an elevated risk of recurrence was simulated (appendix pp 50–56). We assumed that 50% of women with invasive cervical cancers would have access to high quality surgery, radiotherapy, and chemotherapy by 2023, and this would increase to 90% by 2030. Once treatment access was scaled up to 90% in 2030, 10-year survival was assumed to increase to 78% for women diagnosed at FIGO Stage 1, 69% at FIGO Stage 2, 52% at FIGO Stages 3–4A, and 8% at FIGO Stage 4B (appendix p 71).

For this analysis we considered two types of intervention packages—vaccination alone or vaccination combined with cervical screening and treatment for precancer and screen-detected cancer, delivered in conjunction with scaled-up treatment services for clinically detected cancer. This approach took into account the feasibility and acceptability of whether interventions could be considered in isolation from each other. Although vaccination can be considered in isolation since it is prophylactic, population-wide implementation of cervical screening leads to screening-related detection of precancer and invasive cervical cancer (with favourable effects on stage-shifting). Referral pathways should be organised so that women with screen-detected invasive cancer are offered prompt and effective treatment (with treatment capacity scaling up as screening expands), since this approach then leads to improved survival outcomes.

Comparative modelling approach and outcomes

Each single-model analysis was done independently at a country level. The coordinating centre for the analysis (Cancer Council NSW, Australia) aggregated all results,

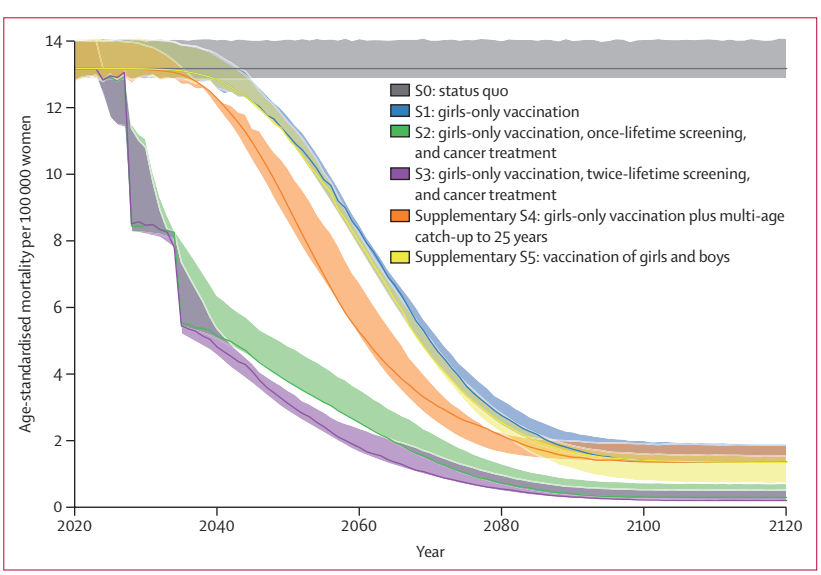

Figure 1: **Age-standardised cervical cancer mortality over time for all 78 LMICs**
The solid lines represent the median outcome of the three models; the shading represents the range of model outputs. HPV=human papillomavirus. LMICs=low-income and lower-middle-income countries. S0=status quo (no scale-up of vaccination, screening or treatment). S1=female-only vaccination at 9 years with multi-age cohort catch-up to age 14 years in 2020. S2=female-only vaccination and once-lifetime HPV testing at age 35 years with cancer treatment scale-up. S3=female-only vaccination and twice-lifetime HPV testing at age 35 years and 45 years with cancer treatment scale-up. Supplementary S4=female-only vaccination at 9 years with extended multi-age cohort catch-up to age 25 years in 2020. Supplementary S5=female and male vaccination at age 9 years with multi-age cohort catch-up to age 14 years in 2020. All scenarios assume the use of a broad-spectrum HPV vaccine with protection against seven oncogenic types.

	S1: girls-only vaccination		S2: girls-only vaccination, once-lifetime screening, and cancer treatment scale-up		S3: girls-only vaccination, twice-lifetime screening, and cancer treatment scale-up		Supplementary S4: girls-only vaccination plus multi-age catch-up to age 25 years		Supplementary S5: vaccination of girls and boys	
	Age-standardised rate	Reduction vs S0 (%)	Age-standardised rate	Reduction vs S0 (%)	Age-standardised rate	Reduction vs S0 (%)	Age-standardised rate	Reduction vs S0 (%)	Age-standardised rate	Reduction vs S0 (%)
Women aged 0–99 years										
2030	13·2 (12·9 to 14·0)	0·1% (0·1 to 0·5)	8·5 (8·2 to 11·1)	34·3% (21·4 to 37·4)	8·5 (8·2 to 10·8)	34·2% (23·3 to 37·8)	13·1 (12·9 to 13·9)	0·2% (–0·3 to 1·5)	13·2 (13·0 to 14·1)	0·1% (–0·7 to 0·2)
2070	5·0 (4·5 to 5·4)	61·7% (61·4 to 66·1)	1·4 (1·4 to 2·2)	88·9% (84·0 to 89·3)	1·0 (0·9 to 1·6)	92·3% (88·4 to 93·0)	3·2 (2·7 to 3·8)	77·5% (70·8 to 79·7)	4·5 (4·5 to 5·0)	65·3% (64·3 to 65·6)
2120	1·3 (1·3 to 1·9)	89·5% (86·6 to 89·9)	0·3 (0·3 to 0·7)	97·9% (95·0 to 98·0)	0·2 (0·2 to 0·5)	98·6% (96·5 to 98·6)	1·3 (1·3 to 1·8)	89·7% (86·9 to 89·9)	1·3 (0·7 to 1·5)	89·9% (89·2 to 94·6)
Women aged 30–69 years* (premature mortality)										
2030	23·7 (23·0 to 25·5)	0·2% (0·0 to 0·5)	15·2 (14·8 to 20·0)	34·2% (22·1 to 37·4)	15·2 (14·7 to 19·4)	33·9% (24·4 to 37·9)	23·6 (23·1 to 25·3)	0·1% (–0·2 to 1·4)	23·7 (23·3 to 25·6)	0·0% (–0·8 to 0·1)
2070	5·5 (5·1 to 6·2)	76·1% (75·7 to 78·5)	1·3 (1·2 to 2·3)	94·4% (91·1 to 94·6)	0·9 (0·8 to 1·4)	96·2% (94·3 to 96·8)	3·3 (3·1 to 3·9)	85·9% (84·9 to 86·8)	5·2 (4·4 to 5·4)	78·9% (77·9 to 81·0)
2120	2·4 (2·1 to 3·4)	89·9% (86·6 to 91·1)	0·5 (0·4 to 1·2)	98·0% (95·5 to 98·3)	0·3 (0·3 to 0·8)	98·6% (96·9 to 98·8)	2·4 (2·0 to 3·4)	89·9% (86·8 to 91·2)	2·4 (0·9 to 2·8)	89·9% (89·2 to 96·2)

Results shown represent age-standardised rates per 100 000 women for a given year, and relative reductions are compared to the status quo (S0) in that year. Results represent the median (range) of estimates across all three models. Detailed results for each decade are provided in the appendix (pp 8–10). S0=status quo (no scale-up of vaccination, screening, or treatment). S1=female-only vaccination and once-lifetime HPV testing at age 35 years and treatment scale-up. S2=female-only vaccination and twice-lifetime HPV testing at age 35 years and 45 years and treatment scale-up. Supplementary S4=female-only vaccination with multi-age cohort catch-up to 25 years in 2020. Supplementary S5=vaccination of girls and boys at age 9 years. All vaccination strategies assume the use of a broad-spectrum HPV vaccine with protection against the seven oncogenic types: 16, 18, 31, 33, 45, 52, and 58. Population projections were obtained from the UN and further projected out to 2120 (appendix pp 46–49). Model methods incorporate randomness and heterogeneity in estimates, which can occasionally, over shorter term timeframes, lead to relative increases rather than decreases in rates compared to the status quo, shown here as negative values. Randomness and heterogeneity can also lead to slight decreases in the percentage reduction in predicted rates even in the first year modelled (2020) and small differences from the expected relative ordering of the impact of different scenarios or the expected relative reductions over time. Caution should be applied in interpreting comparative differences between the values in this table, which represent the median and range across models; any individual median result could represent the findings of any one of the WHO Cervical Cancer Elimination Modelling Consortium (CCEMC) models. *Note that relative reductions in premature mortality are very similar if using the probability of dying between the ages of 30 and 70 years as a measure (appendix pp 8–10).

Table 2: **Projected cervical cancer mortality rates over time, across all 78 low-income and lower-middle-income countries**

applied standard populations and population projections, and estimated the median and range of results. Results are presented across all 78 LMICs, regionally, and by country. Rates were age-standardised by applying the age structure of the 2015 World Female Population aged 0–99 years. Premature mortality from cervical cancer was estimated by applying the 2015 World Female Population for ages 30–69 years, and in sensitivity analysis it was based on the probability of death from cervical cancer from age 30 years to 70 years.[16] For calculation of deaths averted, country-specific and age-specific population projections were based on the UN World Population Prospects: 2017 Revision.[25] Relative reductions over time were compared to the status quo. We summarised results for mortality reductions, and deaths averted were calculated from the beginning of 2020 to the end of 2030, 2070, and 2120, with the median (range) of model predictions for each result. See the appendix (pp 46–49) for more details.

Sensitivity analysis

The analysis was a comparative exercise based on three models with different structural and parameterisation assumptions and a form of sensitivity analysis is built into the reported ranges of results. We reported on key model-specific findings for calibration outcomes and for age-specific mortality rates (appendix pp 3–7, 11–25). We also ran explanatory (but counterfactual) scenarios to understand the sensitivity of the model results to underlying aspects of the impact modelling, including an extreme sensitivity analysis on the impact of cancer treatment scale-up. We also assessed the impact of using alternative population structures for age standardisation on the predicted age-standardised rate and the impact of different underlying fertility assumptions for population projections on the cumulative number of cervical cancer deaths averted.

Role of the funding source

This research was partly funded by WHO, which contributed to study design, data analysis, data interpretation, and writing of the report. Other funders had no role in the design of this analysis or the decision to submit for publication. KC, JJK, and MB had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Predictions from the three models were broadly consistent for all scenarios. Figure 1 shows the summary results across the models for the reduction in age-standardised mortality from 2020 to 2120, table 2 depicts these findings as numerical snapshots of the rates and relative reductions compared to the status quo scenario over time, and the reductions in premature mortality in women aged 30–69 years. Snapshots of the age-specific findings in 2020, 2070, and 2120 for each of the three CCEMC models are shown in the appendix (pp 11–25).

Figure 2A depicts annual cervical cancer deaths over time and figure 2B provides information about the cumulative cervical cancer deaths averted. Table 3 summarises these findings for the cumulative deaths and deaths averted over the periods 2020–2030, 2020–2070, and 2020–2120, for all core and supplementary scenarios.

In 2020, the predicted age-standardised rate for cervical cancer mortality across all 78 LMICs was 13·2 (range 12·9–14·1) per 100 000 women. By 2030, vaccine-only strategies would have minimal impact on cervical cancer mortality, which would remain at 13·2 (12·9–14·0) deaths per 100 000 women, corresponding to a 0·1% (0·1–0·5) reduction, averting a median of 620 deaths across all 78 LMICs by 2030 (rounded to 0·0 million in table 3). However, scaling up twice-lifetime cancer screening and treatment in addition to vaccination would result in a mortality rate of 8·5 (8·2–10·8) by 2030, corresponding to a 34·2% (23·3–37·8) reduction, averting 300 000 (300 000–400 000) deaths, mainly due to the impact of improved access to cancer treatment. In this 10-year timeframe, vaccination plus once-lifetime screening or twice-lifetime screening and treatment scale-up would lead to similar mortality reductions. For further information about the relative contribution of the interventions, see the appendix (pp 33–40).

By 2070, girls-only vaccination would lead to a mortality rate of 5·0 (range 4·5–5·4) per 100 000 women, corresponding to a reduction of 61·7% (61·4–66·1), averting 4·8 million (4·1–4·8) deaths, but scaling up once-lifetime screening and treatment in addition to vaccination would result in a rate of 1·4 (1·4–2·2) per 100 000 women, corresponding to a reduction of 88·9% (84·0–89·3), averting 13·3 million (13·1–13·6) deaths. By 2070, girls-only vaccination, twice-lifetime screening, and treatment would result in a mortality rate of 1·0 (0·9–1·6) per 100 000 women, corresponding to a reduction of 92·3% (88·4–93·0), averting 14·6 million (14·1–14·6) deaths. Compared to girls-only vaccination with catch-up to age 14 years (S1), extended-multi-age cohort vaccination to 25 years (S4) would result in increased intermediate-term mortality benefits, bringing forward the benefits of vaccination by about a decade (figure 1). At the high levels of vaccination coverage for girls assumed in the analysis, additional vaccination of boys at age 9 years (S5) would have minimal additional impact on cervical cancer mortality in women over the next 50 years and would have similar intermediate-term benefits to girls-only vaccination by 2070 (figure 1, figure 3, table 2).

By 2120, girls-only vaccination would result in a mortality rate of 1·3 (range 1·3–1·9) per 100 000 women, corresponding to a mortality reduction of 89·5% (86·6–89·9), averting 45·8 million (44·7–46·4) deaths. By 2120, a mortality rate of 0·2 (0·2–0·5) per 100 000 women, corresponding to a reduction of 98·6% (96·5–98·6), would be achievable with the WHO triple-intervention strategy, averting 62·6 million (62·1–62·8) deaths. If screening were done once per lifetime instead of twice, 60·8 million (60·2–61·2) deaths would be averted over the same period. The specific estimate for the incremental benefit of the twice-lifetime versus once-lifetime screening package over this period was 1·6 million (1·3–2·5) additional deaths averted, with most of these additional deaths averted before 2070. Compared to girls-only vaccination alone, 16·8 million (16·4–17·4) additional deaths would be averted via the triple-intervention strategy by 2120.

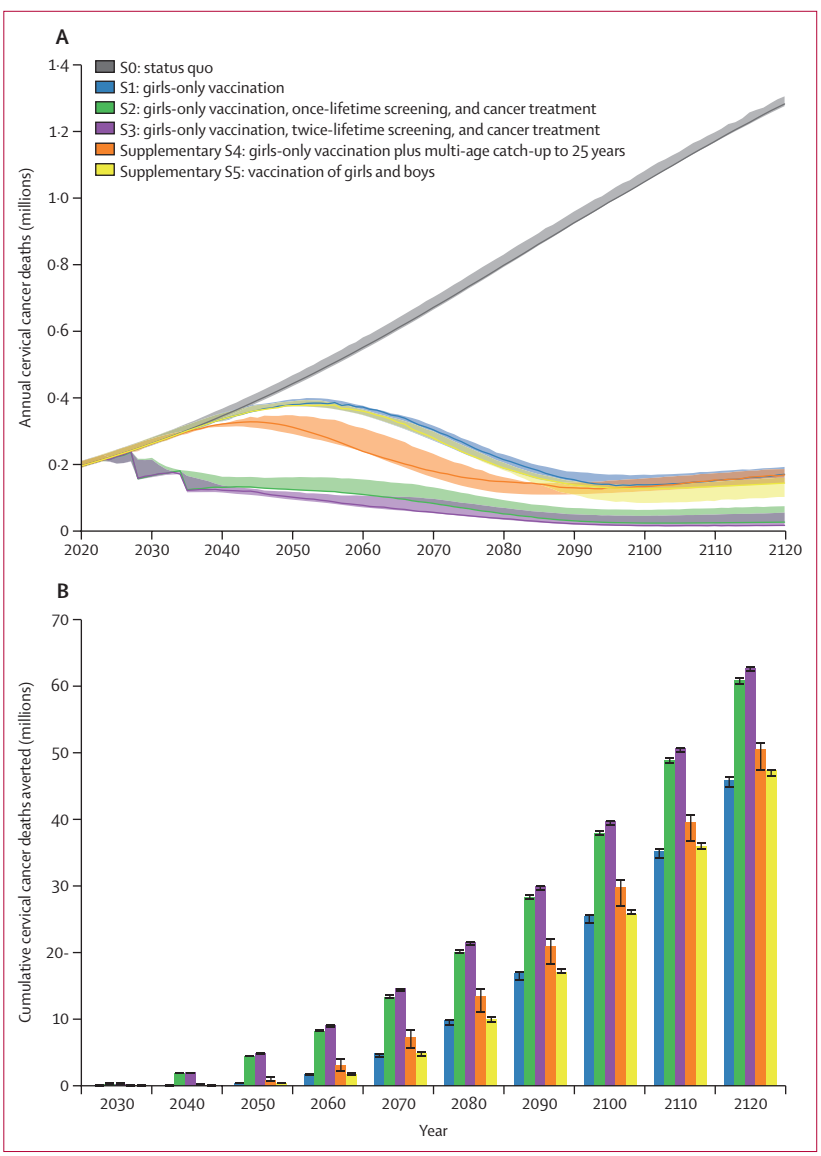

Figure 2: **Projected cervical cancer deaths across all 78 low-income and lower-middle-income countries**
(A) Annual cervical cancer deaths. (B) Cumulative cervical cancer deaths averted. The solid lines in panel A represent the median of the three models and the shading represents the range of the model outputs. In panel B the column height represents the median of the three models and the error bars represent the range of the three models. HPV=human papillomavirus. S0=status quo (no scale-up of vaccination, screening, or treatment). S1=female-only vaccination at age 9 years with multi-age cohort catch-up to age 14 years in 2020. S2=female-only vaccination and once-lifetime HPV testing at age 35 years with cancer treatment scale-up. S3=female-only vaccination and twice-lifetime HPV testing at age 35 years and 45 years with cancer treatment scale-up. Supplementary S4=female-only vaccination at age 9 years with extended multi-age cohort catch-up to age 25 years in 2020. Supplementary S5=female and male vaccination at age 9 years with multi-age cohort catch-up to age 14 years in 2020. All scenarios assume the use of a broad-spectrum HPV vaccine with protection against seven oncogenic types.

	S0: status quo	S1: girls-only vaccination	S2: girls-only vaccination, once-lifetime screening, and cancer treatment scale-up	S3: girls-only vaccination, twice-lifetime screening, and cancer treatment scale-up	Supplementary S4: girls-only vaccination plus multi-age catch-up to age 25 years	Supplementary S5: vaccination of girls and boys
Cumulative deaths by 2030 (2020–2030)	2·5 (2·5–2·7)	2·5 (2·5–2·7)	2·2 (2·2–2·4)	2·2 (2·2–2·4)	2·5 (2·5–2·7)	2·5 (2·5–2·7)
Deaths averted	..	0·0 (0·0–0·0)*	0·3 (0·3–0·3)	0·3 (0·3–0·4)	0·0 (0·0–0·0)	0·0 (0·0–0·0)
Reduction *vs* S0 (%)	..	0% (0–0)*	12% (11–12)	12% (10–13)	0% (0–1)	0% (0–0)
Cumulative deaths by 2070 (2020–2070)	20·7 (20·4–22·0)	16·3 (15·9–17·1)	7·1 (7·1–8·8)	6·4 (6·1–7·4)	13·5 (13·4–14·8)	16·0 (15·9–16·9)
Deaths averted	..	4·8 (4·1–4·8)	13·3 (13·1–13·6)	14·6 (14·1–14·6)	7·3 (5·6–8·5)	4·8 (4·4–5·1)
Reduction *vs* S0 (%)	..	22% (20–23)	65% (60–66)	69% (66–71)	35% (27–39)	23% (22–23)
Cumulative deaths by 2120 (2020–2120)	70·1 (69·7–73·0)	25·1 (23·7–27·1)	8·9 (8·9–12·8)	7·6 (7·3–10·3)	21·5 (19·7–22·5)	23·8 (22·4–25·5)
Deaths averted	..	45·8 (44·7–46·4)	60·8 (60·2–61·2)	62·6 (62·1–62·8)	50·5 (47·2–51·4)	47·3 (46·3–47·5)
Reduction *vs* S0 (%)	..	64% (63–66)	87% (82–87)	89% (86–90)	70% (68–72)	66% (65–68)

Cumulative cervical cancer deaths (in millions) across all 78 low-income and lower-middle-income countries over three time periods are shown. The values show the median (range) of three model outputs. All relative reductions are compared to the status quo (S0) predictions in the same year. HPV=human papillomavirus. S0=status quo (no scale-up of vaccination, screening, or treatment). S1=female-only vaccination at 9 years with multi-age cohort catch-up to 14 years in 2020. S2=female-only vaccination and once-lifetime HPV testing at age 35 years and treatment scale-up. S3=female-only vaccination and twice-lifetime HPV testing at age 35 years and 45 years and treatment scale-up. Supplementary S4=female-only vaccination with multi-age cohort catch-up to 25 years in 2020. Supplementary S5=vaccination of girls and boys at age 9 years, with multi-age catch-up to 14 years in 2020. All vaccination strategies assume the use of a broad-spectrum HPV vaccine with protection against the seven oncogenic types: 16, 18, 31, 33, 45, 52, and 58. Population projections were obtained from the UN and further projected out to 2120 (appendix pp 48–49). The median for deaths is the median of three possible model outputs for a given time period, and might use results from different models at different periods; similarly, the median for deaths averted and percentage reduction versus S0 is the median model for these metrics independently, and might be different to the median model selected for total deaths metric, and might also be different across the different periods. Caution should be applied in interpreting comparative differences between the values in this table, which represent the median and range across models; any individual median result could represent the findings of any one of the Cervical Cancer Elimination Modelling Consortium models. Note that the sum of averted cases and cases predicted for a given strategy might also not be identical to cases predicted for S0 because of rounding. *Note that table entry is zero due to rounding. Actual median and range of estimates for deaths averted: 620 (–1100 to 3600) deaths (model methods incorporate randomness and heterogeneity in estimates, which can occasionally, over shorter-term timeframes, lead to relative increases rather than decreases in rates compared to the status quo, shown here as a negative value).

Table 3: **Estimated cervical cancer deaths and deaths averted (in millions) from 2020 to 2030, 2020 to 2070, and 2020 to 2120**

In terms of premature mortality outcomes (deaths at age 30–69 years), the triple-intervention strategy would result in rate reductions of 33·9% (range 24·4–37·9) by 2030, 96·2% (94·3–96·8) by 2070, and 98·6% (96·9–98·8) by 2120 (table 2).

Figure 3 shows the regional results across the models for the reduction in age-standardised mortality from 2020 to 2120. The highest mortality rates in 2020, at approximately 30 per 100 000 women, are in sub-Saharan Africa, followed by Latin America and the Caribbean (approximately 16 per 100 000 women). These regions are predicted to have the greatest absolute reductions in mortality rates over the next two decades if the triple-intervention strategy can be successfully scaled up; by 2040, cervical cancer mortality in sub-Saharan Africa could be reduced by more than two-thirds to less than ten per 100 000 women, and in Latin America and the Caribbean it could be reduced to approximately six per 100 000 women. Details about the age-specific cervical cancer incidence and mortality rates in 2020, 2070, and 2120 for each region are provided in the appendix (pp 11–25).

With the WHO triple-intervention strategy, over the next 10 years, about half (48% [range 45–55]) of deaths averted would be in sub-Saharan Africa and almost a third (32% [29–34]) would be in South Asia (including India); over the next century, almost 90% of deaths averted would be in these regions (appendix p 26).

The appendix (pp 27–32) provides information at the country level for the predicted impact of the WHO triple-intervention strategy. In all countries, the median estimates of mortality rates by 2120 approach 1 per 100 000 women or lower.

The findings for model-specific, explanatory, and sensitivity analyses are provided in the appendix (pp 11–25, 33–43). Overall, the findings were concordant between models. The only notable difference was in the level of herd immunity predicted at older ages for unvaccinated individuals, which probably relate to underlying differences in assumptions around assortative sexual mixing among different age groups and different behaviour groups; we consider that the model variation in this area provides a useful reflection of true uncertainty in outcomes. The explanatory results demonstrated that the main benefits by 2030 were via cancer treatment scale-up, and that screening would lead to substantial mortality reductions beyond those conferred by vaccination and cancer treatment scale-up from 2030 to 2070–80. The results of the sensitivity analysis show that the choice of standard population is an important driver for rate estimates and also showed that, for deaths averted, differences between individual model estimates were

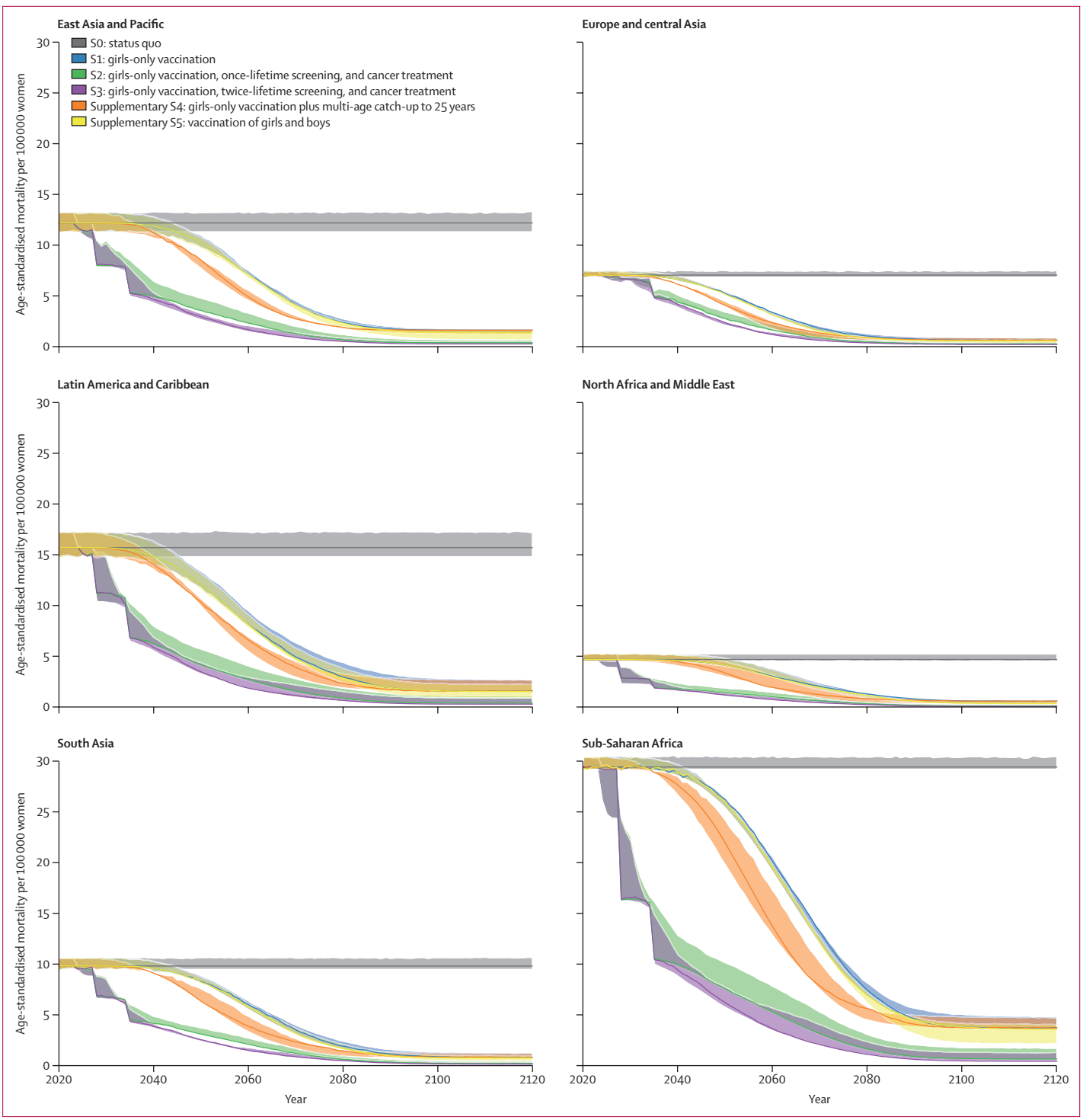

Figure 3: **Age-standardised cervical cancer mortality over time for LMICs in each region**

The solid lines represent the median outcome of the three models; the shading represents the range of model outputs. HPV=human papillomavirus. LMICs=low-income and lower-middle-income countries. S0=status quo (no scale-up of vaccination, screening or treatment). S1=female-only vaccination at 9 years with multi-age cohort catch-up to age 14 years in 2020. S2=female-only vaccination and once-lifetime HPV testing at age 35 years with cancer treatment scale-up. S3=female-only vaccination and twice-lifetime HPV testing at age 35 years and 45 years with cancer treatment scale-up. Supplementary S4=female-only vaccination at 9 years with extended multi-age cohort catch-up to age 25 years in 2020. Supplementary S5=female and male vaccination at age 9 years with multi-age cohort catch-up to age 14 years in 2020. All scenarios assume the use of a broad-spectrum HPV vaccine with protection against seven oncogenic types.

much smaller than the unavoidable uncertainties in future population projections over the next century.

Discussion

In this analysis, we have quantified, for the first time, the number of women's lives that could be saved by the successful implementation of the WHO global strategy for cervical cancer elimination. This report complements our parallel analysis on cervical cancer incidence.[15] Importantly, by extending the analysis to encompass mortality outcomes, we have quantified the impact of scaling up cancer treatment. Taken together, these two modelling analyses show that successful implementation of the WHO 90–70–90 triple-intervention strategy by 2030 would reduce cervical cancer incidence to 0·7 (0·6–1·6) per 100 000 women[15] and mortality to 0·2 (0·2–0·5) per 100 000 women across all 78 LMICs by 2120. This outcome, which is only achievable through a multi-sectoral and integrated approach across the continuum of cancer care, would represent extraordinary reductions in cervical cancer incidence (97% reduction) and mortality (99% reduction). Consequently, around 74·1 million cervical cancer cases and 62·6 million deaths would be averted, representing an enormous gain in terms of both quality of life and lives saved.

A major strength of this study is that we used a comparative approach involving well established model platforms that have been previously validated with data from multiple countries and that have jointly informed many national vaccination and cervical screening policy decisions. Predictions from the three models were broadly consistent for all scenarios, even over a century-long projection period. Our results for vaccination-only strategies are generally consistent with a recent analysis of the shorter-term impact on likely radiotherapy demand in LMICs,[26] which estimated that bivalent HPV vaccination of girls aged 12 years would only result in a 3·9% reduction in incident cervical cancer cases from 2015 to 2035. In line with our findings, the analysis found that incremental scale-up of radiotherapy in LMICs in the shorter term (up to 2035) would yield substantial health gains. Our sensitivity analysis demonstrated that for deaths averted, the variations generated by the differences in models were much smaller than uncertainties due to population size and structure over the next century. The sensitivity analysis also demonstrated that rates are somewhat sensitive to the choice of standard population used; this emphasises the importance of using the 2015 World Female Population for calculating cervical cancer incidence and mortality rates for comparability with our findings and across countries.

There were also some limitations to our analysis. The quality and availability of data about access to cancer treatment services, effective delivery of treatment, stage-distribution at diagnosis, and survival are variable for LMICs. Our modelling of survival was based on the latest data from major WHO reviews and we used updated DIRAC radiotherapy machine density as a surrogate for radiotherapy capacity and treatment access; this approach is reflective of the importance of radiotherapy as a cornerstone of effective treatment for cervical cancer and in line with the approach used by recently published models and the 2015 *Lancet Oncology* Commission on expanding global access to radiotherapy.[26,27] Furthermore, each modelling group independently did country-level model calibration of stage-specific survival to the best available mortality estimates from GLOBOCAN 2018. We incorporated a calibrated quality factor into the final estimated country-specific and stage-specific survival assumptions, which encompasses data limitations in treatment delivery information as well as variations in treatment delivery from established protocols and recommendations, equipment and infrastructure maintenance and logistics, and treatment abandonment due to financial stress or for other reasons. We did not take into account treatment improvements over time, assuming that mortality benefits resulting from cancer treatment scale-up by 2030 will be only due to the delivery of existing, effective treatment modalities, and not to emerging or hypothetical improvements in treatment beyond what is proven to be effective on a large scale in health services in high-income countries today.

Another limitation is that we did not explicitly model HPV infection, precancer and cervical cancer in women living with HIV. Increased progression to precancer and invasive cancer and reduced clearance of HPV is known to occur in women living with HIV, and this group is at increased risk of developing invasive cervical cancer, although this risk might now be partly or largely countered by the beneficial effects of antiretroviral therapy in many settings.[28,29] A separate collaborative group sponsored and coordinated by WHO is analysing the effects of HIV burden on estimates of cervical cancer elimination timing in selected countries. Current WHO cervical screening recommendations specify more frequent screening in women living with HIV,[30] and thus the mortality benefits we predicted are likely to depend on successful implementation of more intensive strategies for screening in high HIV-burden settings.

We did not include vaccination of boys or adult women in our core scenarios, because neither strategy has been found to be universally cost-effective even in high-income countries, and neither approach is recommended as part of the draft WHO elimination strategy. WHO's Strategic Advisory Group of Experts on Immunisation (SAGE) has recommended that vaccinating boys or older women should be delayed until current vaccine supply constraints are alleviated.[31] Priority should be given to vaccination of young girls since this strategy will generate the greatest health benefits overall; boys will derive protection via herd immunity if high-coverage vaccination can be achieved in girls, and older women will be offered protection via scale-up of screening and treatment services. In this analysis,

we did not explicitly consider cost-effectiveness, although previous work has shown the cost-effectiveness of combined vaccination and cervical screening approaches in various upper-middle-income countries and LMICs.[32,33] Cost-effectiveness will be required to weigh the trade-offs of the different strategies assessed here, including the incremental costs and benefits of vaccinating boys and doing two cervical screening tests instead of one in a lifetime. We found that the additional benefit of twice-lifetime versus once-lifetime screening was 1·6 million more deaths averted over a century, but the differences in cases averted is much higher.[15] Thus, the incremental improvement in quality of life from including a second screen is likely to be substantial. Furthermore, our findings for screening are in the context of rapid and effective scale-up of cancer treatment. If cancer treatment is not as broadly available as we assumed, the incremental benefits of additional cancer prevention via increasing screening to two tests in a lifetime would be larger. Finally, the incremental benefits of a second screen are higher when considered over the next 50 years rather than 100 years, because if vaccination is scaled up successfully then screening will provide the most benefit in the next 50–60 years. In the future, it will be important to assess the potential for future de-intensification of cervical screening, since our findings suggest that this could be considered in some countries after about 2070–80, when the full benefits of vaccination for mortality outcomes are becoming realised. The ongoing work of the CCEMC is focused on more detailed analysis of the incremental benefits of the strategies and on quantifying cost-effectiveness for the 78 LMICs; we are also analysing a larger number of more nuanced alternative scenarios at a country level, including optimal triage policy. In general terms, more detailed country-level analyses, taking into account specific local factors important for the effective delivery of vaccination and screening interventions, will continue to be required, and should be viewed as an important complement to the current large-scale analysis.

The WHO scale-up targets for elimination can be considered aspirational. Many challenges will need to be overcome, including vaccine and screening test supply and delivery challenges, and the infrastructure challenges associated with scale-up of invasive cancer diagnostics, treatment, and supportive and palliative care services. If scale-up is achieved more slowly than we have assumed, then reductions in mortality will be correspondingly delayed. With respect to HPV vaccination, the assumed scaled up 90% coverage rate is broadly in line with data suggesting that global coverage of other vaccines in LMICs (including measles, poliomyelitis, hepatitis B and diphtheria-tetanus-pertussis) is 84–90%.[34] Our analysis for screening broadly applies to a wide range of clinically validated HPV tests that can achieve benchmark sensitivity and specificity. Testing could be done either at a central laboratory or in a point of care environment, with clinician-collected or self-collected samples; the sensitivity of PCR-based self-collected tests has been shown to be comparable to that of clinician-collected samples.[35] In principle, our findings also apply to any future screening test with similar performance to that of primary HPV testing. For example, machine learning approaches for analysing digitised cervical images hold promise in some settings.[36] Our modelling of screening assumed that the majority (90%) of HPV-positive women were treated, with visual assessment for treatment done only to exclude the possibility of a frank cancer or a large precancerous lesion (which would require referral). Therefore, our findings for the impact of the cervical screening and referral pathway are likely to represent the maximum attainable benefit. In practice, resource-stratified guidelines recommend different approaches in different settings and, where possible, women are triaged to treatment to minimise the potential harms, which include psychosocial impact, potential overtreatment, and a possible impact on obstetric outcomes. WHO is revising its guidelines for cervical screening and has already revised its guidelines for precancer treatment to take into account the latest evidence and the elimination strategy.[30,37]

One of our main findings is that although achieving cervical cancer elimination per se will take many decades, the benefits of scaling up to the WHO elimination coverage targets will start to be realised within a decade. Key to this insight is an understanding of the timing of the effects of each intervention. Over the next 10–20 years, scaling up cancer treatment services will have the greatest impact because thousands of women in LMICs are being diagnosed every year with cervical cancer but have no access to adequate treatment. With appropriate treatment, survival prospects for early-stage and locally advanced cervical cancer are high. As a linked issue, offering appropriate palliative care to women who require it is an ethical and moral imperative. Over the intermediate term (the next 50–60 years), cervical screening will make an important contribution to outcomes, and over the longer term the full benefits of vaccination will be realised. The realisation of the major benefits of screening and vaccination over the intermediate and longer term will, however, require immediate action to implement these initiatives.

Scaling up to national vaccination, screening, and cancer treatment services in LMICs will be greatly facilitated by the successful realisation of universal health coverage in countries (SDG target 3.8). The 2019 Political Declaration of the UN high-level meeting on universal health coverage reaffirmed that health is a precondition for, and an outcome and indicator of, all dimensions of sustainable development, and countries strongly recommitted to achieving universal health coverage by 2030.[38] Building resilient and sustainable health systems could also be facilitated by the cervical cancer elimination initiative.[39] For example, cervical screening initiatives might be able to support or build on

HIV services, since women receiving antiretroviral therapy return for refills regularly. Opportunities exist to link screening with sexual and reproductive health services, potentially increasing both uptake of screening and of contraception services. The elimination initiative could assist with building cancer literacy and addressing stigma in communities, and scaling up treatment as well as supportive and palliative care services for cervical cancer should have positive implications for various other tumour types. Access to universal health coverage will be a key underlying factor for the achievement of SDG goal 3.4, to reduce premature mortality from non-communicable diseases by a third by 2030. We have shown that, when considered at a level across all 78 LMICs, the cervical cancer elimination initiative will specifically support efforts to achieve this target. More broadly, the elimination agenda will support a reduction in poverty (SGD1), an increase in gender equality (SDG5), and reduction in inequalities (SDG10). Thus, successful implementation of the elimination initiative will have both nearer-term and enduring positive consequences, not only for women but also for their families and broader society.

In conclusion, these findings emphasise the importance of acting now on three fronts to scale up HPV vaccination, screening, and treatment for cervical cancer. In the next 10 years, achieving substantial reductions in cervical cancer mortality will depend on successful scale-up of cancer treatment services in LMICs, and supportive and palliative care will need to be scaled up alongside such services. Implementing the WHO strategy towards cervical cancer elimination will result in large-scale mortality reductions and more than 62 million women's lives saved over the next century in LMICs. These findings have informed the draft WHO global strategy for cervical cancer elimination, which will be presented to the WHO Executive Board in February, 2020, and thereafter considered at the World Health Assembly in May, 2020.

Contributors

KC, JJK, and MB co-designed the study and co-led overall data interpretation. KC led the Policy1-Cervix analysis, JJK led the Harvard analysis, and MB led the HPV-ADVISE analysis. AK, KTS, MC, EAB, JT, FB, NB, and RH also participated in study design. AI, DT, EF, NB, and RH led the systematic review and analysis of cancer treatment access and survival in LMICs. KC, JJK, MB, MC, AK, DTNN, KTS, EAB, CR, SS, MD, GG, DM, EB, J-FL, AI, DT, EF, and FB participated in data collection. KC, JJK, MB, AK, KTS, MC, EAB, DM, DTNN, EB, SS, CR, MD, GG, J-FL, MAS, EF, DT, AI, and FB participated in data analysis. MC, AK, DTNN, KTS, and KC produced the tables and figures. KC, JJK, and MB drafted the Article and RH coordinated the CCEMC. All authors interpreted the results and critically revised the manuscript for scientific content. All authors approved the final version of the Article.

Declaration of interests

KC, AK, KTS, MC, DTNN, and MAS report grants from the National Health and Medical Research Council Australia during the conduct of the study. KC and MC are investigators of an investigator-initiated trial of cervical screening in Australia (Compass; ACTRN12613001207707 and NCT02328872), which is conducted and funded by the VCS Foundation, a government-funded health promotion charity; the VCS Foundation received equipment and a funding contribution from Roche Molecular Systems and Ventana USA but KC and MC (or their institution on their behalf) do not receive direct funding from industry for this trial or any other project. MAS also reports grants from Cancer Institute NSW during the conduct of the study. JJK, MB, EAB, MD, GG, DM, EB, J-FL, SS, and CR report grants from WHO during the conduct of the study. JT, EF, DT, FB, AI, NB, and RH declare no competing interests.

Acknowledgments

We acknowledge May Abdel-Wahab and Jose Alfredo Polo Rubio from the Division of Human Health of the International Atomic Energy Agency for providing updated DIRAC data, which have been used to estimate cervical cancer treatment access rates in this study. Where authors are identified as personnel of WHO or the International Agency for Research on Cancer, the authors alone are responsible for the views expressed in this Article and they do not necessarily represent the decisions, policy, or views of WHO or the International Agency for Research on Cancer.

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Global strategy to accelerate the elimination of cervical cancer as a public health problem

World Health Organization

"Through cost-effective, evidence-based interventions, including human papillomavirus vaccination of girls, screening and treatment of precancerous lesions, and improving access to diagnosis and treatment of invasive cancers, we can eliminate cervical cancer as a public health problem and make it a disease of the past."

Dr Tedros Adhanom Ghebreyesus,
Director-General, World Health Organization

Cover image credits:
Millicent Kagonga, survivor and advocate for cervical cancer elimination, with her daughter Grace. WHO/Ash Appleton.

Global strategy to accelerate the elimination of cervical cancer as a public health problem

ISBN 978-92-4-001410-7 (electronic version)
ISBN 978-92-4-001411-4 (print version)

Suggested citation
Global strategy to accelerate the elimination of cervical cancer as a public health problem. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data
CIP data are available at http://apps.who.int/iris.

In their own words

My daughter is young — she is a teenager — and yet she had to look after me, dressing my wounds, which had broken through my skin. For a long time I had to put up with pains which went through my whole body, especially in my back and my lower body areas. We had no morphine at home and so I was in a terrible state. ... I grew up in a poor family and we didn't have information about HIV and cancer. ... Often it is too late when people go to the doctor and most people don't even know the signs. If I had the chance, I would love to be part of a campaign to tell people about [it]. ... The clinics need to help us be more aware of these, especially about cervical cancer — we need more testing.

Ubuhle, who worked in a dairy as the main breadwinner for her family when she was laid off due to the severity of her cervical cancer symptoms (South Africa).[1]

I was snatched from the beginning of my career ... and tossed into a battle for my life ... diagnosed with stage IV-A cervical cancer. ... [A] flood of questions rushed forward — how could this be? The cervical cancer spread to my bladder? To the lower lymph nodes? And possibly to my ovaries? I likely would not be able to conceive and/or carry a child? And probably enter menopause as a 31-year-old? I felt betrayed by my body. ... I came across an article with this startling statement: "Cervical cancer has become a disease of the poor, uneducated minority." Excuse me? As a Latina, those three bold words seemed to lift off the screen and morph into a finger pointed at me. But ... data out there that lends itself to the heartbreaking finding that black women ... and Latinas suffer from the highest incidence rate ... this was and remains one of the many hard truths that I have confronted since my diagnosis and I will continue to shine a light on as an advocate.

Jeanette, a cervical cancer advocate and law clerk, passed away one year after her diagnosis (United States of America).

My stomach started bloating. ... When walking I felt like I would fall any moment. My legs would ache, it was unbearable. ... I went to the hospital. They scanned and said that there were three small fibroids. I did not do anything about it. My life was a mess, my husband was having a relationship with another woman. ... I went to live with my parents. My brother's sons took my scan report to [the hospital]. ... They said that I had cervical cancer. But they said that the condition was advanced and that they could not operate on me. We consulted many other places, and everyone said the same. ... Finally, a lady doctor ... said that I was a risky case but since I was so firm in my decision to have a surgery for uterus removal, she would do it. ... I had lost everything in my life — my marriage, my job. I lost all my hair and would not feel like going out in public. One day ... a nurse ... took me to a counselling centre. ... I learnt to hold on to the positive things in my life. ... I started doing business — bought and sold rice, made good money. ... I feel well, life goes on.

Anonymous cervical cancer survivor, whose husband remarried when she was unable to have children. Today she is a landowner who supports herself as a rural entrepreneur (India).[2]

I started suffering from aches, mainly in my ovary. ... With time the pain was becoming severe ... very severe ... almost unbearable. Until one night I woke up screaming as I was not able any more to endure the pain. ... I was diagnosed with cervical cancer [and] was informed that I had to undergo a hysterectomy and remove the left ovary as well. ... I did recover physically from the operation but I am still under the shock that I will not ever be able to give birth to a child of my own. ... Can you imagine how painful it is to lose the hope to have your own child? ... I might have lost the hope to have a child of my own, but I still have hope that some day we will be able to prevent this from happening to other women.

Anonymous member of a regional support group for women living with HIV (Egypt).

[1]Testimony provided by Hillcrest AIDS Centre Trust.
[2]Testimony provided by the Rural Women's Social Education Centre, Tamil Nadu, India. Translated from Tamil by T.K. Sundari Ravindran.

I developed a wound and that did not go. It became very painful. It was too late when I got treatment. My son is such a good boy. He would cook for me and try to care for me but it was too much for him. He is so caring, it breaks my heart. Now he is staying with his father who I don't have much contact with since I have been ill. ... The youth must learn about cancer as well as about HIV, and go to the clinics early to get tested. I didn't have this information.

Nonjabulo, who lived with HIV, battled cervical cancer at the age of 37. Her 16-year-old son was her sole caretaker until she was admitted to an NGO clinic for palliative care (South Africa).[3]

The doctor called me in earlier than the scheduled time. That turned out to be a bad sign. She told me that she had bad news. That I had cervical cancer. ... My daughter asked me to promise her that I would stay alive, but I told her that I couldn't. I didn't want to lie. ... When I went to the specialized hospital they told me after some tests that I could get surgery. I was really relieved and immediately called my kids. From that point on I felt positive. ... The radiation took a big toll on my bladder, intestines and stomach. It also causes an immediate menopause. ... The people around me forget easily that I was sick once. Which is normal of course; everybody needs to move on. But for a former cancer patient there is no real moving on. ... At the same time I'm of course very happy to still be alive. I'm enjoying my life more fully with my children and I'm very grateful for what I have.

Kim, a cancer survivor and patient advocate. She was diagnosed at the age of 39, a single mother of a 9-year-old son and a 13-year-old daughter (the Netherlands).

There was a lot of white vaginal discharge. There was also heavy bleeding — chunks of blood. This would go on for 15—20 days at a time and then stop. Come back again after 10 days. I was unable to go out for farm work or carry out household work. My hands and legs would feel weak and tremble. I went to Dr A in the local town. ... It cost me more than 5000 rupees. There was no change in my condition. Then the same doctor referred me to the medical college hospital. I went there. ... Nothing worked. ... I went with my son to the cancer hospital in Chennai. ... When I returned for the test results, they told me that it was the beginning stage of cervical cancer. ... I got admitted. They gave me tablets, and also radiation treatment. ... I am doing good now, I can do housework and also do some work in our farm.

"L", a cervical cancer survivor and mother of four from a rural farming family, whose travel for treatment took 3–4 hours each way (India).[4]

I am a Kariyarra woman from the Pilbara region of Western Australia who was diagnosed and received treatment in Perth (Boorloo) which is Whadjuk Noongar land. I'm a mum, three kids, I'm a wife, I'm also a cancer survivor. I was like right, okay. ... What about my kids? I wasn't so much worrying about myself and what it might mean for me, but more so what it meant to my family and how it would affect them. Part of my treatment plan was that I would have 35 rounds of radiotherapy and four lots of brachytherapy. That whole time was such a blur, I don't think I've ever felt as tired in my life trying to not be emotional about that, thinking that I can't even buy food for my kids, was horrible, simple things that you take for granted that you do as a mum. ... I had my screening test and it saved my life.

Natasha, a cervical cancer survivor (Pilbara Region, Australia).

A series of events led to the loss of my husband and two children due to AIDS-related illnesses. Just when I thought I was done with the hurt and the pain, I was diagnosed with stage II cervical cancer. This was the beginning of a long, rough and many times uncertain journey. The sights and sounds of hospital rooms and corridors became commonplace, the agony of being stigmatized by those I thought I could depend on only added salt to my open wounds, I had reached the end of my tether! As a victor, my experience revealed that indeed, cervical cancer is curable. Though I remain with lifetime scars. ... I have to walk around with ... a colostomy bag that collects my stool.... I need two in a day and each costs between 600 and 1000 Kenyan shillings. ... Early diagnosis, easy access to treatment facilities and support groups for the many people struggling with this disease can be a reality. I am an advocate for cancer and my message to the world is NO WOMAN SHOULD DIE OF CERVICAL CANCER. LET US JOIN HANDS AND ELIMINATE IT!

Sally, a cervical cancer survivor, advocate, and self-described "global hero of hope" (Kenya).

[3]Testimony provided by Hillcrest AIDS Centre Trust.
[4]Testimony provided by the Rural Women's Social Education Centre, Tamil Nadu, India. Translated from Tamil by T.K. Sundari Ravindran.

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Foreword

The success of the drive to eliminate cervical cancer depends on political will, country-led action investments, and global solidarity, as well as sustainable and adaptable partnerships. Member States have committed themselves to the attainment of universal health coverage and the Sustainable Development Goals, leaving no one behind.

Eliminating cervical cancer as a public health problem is part of honouring this commitment and many others related to tackling inequities and upholding the right of women and adolescent girls to high quality, people-centered equitable health services.

Even though the COVID 19 pandemic has taken a heavy toll on health systems across the world, ensuring that women and adolescents continue to receive the health services they need, is a moral imperative.

We have the knowledge and the tools to stop women from suffering and dying from this preventable disease. The time is now for all Member States and development partners to rally behind this strategy to eliminate cervical cancer as a public health problem.

Together, we can make history – it is within our reach!

Elimination is within the reach of all countries.

We can all leave behind a great legacy if we seize the opportunities that are within our reach now, so that girls who are born today will live to see a world free of this disease.

Dr Tedros Adhanom Ghebreyesus

Director-General,
World Health
Organization

Dr Zsuzsanna Jakab

Deputy Director-General,
World Health
Organization

"One woman dies of cervical cancer every two minutes...Each one is a tragedy, and we can prevent it."

Call to Action - May 2018: Cervical Cancer: An NCD We Can Overcome

Dr Tedros Adhanom Ghebreyesus
Director-General, World Health Organization

1. Background: why is a global strategy needed?

Cervical cancer is a preventable disease. It is also curable if detected early and adequately treated. Yet it remains one of the most common cancers and causes of cancer-related death in women across the globe. The annual number of new cases of cervical cancer has been projected to increase from 570 000 to 700 000 between 2018 and 2030, with the annual number of deaths projected to increase from 311 000 to 400 000. More than 85% of those affected are young, undereducated women who live in the world's poorest countries. Many are also mothers of young children whose survival is subsequently truncated by the premature death of their mothers *(1)*.

Few diseases reflect global inequities as much as cancer of the cervix. In low- and middle-income countries its incidence is nearly twice as high and its death rates three times as high as in high-income countries.

Proven and cost-effective measures for eliminating cervical cancer exist, but to date have not been widely implemented in regions of the world where the disease burden is highest. To be optimally effective, these measures must be scaled to national levels and delivered using health service platforms that are sensitive to women's needs, their social circumstances, and the personal, cultural, social, structural and economic barriers hindering their access to health services. Health services that are integrated and people centred, and that respect and uphold women's rights and dignity, are vital.

Urgent and bold action is needed to scale up and sustain implementation of the evidence-based interventions (human papillomavirus (HPV) vaccination, cervical cancer screening and management of detected disease) for eliminating cervical cancer as a public health problem, but such action must be strategic.

This global strategy to eliminate cervical cancer proposes:

- a vision of a world where cervical cancer is eliminated as a public health problem;
- a threshold of 4 per 100 000 women-years for elimination as a public health problem;
- the following 90-70-90 targets that must be met by 2030 for countries to be on the path towards cervical cancer elimination:

- a mathematical model that illustrates the following interim benefits of achieving the 90-70-90 targets by 2030 in low- and lower-middle-income countries:
  - median cervical cancer incidence rate will fall by 42% by 2045, and by 97% by 2120, averting more than 74 million new cases of cervical cancer;
  - median cumulative number of cervical cancer deaths averted will be 300 000 by 2030, over 14 million by 2070, and over 62 million by 2120.

The global strategy to eliminate cervical cancer as a public health problem will require (a) political support from international and local leaders; (b) coordinated cooperation among multisectoral partners; (c) broad support for equitable access in the context of universal health coverage; (d) effective resource mobilization; (e) health system strengthening; and (f) vigorous health promotion at all levels. The interconnected nature of gender and health must stand as the strategic centrepiece of interventions.

The strategy must also be open to the exploration and exploitation of new ideas and opportunities, including advances in developing new medicines, vaccines, diagnostics and treatment modalities. In order to achieve its targets, the strategy must embrace innovative models of service delivery and computerized data and information systems, together with new and expanded training methods (for example, using virtual reality simulations) and interventions scaled up to population level (for example, mass campaigns to screen and treat cervical cancer, and surgical camps). Management science and modern forms of communications technology must be integrated into all aspects of service delivery. The market must be reshaped to eliminate cost as a barrier to prevention and treatment in the world's poorest countries.

The moment has arrived for an ambitious, concerted and inclusive strategy to accelerate eliminating cervical cancer as a public health problem. Elimination is within the reach of all countries. We know what works. The technology and tools exist. We know that prevention and early diagnosis and treatment are highly cost effective. The current focus on universal health coverage demonstrated by the United Nations General Assembly in September 2019 offers a unique opportunity for countries to strengthen interventions for the management of invasive cervical cancer *(2)*.

Half measures and incremental approaches will not suffice. It is time to implement at scale, worldwide. A disease that now stands as one of the world's greatest public health failures can be eliminated.

Adolescent girls enjoying a day in Moscow – Russia

For the first time ever, the world has committed to eliminate a cancer.

2. Context:

This is the first global health strategy for the elimination of a cancer as a public health problem. It builds on the Director-General's call in May 2018 for all countries to take action to help end the suffering caused by cervical cancer, in which he argued for renewed political will to realize elimination and urged all stakeholders to unite behind this common goal *(3)*. The global effort is aligned with human rights instruments upholding health as a human right *(4)*, as well as the 2030 Agenda for Sustainable Development and its overarching principle of leaving no one behind. The effort supports the attainment of several Sustainable Development Goals and targets (Box 1) *(5)* and is a component of the United Nations Secretary-General's Global Strategy for Women's, Children's and Adolescents' Health (2016–2030) *(6)*.

Box 1. Eliminating cervical cancer contributes to attainment of several Sustainable Development Goals and targets

Goal 1:	End poverty in all its forms everywhere.
Goal 3:	Ensure healthy lives and promote well-being for all at all ages: Goal 3, target 3.4: By 2030, reduce by one third premature mortality from noncommunicable diseases through prevention and treatment and promote mental health and well-being. Goal 3, target 3.7: By 2030, ensure universal access to sexual and reproductive health-care services, including for family planning, information and education, and the integration of reproductive health into national strategies and programmes. Goal 3, target 3.8: Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all.
Goal 5:	Achieve gender equality and empower all women and girls.
Goal 10:	Reduce inequality within and among countries.

The World Health Organization (WHO) Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020 identifies HPV vaccination and cervical cancer screening and treatment as best buys *(7)*. They are included in the WHO list of interventions recommended for inclusion in Member States' national health plans.

In addition, the 2016 United Nations General Assembly adopted the Political Declaration on HIV and AIDS *(8)*, which aimed to end the AIDS epidemic by 2030 and emphasized the need for integrated services to address coinfections and comorbidities, including prevention, screening and treatment for viral hepatitis and cervical cancer, as well as other sexually transmitted infections, to guarantee the sustainability of HIV prevention, treatment, care and support services.

Nine in ten cervical cancer deaths worldwide occurred in low-and-middle income countries.

Women living with HIV are six times as likely to develop cervical cancer compared to women who are HIV negative.

3. Global burden of cervical cancer: a manifestation of inequality

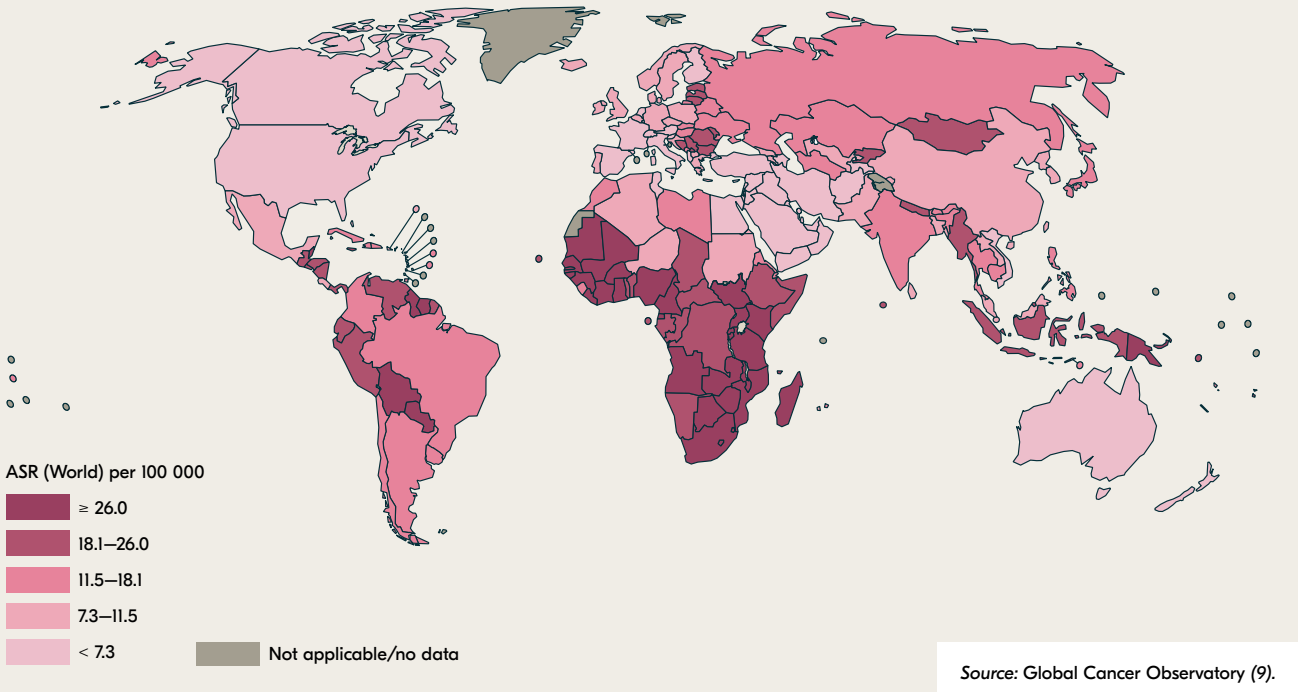
3.1 *Cervical cancer incidence and mortality*

Cervical cancer is the fourth most common cancer among women globally, with an estimated 570 000 new cases in 2018 *(9)*. All countries are affected, but the incidence is higher in low- and middle-income countries (Fig. 1). Age-standardized incidence rates vary from 75 per 100 000 women in the highest-risk countries to fewer than 10 per 100 000 women in the lowest-risk countries *(9)*.

Nearly 90% of the 311 000 deaths worldwide in 2018 occurred in low- and middle-income countries (Fig. 2). Further, the proportion of women with cervical cancer who die from the disease is greater than 60% in many low- and middle-income countries, which is more than twice the proportion in many high-income countries, where it is as low as 30% *(10)*.

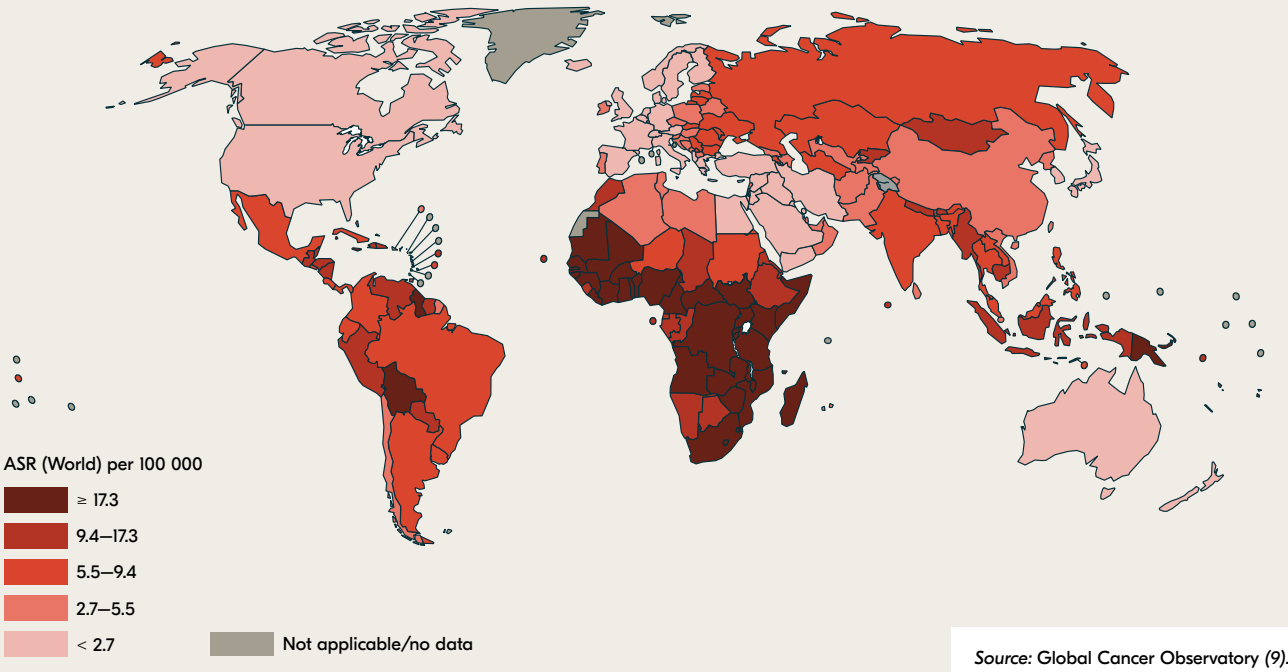
The global burden of cervical cancer is projected to continue to increase, rising to 700 000 cases and 400 000 deaths in 2030, with analogous increases expected in future years *(11)*. These rises represent a 21% increase in the number of cases and a 27% increase in the number of deaths over just the 12-year period from 2018. The vast majority of these increases will be in women in low- and middle-income countries, reflecting the severity of the global divide in cervical cancer morbidity and mortality.

Fig. 1. Estimated age-standardized cervical cancer incidence, 2018



Source: Global Cancer Observatory *(9)*.

Fig. 2. Estimated age-standardized cervical cancer mortality, 2018



Source: Global Cancer Observatory *(9)*.

3.2 *HPV and cervical cancer*

The primary cause of precancerous and cancerous cervical lesions is infection with a high-risk or oncogenic HPV type *(12)*. HPV makes up a group of viruses that are extremely common worldwide — there are more than 100 types, of which at least 14 cause cancer. A subset of HPV types is responsible for virtually all cases of cervical cancer. HPV 16 and 18, which together are responsible for about 70% of cervical cancer worldwide, are the most oncogenic types. Cervical HPV is the most common sexually transmitted infection. The pathogenesis of cervical cancer is the same worldwide. The higher rates of cervical cancer incidence and mortality in low- and middle-income countries are not attributable to differences in cervical infection with oncogenic HPV types. Instead, they are mainly attributable to the relative lack of high-quality cervical cancer screening and lack of widespread high-quality treatment of invasive cervical cancer in those countries. Infection with certain HPV types also causes a proportion of cancers of the anus, vulva, vagina, penis and oropharynx, which are preventable using primary prevention strategies similar to those for cervical cancer *(13)*.

3.3 *HIV and cervical cancer*

Cervical cancer is the most common cancer among women living with HIV. Compared with women who are HIV-negative, women living with HIV have a risk several times higher of persistent HPV infection, are six times as likely to develop cervical cancer *(14)* and are more likely to develop it at a younger age *(15, 16)*.

Despite the gains in prolonged life expectancy associated with access to HIV care and treatment in countries worst hit by the HIV epidemic, cervical cancer in women living with HIV has not received the attention and resources that are needed to address its prevention and treatment, and screening coverage has often been low. Reaching vulnerable women at high risk of developing cervical cancer and acquiring HIV infection will need prioritization of integrated preventive, screening and treatment services for both diseases to increase efficiencies and maximize impact.

Between 2006 and 2017, 100 million adolescent girls received at least one dose of the HPV vaccine – 95% were in high income countries.

Around 30% of low-income countries reported having pathology services, cancer surgery, chemotherapy and radiotherapy generally available in the public sector, compared with more than 90% of high-income countries.

*Less than 25% of low-income countries have introduced the HPV vaccine into their national immunization schedules.**

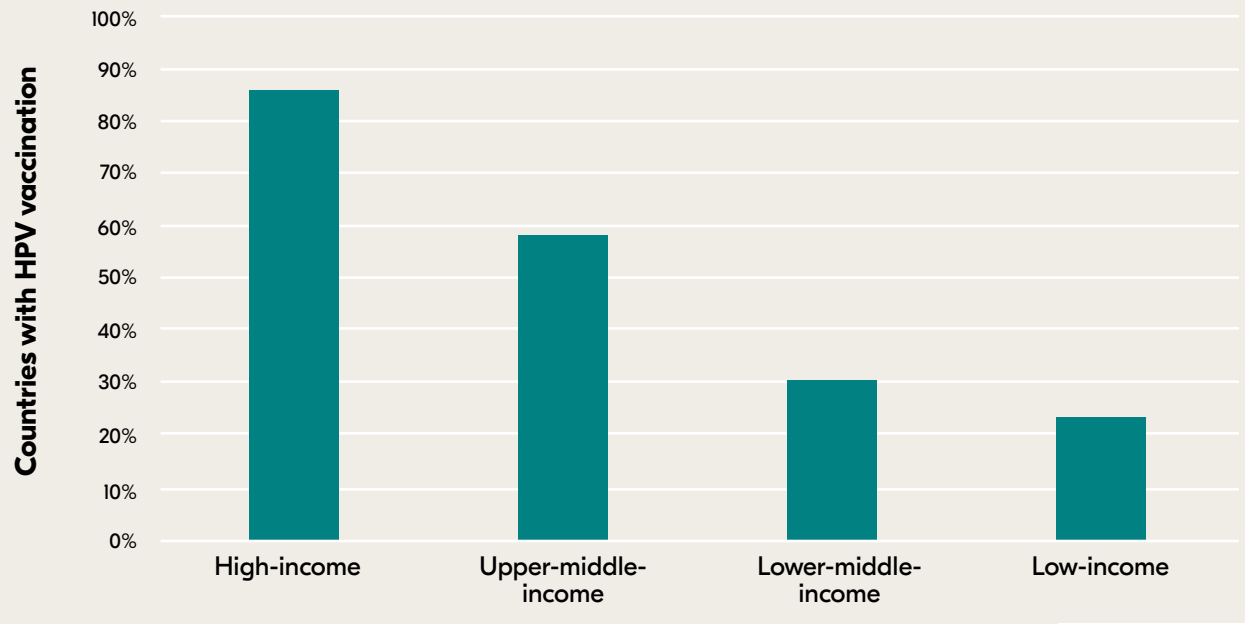
*As of 2020

4. Cervical cancer control interventions: current status of access to HPV vaccines, screening and treatment

Between 2006, when the first HPV vaccine was licensed, and 2017, more than 100 million adolescent girls worldwide received at least one dose of HPV vaccine, 95% of whom were in high-income countries *(17)*. Access to HPV vaccination is improving, and in 2019 more than 65% of the girls being vaccinated each year globally were living in low- and middle-income countries.[5]

As of 2020, less than 25% of low-income and less than 30% of lower-middle-income countries had introduced the HPV vaccine into their national immunization schedules, while more than 85% of high-income countries had done so (Fig. 3). A similar breakdown is observed in the establishment of cervical cancer screening programmes when examining countries based on income level (Fig. 4).

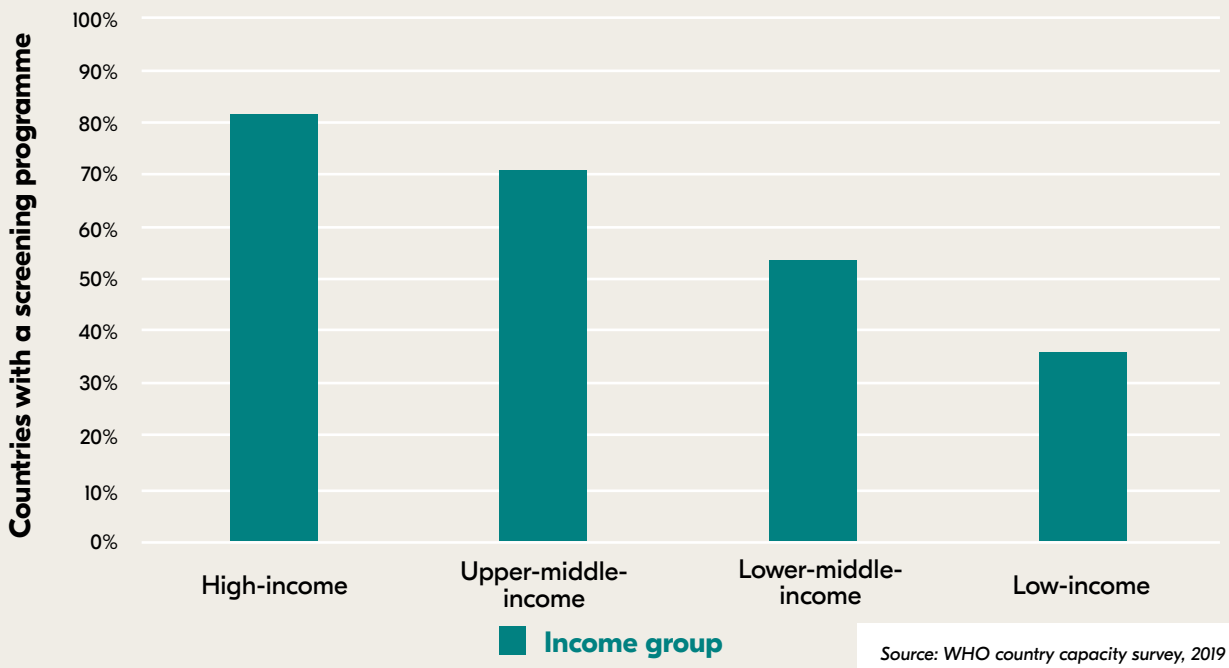
Fig. 3. Percentage of countries with HPV vaccine in the national immunization schedule, by World Bank income group, 2020



Source: WHO data, 2020.

[5]WHO Department of Immunization, Vaccines and Biologicals database.

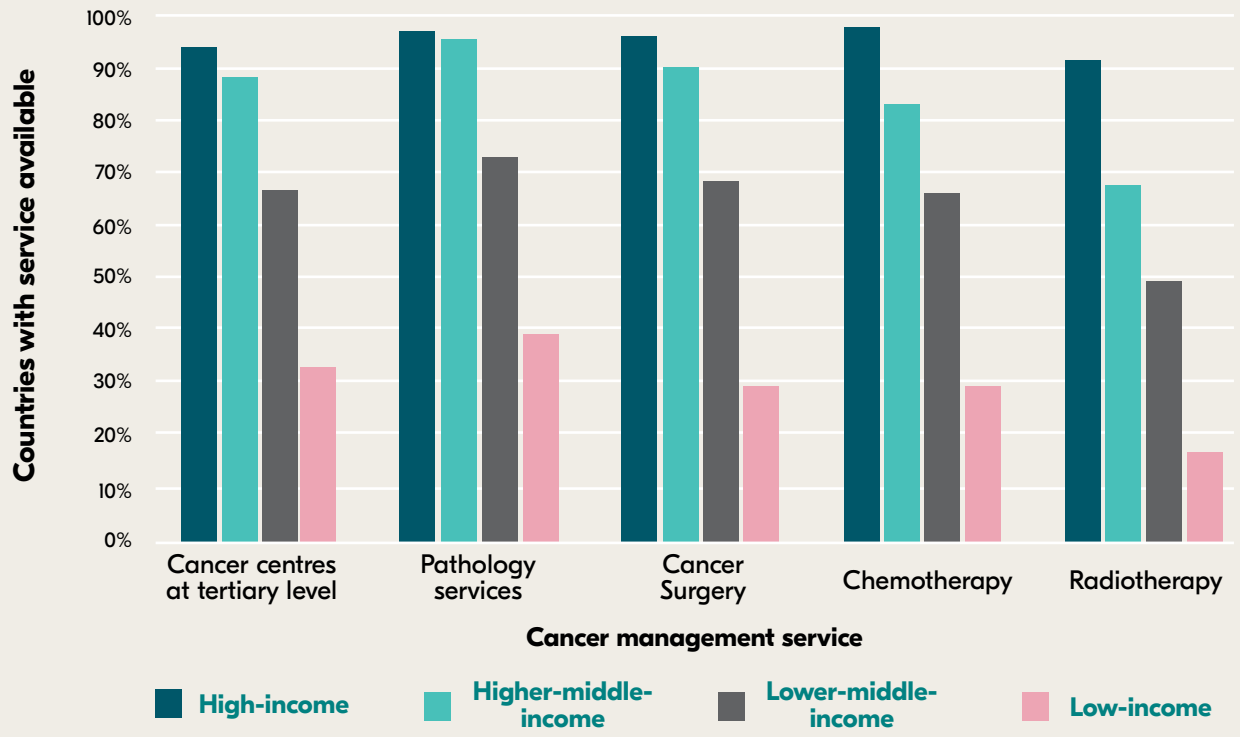
Fig. 4. Percentage of countries with a national cervical cancer screening programme, by World Bank income group, 2019



Source: WHO country capacity survey, 2019 (18).

The disparities among countries in the availability of cancer management services are similarly striking (Fig. 5) *(18)*. Around 30% of low-income countries reported having pathology services, cancer surgery, chemotherapy and radiotherapy generally available in the public sector, compared with more than 90% of high-income countries.

Fig. 5. Percentage of countries with generally available cancer diagnosis and treatment services in the public sector, by World Bank income group, 2019



Source: WHO country capacity survey, 2019 (18).

Achieving the 90-70-90 targets by 2030 would result in over 62 million cervical cancer deaths averted by 2120.

5. The path to eliminating cervical cancer

The huge burden of mortality related to cervical cancer is a consequence of decades of neglect by the global health community. However, with the recent rise in global advocacy for women's health, the commercial availability of prophylactic vaccines, low-cost approaches to screening and treating cervical cancer precursors, development of resource-appropriate management guidelines, novel approaches to surgical training, and initiatives to increase global access to anti-cancer drugs, the script can be rewritten.

Clearing the path to cervical cancer elimination will require bold strategic actions that are designed to improve community awareness; rapidly expand workforce capacity; strengthen health systems; shape the market so as to lower the prices of life-saving products; accelerate the introduction of affordable technology into screening and treatment algorithms; and nationally scale up organized, population-based prevention and treatment platforms. In order to ensure optimal effectiveness, the strategic actions must be developed in concert with front-line health care policy-makers and providers, advocates, and women themselves.

5.1 *Principles and elimination goal*

The term "elimination as a public health problem" is defined as achieving the measurable global targets set by WHO for a specific disease, based on population data. To determine the threshold for eliminating cervical cancer as a public health problem, WHO evaluated the epidemiological data and the distribution of incidence rate across countries *(19)*, considered established definitions of rare cancers *(20)*, and conducted an expert consultation in 2018–2019. To eliminate cervical cancer as a public health problem globally, all countries must work towards an incidence below 4 per 100 000 women-years. To achieve that goal, high coverage targets for HPV vaccination, screening and treatment of precancerous lesions, and management of cancer must be reached by 2030 and maintained at this high level for decades (Box 2).

All recommended interventions, services and policies are evidence based and should be delivered in the context of national efforts to achieve universal health coverage, focusing on primary health care, the public health approach,[6] the life-course approach to health *(21)*, and integrated people-centred health services *(22)*.

The elimination threshold is achievable in the vast majority of countries, including the 78 low- and lower-middle-income countries with the highest burdens of disease *(23)*. Once the elimination threshold is reached, interventions must be sustained to keep incidence rates below the threshold and to maintain low mortality. More ground-breaking technology, effective interventions and sound practices are needed to enable further reduction in the incidence of cervical cancer.

[6]The core public health functions involve assessing and monitoring the health of specific, most affected populations to identify health threats and priorities, formulating public policies to solve identified health problems and priorities, ensuring that all populations have access to appropriate and cost-effective care, and evaluating the effectiveness of that care.

5.2 *Interim targets on the path towards elimination (90-70-90)*

As countries facing potential barriers to achieving the necessary uptake of the vaccine (for instance, acceptability, cost, programme infrastructure and the anti-vaccine movement) seek solutions, women previously infected with oncogenic HPV types will continue to be at risk for cervical cancer and its sequelae. Therefore, improving access to secondary and tertiary preventive interventions must remain a top priority of the global strategy to eliminate cervical cancer. The business-as-usual trajectory is unacceptable, as every year more and more women will suffer from and die of a preventable condition.

Box 2 presents a set of targets or milestones for 2030 based on the principles and strategy for elimination.

Box 2. The 2030 targets towards elimination of cervical cancer

Meeting the following 90-70-90 targets by 2030 will put all countries on the path to elimination *(24)*:

- **90**% of girls fully vaccinated[7] with HPV vaccine by 15 years of age
- **70**% of women screened using a high-performance test[8] by 35 years of age and again by 45 years of age *(25)*
- **90**% of women identified with cervical disease are treated:
  - **90**% of women with precancer treated
  - **90**% of women with invasive cancer managed.

5.3 *Why the 90-70-90 targets are the key to success*

For maximum impact, interventions to meet the three targets must be implemented simultaneously and at scale.

Implementing all three pillars of the strategy will contribute to the immediate and accelerated reduction in mortality rates that results from the treatment of invasive cervical cancers. Incidence rates will gradually decrease as a result of wide-scale implementation of population-based screen and treat services, and vaccination against HPV offers protection against cervical cancer for girls and future generations *(26)*.

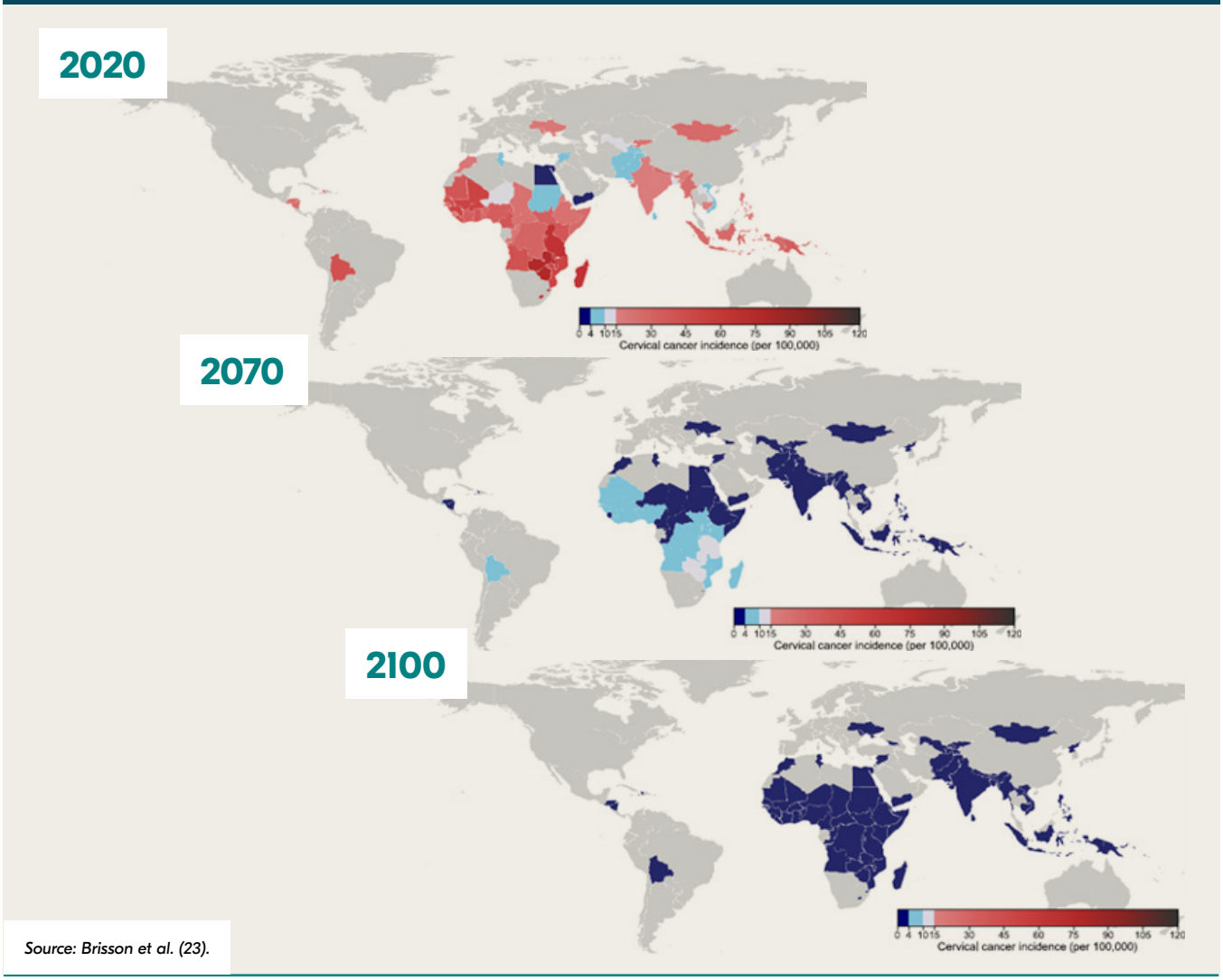
Kim Hulscher, a cervical cancer survivor, with her family right after her diagnosis in Almere, The Netherlands.

[7] In accordance with the latest recommendations.
[8] A high-performance test refers to a test that would have performance characteristics similar to or better than a HPV test. In future, however, new technologies may become available.

5.4 *Impact of achieving the 2030 targets on incidence and mortality in high-burden countries*

The WHO Secretariat modelled the health and socioeconomic impacts of achieving the 90-70-90 targets by 2030 in 78 low- and lower-middle-income countries (see Annex 1 for details of the modelling). The current heterogeneity in incidence between countries will lead to ongoing variations in cervical cancer incidence and the time frame to reach elimination (Fig. 6).

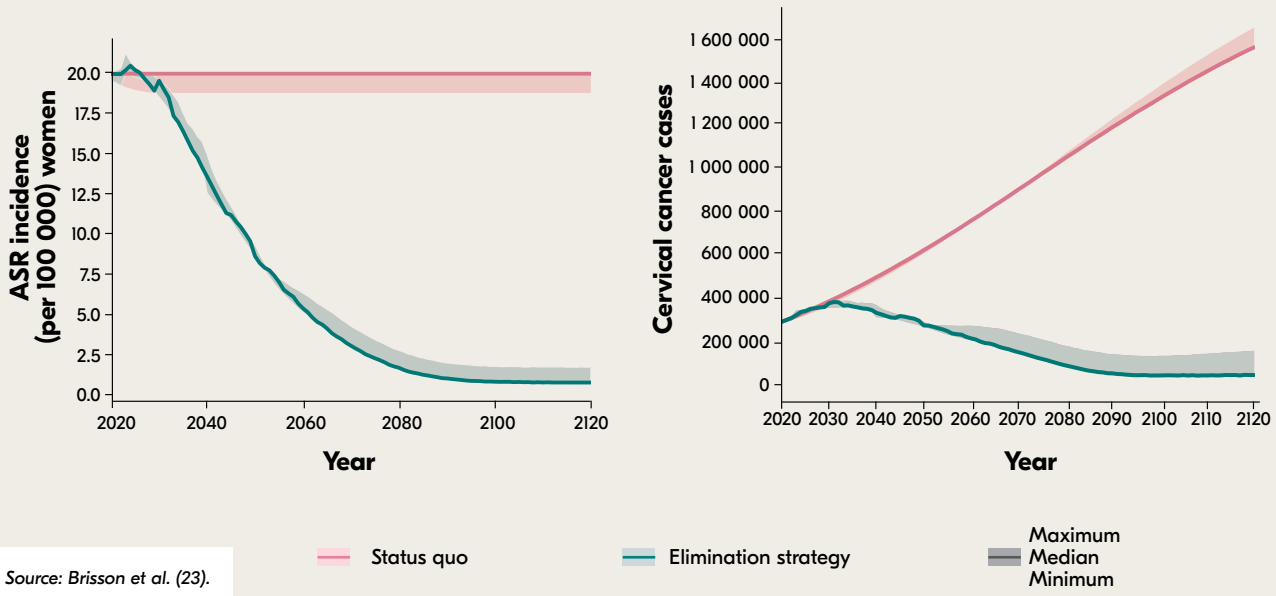
Fig. 6. Age-standardized cervical cancer incidence rate in 78 low- and lower-middle-income countries in 2020, 2070 and 2100 after implementation of the elimination strategy



Source: Brisson et al. (23).

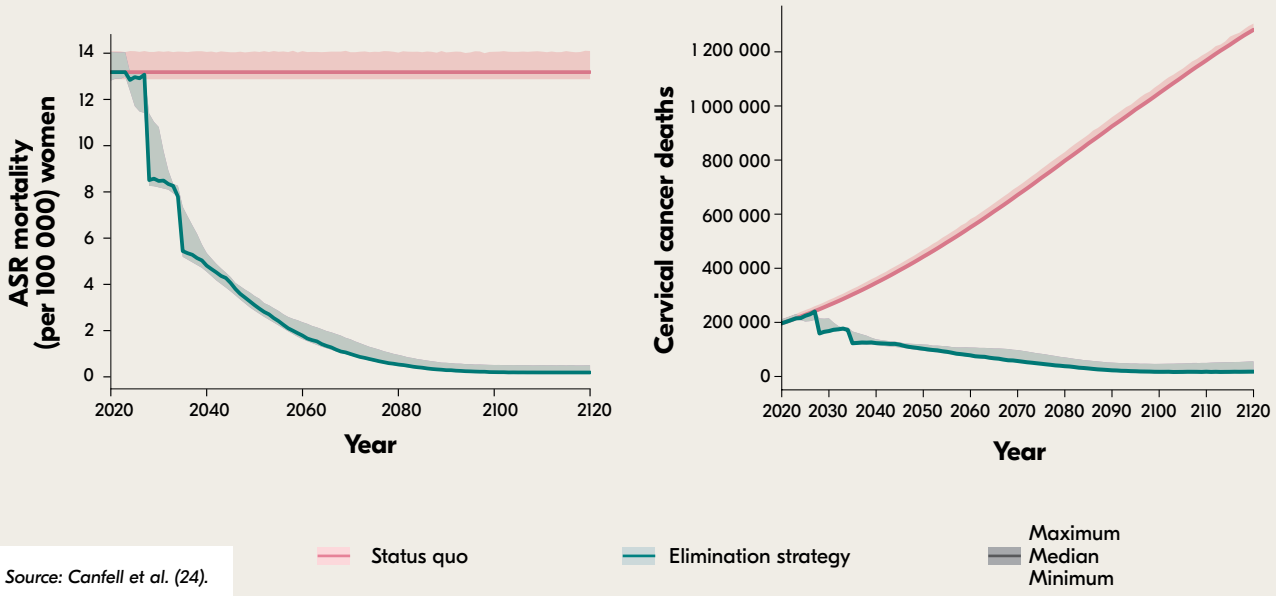
Achieving the 90-70-90 targets by 2030 would mean that median reduction in cervical cancer incidence rate would be 2%, 42% and 97% by 2030, 2045 and 2120, respectively, resulting in 74 million cases averted (Fig. 7). Correspondingly, the cumulative number of cervical cancer deaths averted would be about 2 million, 5 million and over 62 million by 2040, 2050 and 2120, respectively (Fig. 8)*(23, 24)*. Because settings with high HIV prevalence rates currently have some of the highest cervical cancer rates, greater effort may be needed to achieve elimination there.

Fig. 7. Cervical cancer incidence rate and cervical cancer case projections in 78 low- and lower-middle-income countries, 2020–2120, by elimination strategy and with status quo



Source: Brisson et al. (23).

Fig. 8. Cervical cancer mortality (age-standardized) rate and cervical cancer death projections in 78 low- and lower-middle-income countries, 2020–2120, by elimination strategy and with status quo



Source: Canfell et al. (24).

5.5 *Investment case for eliminating cervical cancer in high-burden countries*

Investing in the interventions to meet the 90-70-90 targets offers immense economic and societal benefits. An estimated US$ 3.20 will be returned to the economy for every dollar invested through 2050, owing to increases in women's workforce participation, with this figure rising to US$ 26.00 when societal benefits are incorporated *(27)*.

It is estimated that about 250 000 women will remain productive members of the workforce, adding an estimated US$ 28 billion to the world's economy: US$ 700 million directly through increased workforce participation and almost US$ 27.3 billion through the indirect socioeconomic benefits of good health. High socioeconomic benefits would accrue if the 78 low- and lower-middle-income countries achieve the 90-70-90 targets by 2030, by mobilizing and spending the estimated US$ 10.5 billion needed to scale up cervical cancer prevention and treatment interventions between 2018 and 2030 *(26)*.

Sally Kwenda, a cervical cancer survivor, advocate, and self-described "global hero of hope".

“Through cost-effective, evidence-based interventions, we can eliminate cervical cancer as a public health problem. Half measures and incremental approaches will not suffice. It is time to implement at scale worldwide”

Dr Tedros Adhanom Ghebreyesus
Director-General, World Health Organization

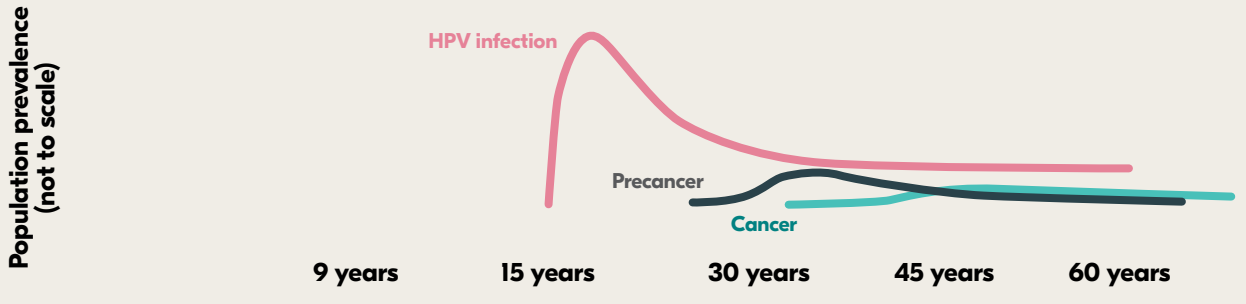
6. Strategic actions to achieve the 2030 targets:

Strategic actions to achieve the 90-70-90 targets should be pursued within the framework of a national policy to eliminate cervical cancer. Scale-up should be incorporated into countries' national strategic health plans to reach universal health coverage. High-level political commitment and stewardship should drive and guide implementation, supported by collaborative partnerships.

Each evidence-based intervention for cervical cancer elimination has its own set of requirements for implementation, and each poses unique challenges. Biomedical and clinical interventions alone will not be sufficient for reaching the targets, as many of the implementation challenges are related to health care system weaknesses that commonly affect low- and middle-income countries, where the disease burden is the highest. Strategic actions must be customized by each country to take into consideration its unique structural deficiencies, level of readiness to implement, and other factors to care (such as sociocultural or gender, and myths and misconceptions about the disease and its prevention and treatment) that drive cervical cancer incidence, morbidity and mortality. Approaches to scaling up interventions in urban settings may differ from those in remote and rural areas. Inequities in health outcomes among vulnerable or underserved populations, including women with HIV, call for tailored approaches.

The global elimination strategy calls for governments to work with key partners, including the private sector and civil society, and for meaningful engagement with and empowerment of affected populations. Private sector efficiencies in management can be leveraged to improve workflow and output in the public sector. Civil society can advocate for accessible, affordable, acceptable health products and services and can increase awareness of cervical cancer prevention and control within their communities, especially those at high risk for the disease. Cervical cancer survivors can serve as advocates for educating women and girls about the benefits of vaccination, screening and treatment and for overcoming stigmatization. WHO recommends a life-course approach to a comprehensive strategy for cervical cancer elimination to ensure that lifetime benefits are maintained (Fig. 9).

Fig. 9. Life-course approach to cervical cancer interventions



Primary Prevention

Girls 9–14 years
- HPV vaccination

Girls and boys, as appropriate
- Health information and warnings about tobacco use
- Sexuality education tailored to age and culture
- Condom promotion/provision for those engaged in sexual activity
- Male circumcision

Secondary Prevention

Women > 30 years of age
- Screening with a high-performance test equivalent to or better than HPV test
- Followed by immediate treatment or as quickly as possible, of precancerous lesions.

Tertiary Prevention

All women, as needed

Treatment of invasive cancer at any age
- Surgery
- Radiotherapy
- Chemotherapy
- Palliative care

6.1 *Primary prevention: HPV vaccination*

Vaccination of adolescent girls is the most effective long-term intervention for reducing the risk of developing cervical cancer. The great long-term benefit of HPV vaccination makes it important to initiate and sustain this approach in all countries. There is also strong evidence that high HPV vaccination coverage leads to protection of unvaccinated individuals through herd immunity, further enhancing the protective effect for the community *(28)*. WHO's current guidelines recommend that young adolescent girls between 9 and 14 years receive two doses of vaccine to be fully protected. Data suggesting protection after a single dose have led to trials that will provide evidence for future schedule optimization *(29, 30)*.

HPV vaccine coverage is inequitably distributed across geographical settings and income, with higher-income countries achieving higher vaccine coverage. High vaccine prices coupled with recent supply challenges have significantly constrained the ability of many countries to introduce the HPV vaccine into national immunization programmes and to ensure sustainability of current programmes (*31*). To ensure high levels of acceptance and sustained coverage, the introduction of HPV vaccination programmes must be accompanied by strong communication strategies for advocacy and social mobilization to affirm the efficacy, safety and benefits of the vaccine. Tailored strategies to address the rising anti-vaccine movement are essential.

In addition to HPV vaccination, a comprehensive prevention strategy must include age-appropriate information on sexual and reproductive health, safer sexual practices — such as delaying sexual debut, decreasing the number of sexual partners, condom use, and male circumcision where appropriate — and cessation of tobacco use. Concerted efforts to promote healthy lifestyles among adolescents (boys and girls) are critical for a healthier population for sustainable development.

Multisectoral delivery platforms, such as school immunization programmes, can play a role in improving coverage of HPV vaccination among girls. — Lao People's Democratic Republic

6.2 *Strategic actions to achieve 90% coverage of HPV vaccination*

Secure sufficient and affordable HPV vaccines	A concerted effort will be needed between partners and the private sector to overcome vaccine supply constraints. Additionally, through appropriate market-shaping interventions, more affordable prices can be achieved while ensuring a healthy HPV vaccines market.
Increase the quality and coverage of vaccination	Increasing the coverage of HPV vaccination will require efficient and sustainable multisectoral delivery platforms (such as school immunization programmes) and innovative community-based approaches to reach vulnerable populations (such as adolescent girls who are not in school). Monitoring systems or registers should track and improve coverage and quality.
Improve communication and social mobilization	As HPV vaccination programmes are introduced and expanded, they will need nationwide, evidence-based communication and social mobilization efforts. Understanding the social, cultural, societal and other barriers that may affect the acceptance and uptake of the vaccine will be critical. Some communities will need extra engagement to overcome vaccine hesitancy and counter misinformation.
Innovate to improve efficiency of vaccine delivery	National guidelines, policies and strategies should be updated as new evidence and innovations become available on better and more efficient approaches to HPV vaccination.

Karen Nakawala, a cervical cancer survivor and advocate — Lusaka, Zambia

6.3 *Secondary prevention: screening and treating precancerous lesions*

The principal goal of secondary prevention is to reduce cervical cancer incidence and mortality by identifying and treating women with precancerous lesions. Cytology-based screening has been successfully used to achieve these goals when implemented as part of national programmes with high coverage and in settings where resources exist for patient follow-up, additional diagnostic tests (colposcopy and pathology) and disease management. In low- and middle-income countries cytology-based programmes have been difficult to implement, and where they have been implemented screening coverage is low. Visual inspection of the cervix with acetic acid followed by treatment (screen and treat) is an alternative approach to secondary prevention in resource-constrained settings. Although relatively easy to establish, the quality of such visual inspection depends heavily on the provider and its sensitivity is variable.

Testing for HPV offers superior specificity, and its strong negative predictive value means that women who test negative only need to be retested after a minimum interval of five years. Providing women with the option of self-sampling contributes to acceptability and access to services. Existing technological platforms that are being used in countries to test for HIV, tuberculosis and other infections can also be used for HPV testing, enabling rapid scale-up. Because of its high level of performance, countries should ideally transition to HPV testing as the primary method of screening for cervical cancer. Evidenced-based strategies for the evaluation and management of women who test HPV-positive are available.

Cervical cancer screening will require a matching increase in capacity for treatment of the detected lesions, as screening women without access to treatment is unethical. WHO's treatment guidelines were recently expanded to include thermal ablation as a therapeutic modality for women who have precancerous lesions eligible for ablation *(32)*.

Market-shaping initiatives to secure affordable, high-quality diagnostics and related supplies will be prioritized. Research on artificial intelligence-based diagnostic technology and simple handheld devices for ablative therapy offers immense opportunities and moves the world closer to the vision of cervical cancer elimination *(33)*.

Waiting room of gynaecologic health outpatient department — Nepal.

6.4 *Strategic actions to achieve 70% coverage for screening and 90% treatment of precancerous lesions*

Understand barriers to accessing services and create an enabling environment	A robust understanding of the social, cultural, societal and structural barriers to the uptake of services is crucial. Such knowledge will inform the development of context-specific and culturally appropriate demand-creation strategies and the design of acceptable, accessible service delivery platforms. Local communities, especially women, must be engaged and empowered to lead the development of these critical programmes, serve as allies, counter misinformation or stigmatization, and support those needing more complex treatment. Increasing health literacy, knowledge of rights and awareness of cervical cancer prevention and control will help to mobilize, empower and engage communities and civil society, and women in their diversity.
Integrate screening and treatment services into the primary care package	Services integrated into existing sexual and reproductive health services, HIV care and treatment clinics, antenatal care, well women clinics and school-based health outreach are points of entry for reaching women and girls. People-centred referral mechanisms should minimize inconvenience to patients and reduce opportunity costs.
Promote a screen and treat approach	Countries will need to expand the number of facilities where a single-visit screen and treat approach could be implemented. Single-visit screen and treat approaches will not be feasible everywhere; however, they should be promoted and implemented as appropriate.
Ensure an affordable supply of quality-assured, high-performance screening tests and treatment devices	Prompt registration and market shaping for cervical cancer diagnostics and treatment devices will lead to improved access and affordability. WHO will strengthen its prequalification capacity, as appropriate, to remain abreast of emerging technologies. Post-market surveillance for all medical devices, including in vitro diagnostics, will ensure that safety monitoring is in place as programmes scale up.
Strengthen laboratory capacity and quality assurance programmes	Efficient, integrated networks of laboratory services will maximize the impact of limited human and financial resources. Strong quality assurance programmes are crucial to ensuring that services meet the requisite standards. Training and supervision must be an integral component of service delivery.

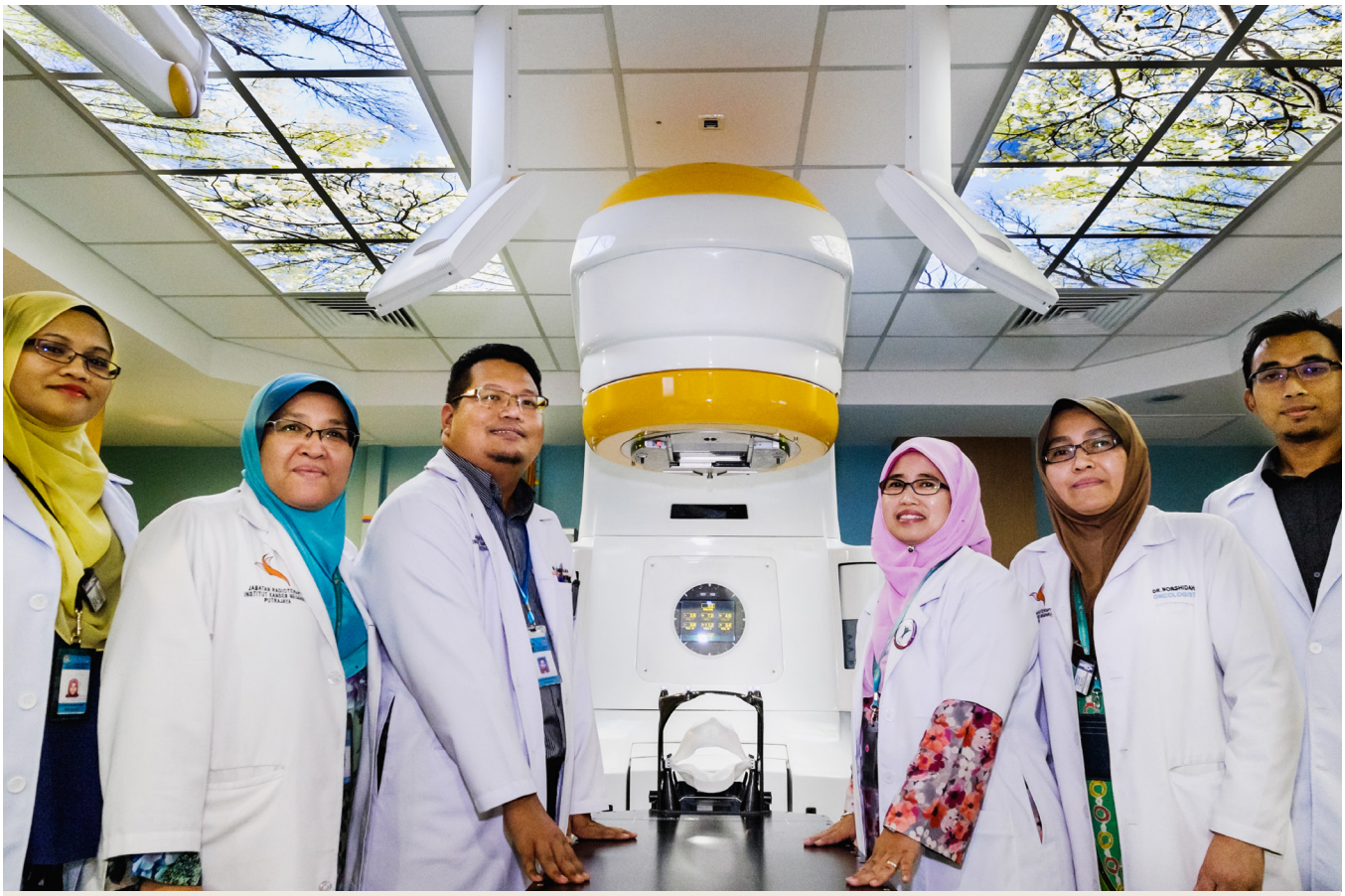
6.5 *Invasive cancer treatment and palliative care*

Timely assessment and referral of women with suspected or confirmed cervical cancer are crucial for saving lives and preventing disability. Comprehensive management of invasive cervical cancer requires well-equipped, appropriately qualified health providers and access to pathology, medical imaging, surgical, radiotherapy and chemotherapy services.

Management of each case is based on adequate staging of the disease (guidelines are available for staging and tumour node metastasis *(34, 35)*). Early stage cervical cancer is highly treatable by surgery and/or radiotherapy, which can result in long-term survival and/or cure *(36)*. The five year survival rate for early stage cancer is more than 80% in countries where timely diagnosis and high-quality treatment are available. Surgery and radiotherapy, with or without chemotherapy, are among the cost-effective interventions that WHO recommends for early stage cervical cancer *(36)*. Even some locally advanced cervical cancers are curable with high-quality concurrent chemoradiation *(37)*.

Palliative care should be integrated into the treatment plan and provided throughout the course of the disease *(38)*. Currently, very few low- and middle-income countries have palliative care programmes in place. Countries are encouraged to expand the availability of palliative care services, which could readily be extended to other forms of advanced cancers and to non-malignant debilitating disease.

Common treatment-related effects experienced by long-term cervical cancer survivors that affect quality of life include bladder dysfunction, bowel dysfunction, sexual dysfunction, lymphoedema and psychosocial problems. Lack of social support, most importantly from spouses, has the greatest adverse impact on quality of life of women cancer survivors in sub-Saharan Africa. In addition to managing pain and other distressing symptoms, care should encompass psychosocial and spiritual support for women and their families *(39, 40)*.



Radiotherapy team, National Cancer Institute — Malaysia

6.6 *Strategic actions to achieve 90% treatment and care for cervical cancer cases*

Implement cervical cancer management guidelines	Developing and implementing national cervical cancer management guidelines, adapted to the national context, is central to ensuring high-quality care *(41)*.
Establish referral pathways and people-centred linkages throughout the continuum of care	Streamlining care pathways and referral networks linking all levels of care will ensure timely management of patients.
Strengthen pathology services	Access to high-quality pathology services is crucial for management of invasive cancer. The development of regional pathology centres, making use of affordable telepathology platforms, is possible for countries with limited or no capacity to interpret samples. Where telepathology networks are already being used for complex cases, they could be used for routine ones *(42)*.
Expand surgical capacity	Cervical cancer can often be cured by surgery alone, if diagnosed and treated in its early stages. However, of the cancer patients who live in the world's poorest countries, less than 5% have access to safe, effective and timely cancer surgery *(43)*. In high-income countries the predominant model of postgraduate surgical oncology education consists of multiyear specialty training within accredited programmes, supported by experienced board-certified oncological surgeons and a sophisticated, highly functional surgical infrastructure characterized by readily available anaesthetic services, intensive care units, ubiquitous blood banking and modern laboratory platforms. In most low- and middle-income countries the health care providers performing oncological procedures are generalists (general surgeons, gynaecologists, general practitioners and medical officers) without formal, certified subspecialty training, who provide cancer care out of necessity. Novel attempts to scale up surgical capacity in these environments using focused, competency-based training and North–South twinning partnerships have met with success and should be expanded *(44, 45)*.
Improve access to radiotherapy and chemotherapy	Most patients with cervical cancers in low- and middle-income countries present at stages that require radiation, so sustainable capacity for curative radiation therapy (external beam and brachytherapy) is critical.
Strengthen and integrate palliative care services	Treatment plans should incorporate not only end-of-life care and pain relief for patients but also psychological support, family support and other services from the outset. Where possible, home-based models of palliative care should be integrated into primary health care.

Optimize health workforce competencies throughout the continuum of care	A strategy for long-term national health workforce education and training, recruitment and retention is the key to ensuring sustainable multidisciplinary team-based care. The WHO Global Strategy on Human Resources for Health: Workforce 2030 provides a blueprint for countries to address workforce challenges *(46)*. In addition, a wide range of regional observatories on human resources in health systems provide valuable resources for planning and policy development. More options include twinning programmes, regional training hubs located in centres of excellence, telementoring *(47)*, e-learning *(48)*, mobile learning, and low-cost virtual reality surgical simulation *(49)*. Remote training may be appropriate for areas such as surgery, radiology, pathology and patient consultation.
Reduce cancer stigmatization	Patient awareness, health literacy and education initiatives, especially through survivor groups, contribute to addressing stigmatization associated with cancer.
Provide comprehensive support designed to enhance quality of life and address physical, psychological, social and spiritual challenges faced by survivors	Such programmes are best developed locally, tailored to the sociocultural context of affected communities and engaging advocates of sexual and reproductive health and rights.

Icó Tóth, a cervical cancer survivor and founder of a support group for women in Hungary.

A primary health care approach is the most effective way to sustainably solve today's challenges to health and health systems.

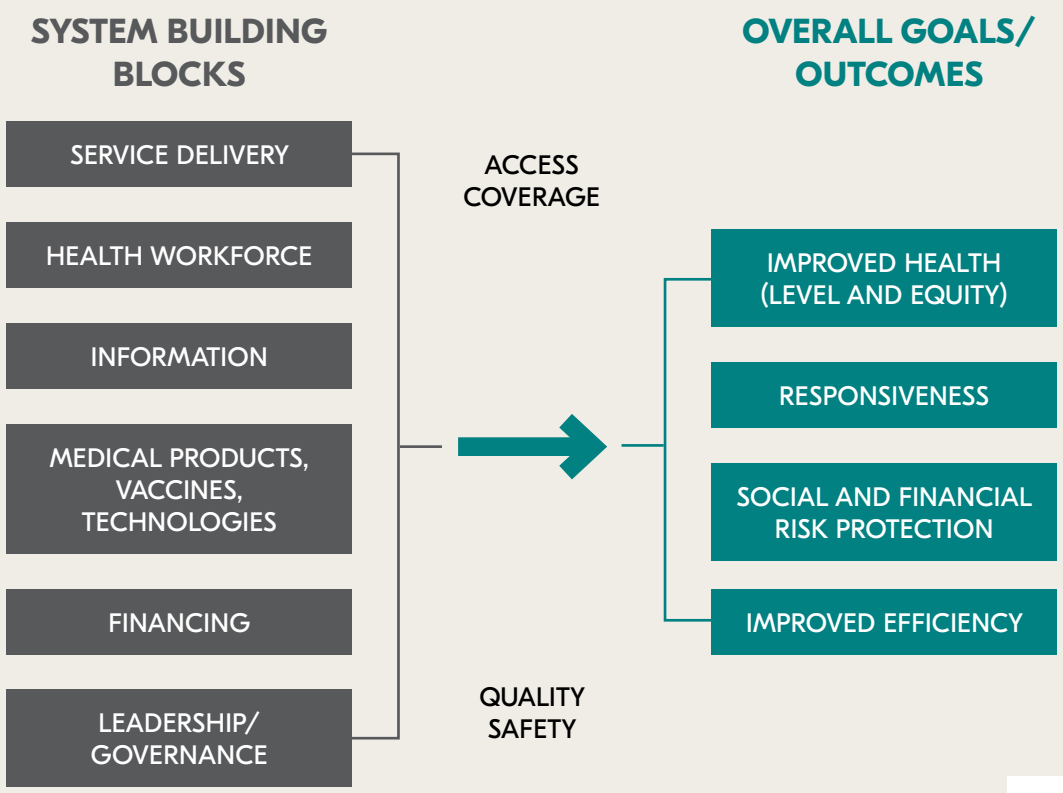
7. Health system enablers:

7.1 *Strengthening health system enablers*

A primary health care approach is the most effective way to sustainably solve today's challenges to health and health systems and is fundamental to achieving the shared global goals of universal health coverage and the health-related Sustainable Development Goals. There is a renewed commitment to primary health care as the pathway for all countries working towards universal health coverage. The Declaration of Astana made at the Global Conference on Primary Health Care (Astana, 25 and 26 October 2018) *(50)* and the Political Declaration of the United Nations High-Level Meeting on Universal Health Coverage (New York, 23 September 2019) *(2)* reaffirmed the world's commitments expressed in the Declaration of Alma-Ata of 1978 and the 2030 Agenda for Sustainable Development.

Fig. 10. WHO's vision of the health system framework

The WHO health system framework



Source: WHO, 2007.

Cervical cancer programmes should be situated within a holistic approach to health systems that is people centred and responsive to the needs of women across the life course (see Fig. 10). Primary care should remain the preferred entry point for cervical cancer prevention interventions, but service structures need to accommodate women presenting at any point in the system. Such efforts should be mutually reinforcing and facilitate the integration of cervical cancer services with other specific programmes. For example, within the health sector, interventions should transcend common dividing lines — between immunization programmes, adolescent health services, HIV and sexual and reproductive health services, and communicable disease and noncommunicable disease programmes, including cancer prevention and control.

7.2 *Priority actions to strengthen health systems*

Reinforce primary health care-oriented models of care	Country programmes should reinforce the drive towards models of care that promote high-quality, people-centred primary health care throughout the life course.
Invest in the primary health care workforce	A sufficiently sized health workforce, with staff who have an optimal mix of skills and who are competent and equitably distributed, can support the delivery of new cervical cancer prevention and treatment interventions, as well as palliative care services.
Improve access to medicines and other health products	Availability and affordability of appropriate, safe, effective, quality medicines and other health products are central to the elimination targets.
Reduce cancer stigmatization	Patient awareness, health literacy and education initiatives, especially through survivor groups, contribute to addressing stigmatization associated with cancer.
Engage with private sector providers	Sound partnerships between public sector and private sector providers for the delivery of integrated health services are required to ensure depth of coverage and affordable access to all.
Universal health coverage and protection from catastrophic costs	Cervical cancer programmes must be fully integrated into universal health coverage. Sustainable financing should be secured through domestic resource mobilization, increased efficiencies in the health system, and ensuring that user fees are not imposed on the poorest, thereby safeguarding their financial protection. Health financing and protection systems, and care delivered closer to where women live and work, are core to achieving elimination.
Innovation and digital technologies for health	Use of digital technologies for health can facilitate access to cervical cancer services, improve effectiveness and efficiency, and promote accountability.
Systems for improving the quality of health care	Systems at the local, subnational and national levels for continuously assessing and improving the quality of integrated health services are important.
Data systems, monitoring and evaluation	Monitoring and evaluation through well-functioning health information systems that generate reliable data on progress towards cervical cancer elimination can support improved decision-making and learning by local, national and global actors.

The role of civil society, women's groups, nongovernmental organizations and a wide range of local networks is fundamental to the successful uptake of services at the community level.

8. Partnerships, advocacy and communication

8.1 *Partnerships*

WHO will use its convening mandate to engage partners across a wide range of sectors to contribute knowledge and expertise to the implementation of the strategy. Strong collaboration has been established with research institutions and implementing partners with extensive experience in scaling up screening and treatment programmes across a diverse range of populations and settings. Partnerships with global institutions, development partners, and multilateral and bilateral entities will play a crucial role, particularly in resource mobilization and strategic policy dialogue. Ongoing work with other organizations in the United Nations system, such as the Joint United Nations Programme on HIV/AIDS, United Nations Children's Fund, United Nations Population Fund, Unitaid, International Atomic Energy Agency, International Agency for Research on Cancer, and United Nations Development Programme, and other bodies such as the Union for International Cancer Control, Gavi, the Vaccine Alliance, and the Global Fund to Fight AIDS, Tuberculosis and Malaria, will be strengthened.

Partnerships with professional associations and academic institutions will also contribute to capacity-building, skills transfer and strengthening existing collaboration, both between developed and developing countries and between developing countries.

The role of civil society, women's groups, nongovernmental organizations and a wide range of local networks is fundamental to the successful uptake of services at the community level. Innovative ways must be found to secure sustainable resources for these partnerships.

8.2 *Multisectoral collaboration*

Multisectoral collaboration is important "for mobilizing and sharing knowledge, expertise, technologies and financial resources to support the achievement of the Sustainable Development Goals in all countries"*(51)*. Collaborations must allow multiple sectors to agree on and pursue a common vision through maximizing comparative advantages. Strong country leadership for and commitment to inclusive multisectoral collaboration *(52)* will enable different arms of government (for example, health, education, finance and labour) to work closely with women, communities, civil society, young people, the media, the private sector, development partners, health professionals' associations, patients' groups and other stakeholders to achieve cervical cancer targets. Inclusive and strategic national, regional and global partnerships that extend beyond the health sector are needed to ensure the promotion of health and protection of human rights of women and girls.

At the regional level, new partnerships between countries can be forged for knowledge exchange and skills building, and existing partnerships should be nurtured and strengthened. Civil society representation and partnership should be ensured in collaborative forums. The Global Action Plan for Healthy Lives and Well-being for All provides a sound platform to support country-led implementation of strategies to achieve Sustainable Development Goal 3 and the targets of other health-related Goals *(53)*.

8.3 *Advocacy and communication*

At the global level, advocacy efforts need to focus on securing sustainable financing for health, affirming the inextricable link between health and development while ensuring that issues pertaining to the health of women and girls remain central in these high-level deliberations.

At the regional level, particularly where the burden of disease is highest, advocacy efforts need to build on declarations and action plans such as the Addis Ababa Action Agenda *(54)* to ensure that the health and livelihood of women and girls are secured.

At the national and local levels, governments need to create an enabling environment for a wide range of nongovernmental organizations, civil society organizations and women's groups with experience in demand-creation strategies to help communities reduce barriers to care.

The fourth industrial revolution, with its proliferation of digital technologies, has dramatically changed the communication landscape, for instance with the proliferation of social media, which has increased the scope and speed of information exchange with consumers. The successful implementation of this strategy to accelerate elimination of cervical cancer demands agile and responsive systems that are able to drive comprehensive, robust and proactive communication to promote the uptake of appropriate interventions, to counter misinformation, and to address vaccine hesitancy and the rising anti-vaccine movement.

Effective advocacy and communication strategies can overcome the many challenges that impede access to and use of cervical cancer prevention and care, if culturally relevant and context-specific content is produced. Such strategies should reflect national policy and be integrated into all levels of the health system.

Media platforms, opinion leaders, influencers, traditional and faith leaders, and patient advocates should be deployed strategically in order to increase access to information. The WHO guidance on community mobilization, education and counselling for cervical cancer prevention and treatment can be used to improve health literacy *(55)*.

The Teal Sisters, Zambia, survivors and advocates for cervical cancer elimination

"Only one in three countries can report high quality [cancer incidence data] at present."

Global Initiative for Cancer Registry Development (GICR)

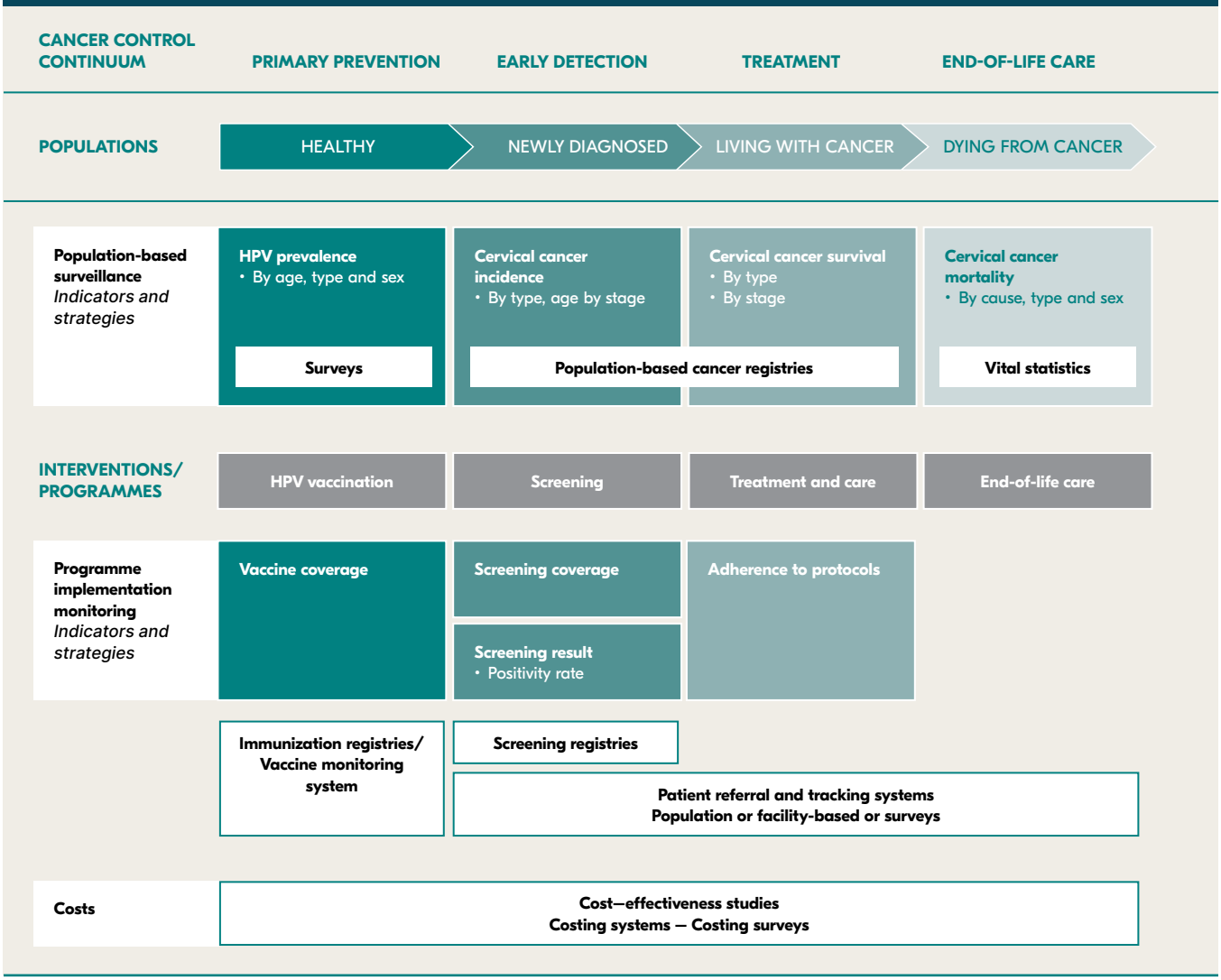
9. Surveillance, monitoring and evaluation

9.1 *Critical strategies for surveillance and monitoring*

The scale-up of cervical cancer prevention activities cannot proceed without the framework and tools to assess and evaluate progress towards cervical cancer elimination. It is fundamental that robust surveillance and monitoring systems are developed at the national or subnational level, both to determine the baseline and to monitor and evaluate the impact of the broad interventions and activities implemented as part of the cervical cancer elimination strategy.

Monitoring and evaluation also enable programme managers to identify gaps and take specific actions to improve coverage, quality and outcomes. Fig. 11 illustrates a framework for data collection and indicator development and the different strategies required to obtain such information, differentiating two major components: population-based surveillance and programme monitoring.

Fig. 11. Surveillance and monitoring for the elimination initiative



9.2 *Population-based surveillance*

At the population level, three complementary measures are essential: (a) cervical cancer incidence (new cases of disease); (b) cervical cancer survival (percentage of patients surviving n years after date of diagnosis); and (c) mortality (number of cervical cancer deaths). These indicators, in addition to HPV prevalence (if the means to measure them are in place), are obtained through surveys, population-based cancer registries and vital statistics systems. Assessing whether cervical cancer is a local public health problem in the current year, or will be in the years ahead, requires an ongoing assessment of the magnitude of the cervical cancer burden using these metrics. The ultimate measure of elimination is the threshold incidence of 4 per 100 000 women- years, based on the incidence data calculated from population-based cancer registries.

9.3 *Population-based cancer registries*

Population-based cancer registries constitute a continuous system of data collection, storage, validation and analysis that enables the dissemination of information on incidence and survival for each of the major types of cancer, and by stage at diagnosis. They are an essential foundation in planning and evaluating cancer prevention activities, informing the planning of cancer services and benchmarking the effectiveness of cancer care delivery in different regions and countries through comparisons of the survival of cancer patients. As with any other public health surveillance strategy, the recording and reporting of data are undertaken in a standardized way to ensure maximum comparability.[9]

9.4 *Vital registration*

Cause-of-death data are a key indicator to evaluate cervical cancer mortality in a population. The evolution of cervical cancer mortality trends is relevant to monitoring the effectiveness of screening programmes. In countries where there is no nationwide death registration, governments should prioritize establishing vital registration, beginning in a well-defined geographical area or population. A well-functioning civil registration and vital statistics system registers all births and deaths, issues birth and death certificates, and compiles and disseminates vital statistics, including information on causes of death. The number of deaths provides a measure of the outcome or impact of cancer.

[9]See International Association of Cancer Registries (http://www.iacr.com.fr).

9.5 *Programme monitoring*

Monitoring implementation of the elimination strategy requires close assessment of the quality and coverage of the different preventive interventions. Vaccination coverage, screening coverage, quality of screening and diagnostic services, and the extent of timely and effective treatment modalities will help to monitor the effectiveness of programmes in achieving a reduction in the disease burden.

As illustrated in Fig. 11, cervical cancer prevention programmes present unique challenges to monitoring and evaluation. Information systems need to span primary through to tertiary prevention measures, requiring the recording and tracking of data on individual women across multiple touchpoints in the continuum of care. Countries are encouraged to use this monitoring and surveillance framework according to the recommended set of processes and outcome indicators. Overall, WHO recommends monitoring the following key indicators *(56)*:

Performance indicators

- HPV vaccination coverage disaggregated by age at vaccination and the number of doses;
- screening rate of the target population (women aged 30—49 years): percentage of women aged 30—49 years who have been screened for the first time in the previous 12-month period;
- positivity rate: percentage of screened women aged 30—49 years with a positive screening test result in the previous 12-month period;
- treatment rate: percentage of screening-test-positive women receiving treatment in the previous 12-month period.

Result indicator

- coverage rate indicator: percentage of women aged 30—49 years who have been screened with a high-performance test at least once between the ages of 30 and 49 years, and the percentage screened at least twice.

Impact indicators

- cervical cancer age-specific incidence
- cervical cancer age-specific mortality

9.6 *Strategic actions for monitoring and evaluation*

The following actions underpin monitoring and evaluation:

- strengthen governance and accountability of programmes related to cervical cancer and conduct regular reviews to help ensure that national strategies, plans and resource allocations reflect actual country needs;
- set country-specific targets, milestones and indicators for monitoring and evaluating the national cervical cancer elimination programme — data on progress towards these objectives should be used to regularly report on the impact of the various interventions being carried out in a country and adjust programme interventions as necessary;
- develop or improve population-based cancer registries so as to inform national cervical cancer elimination programmes and help to track progress towards the goal of elimination;
- track patients throughout the continuum of services to ensure that women and girls in need are being successfully treated;
- work towards disaggregation of data by equity stratifiers to enable detection of differences across population segments and set equity-oriented targets.

9.7 *Accountability for impact*

The WHO Thirteenth General Programme of Work 2019—2023 provides the strategic vision for the work of WHO. This cervical cancer strategy covers six bienniums. The cross-organizational nature of the strategy will help ensure the provision of better-aligned support for implementation. The Impact Framework of the General Programme of Work will strengthen accountability for impact.

The Secretariat will work closely with Member States to bring together different constituencies, sectors, relevant organizations and local implementing partners to ensure alignment and coordinated support. It will continue to work closely with stakeholders, including multilateral and bilateral development agencies, foundations, philanthropies, civil society organizations, the private sector, the research community, academic institutions, health professionals' associations and a wide range of non-State actors in official relations with WHO. Efforts to establish new, strategic and innovative partnerships to support and sustain implementation will be undertaken. Transparent accountability mechanisms will be put in place to bolster momentum and uphold responsibility.

Implementation will focus on strengthening existing programmes and collaborating more closely with partners and organizations in the United Nations system currently providing technical assistance for prevention, screening, and treatment and management of cervical cancer.

9.8 *Implementation*

All six WHO regions have strategies or plans for cervical cancer control that reflect the diverse nature of challenges and offer opportunities to scale up all three pillars of the prevention-to-care continuum. Each region has a range of strategic partnerships, agencies and institutions with context-specific expertise to support implementation of the global strategy. To ensure alignment with the global strategy, the Secretariat will support Member States in implementation as outlined in the mandate from the World Health Assembly when it endorses the strategy.

In front of the main WHO building, a statue commemorates the 30th anniversary of the eradication of smallpox.

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Annex. Costing, financing and investment case

Estimating the economic impacts and implications of an accelerated strategy will help to clarify the benefits and global investments required.

Costing national cervical cancer prevention and elimination plans

To bring low- and middle-income countries onto the pathway towards cervical cancer elimination, financial resources need to be assigned to the early stages of prevention and elimination plans. An initial investment between 2020 and 2030 is necessary to start bending the incidence curves for cervical cancer downward. To mobilize resources to reach the 90-70-90 targets, the Secretariat has already provided support to health ministries in several countries to generate national costing plans for scaling up HPV vaccination, screening cervical cancer, treating precancer and managing invasive cervical cancer *(1)*.

Derivation of the cost projections involved consultation with and validation from multiple stakeholders, including members from academic institutions, civil society, development partners and United Nations partners. The results estimate the total cost of scaling up national plans by activity as well as the costs by service and per capita.

The cost of scaling up the interventions varies by country and depends on specific attributes, such as the existing health system infrastructure, the demographic and epidemiological characteristics and the coverage goals in each country's national cervical cancer plan. Once completed, the cost projections can be used to plan and operationalize a national cervical cancer prevention and elimination programme tailored to a country's needs. WHO will take advantage of these initial detailed costing case studies to develop global guidance for countries' resource mobilization efforts.

Global cost–effectiveness of elimination strategies

WHO's Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020 provides guidance on the cost–effectiveness of interventions to prevent and control those diseases *(2)*. HPV vaccination and cervical cancer screening and treatment have been identified as best buys and thus already form part of WHO's recommended list of interventions for country implementation. To identify the value for money of different intervention scenarios, additional global cost–effectiveness analyses have been conducted for elimination trajectories.

Impact modelling has demonstrated that global elimination is possible within the next century, and the number of cervical cancer cases prevented can be substantial in the 78 low- and lower-middle-income countries studied (see section 2). But since countries face budget constraints, the Secretariat assessed cost–effectiveness and resource use, building on the results of impact modelling.

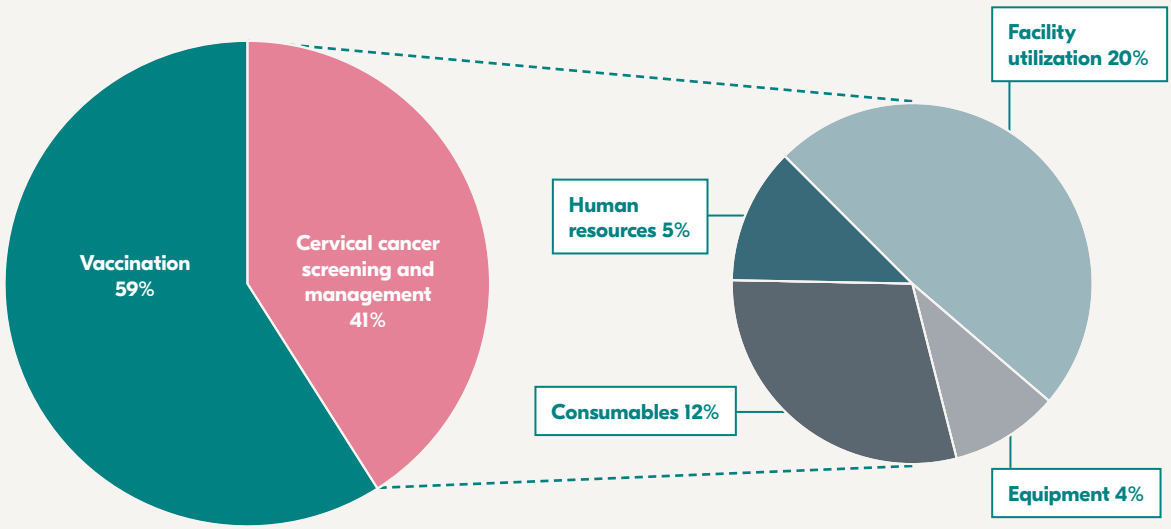
Cost–effectiveness was estimated by comparing the cost, health and economic benefits of various intervention scenarios over time.

Applying information on the costs of the interventions and information on the scale-up of interventions required over the next 100 years (2020–2120), the same impact models were used to analyse cost–effectiveness and determine that the 90-70-90 targets are the optimal strategy for eliminating cervical cancer in the 78 low- and lower-middle-income countries with the highest burdens of cervical cancer. For 74 of those countries (95%), the elimination strategy was found to lead successfully to elimination and to be cost effective over the period 2020–2120 for at least two of three models.

Investment case for cervical cancer elimination

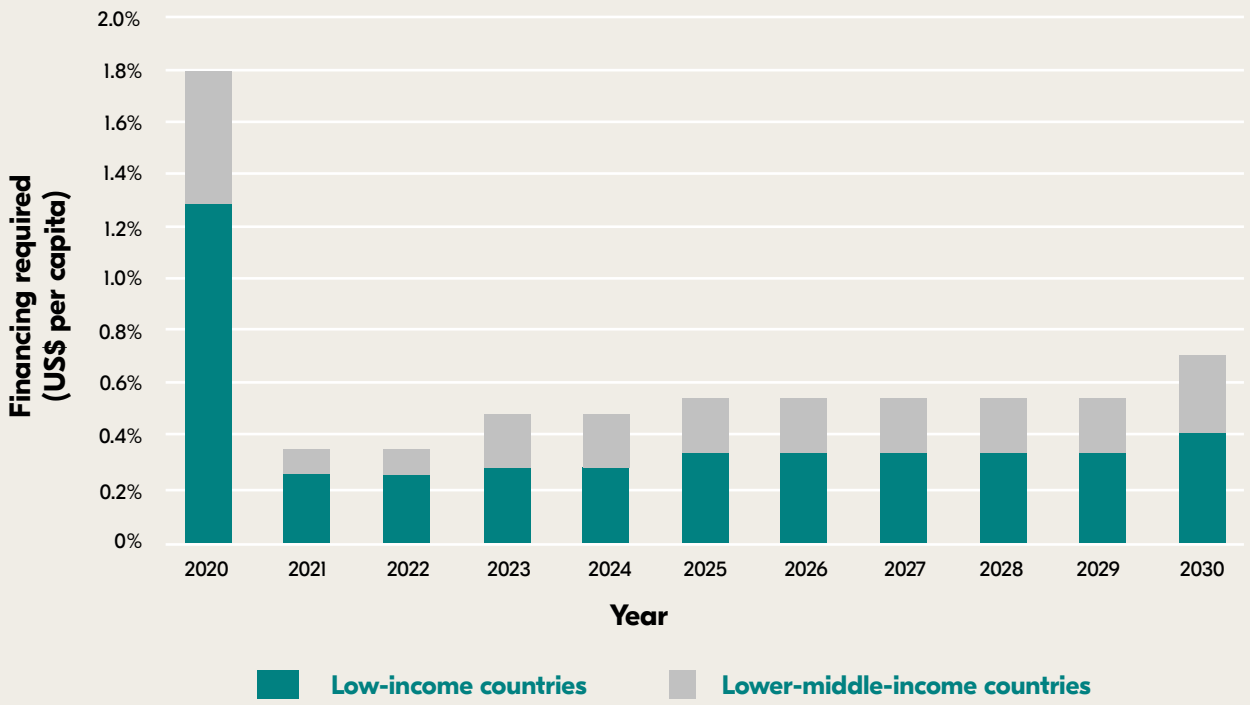
Of the estimated total US$ 10.5 billion financing needs (see section 5.5 above), 59% is for vaccination programmes and 41% for cancer prevention programmes (Fig. A1). By far the greatest need in cancer prevention programmes is related to health system strengthening, dominated by infrastructure needs. Consumables, largely consisting of pharmaceuticals and diagnostics, make up about a quarter of the cancer prevention programme costs. The cost of care, including medication and pathology testing, should be covered by government expenditure — to ensure that the poorest women can access the services they need and to protect all citizens from the possibility of catastrophic expenditure from having to pay out of pocket for expensive treatment.

Fig. A1. Breakdown of costs, 2019–2030 (total = US$ 10.5 billion)



In low-income settings, where locally produced goods have the lowest price but the current vaccination and treatment coverage is also lowest, an average of US$ 0.40 per person per year is needed to finance elimination, while in lower-middle-income countries US$ 0.20 per person per year is needed. Expenditure in the first implementation year dominates these costs, when a catch-up cohort of 10- to 14-year-olds is vaccinated. Costs drop in the second year but increase through 2030, as cancer prevention programme coverage increases and vaccination costs change with cohort size (Fig. A2).

Fig. A2. Total annual per capita needs to finance the elimination of cervical cancer, 2020–2030



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WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition

WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition

Acronyms and abbreviations

AIS	adenocarcinoma in situ
ART	antiretroviral therapy
CIN	cervical intraepithelial neoplasia
CKC	cold knife conization
DOI	declaration of interest
ERG	External Review Group
EtD	evidence-to-decision
GDG	Guideline Development Group
GRC	Guidelines Review Committee
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HPV	human papillomavirus
HRP	UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction
IARC	International Agency for Research on Cancer
IPD-MA	individual patient data meta-analysis
LEEP	loop electrosurgical excision procedure (also known as LLETZ)
LLETZ	large-loop excision of the transformation zone (also known as LEEP)
NAAT	nucleic acid amplification test
PEPFAR	The United States President's Emergency Plan for AIDS Relief
PICO	population (P), intervention (I), comparator (C), outcome (O)
SDG	Sustainable Development Goal
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
VIA	visual inspection with acetic acid
WHO	World Health Organization

Executive summary

Background

Cervical cancer is a leading cause of mortality among women. In 2020, an estimated 604 000 women were diagnosed with cervical cancer worldwide and about 342 000 women died from the disease. Cervical cancer is the most commonly diagnosed cancer in 23 countries and is the leading cause of cancer death in 36 countries. The vast majority of these countries are in sub-Saharan Africa, Melanesia, South America, and South-Eastern Asia.

In May 2018, Dr Tedros Adhanom Ghebreyesus, World Health Organization (WHO) Director-General, issued a call to action for the elimination of cervical cancer. In November 2020, the Director-General launched the Global strategy to accelerate the elimination of cervical cancer, including the following targets for each of the three pillars for 2030: 90% human papillomavirus (HPV) vaccination coverage of eligible girls, 70% screening coverage with a high-performance test and 90% of women with a positive screening test or a cervical lesion managed appropriately. Following the launch of the global strategy, a large panel of experts met to define the key areas of focus to increase access to screening and treatment to reach the 2030 targets. One of the agreed areas of focus was to update the existing WHO recommendations for screening and treatment to prevent cervical cancer, and to simplify the algorithms.

Methods

This updated guideline for screening and treatment to prevent cervical cancer was developed in three steps:

1. Review the current guidelines and identify recommendations to update or to develop de novo.
2. Develop questions based on population **(P)**, intervention **(I)**, comparator **(C)** and outcomes **(O) (PICO questions)** for the recommendations and conduct new systematic reviews or update those conducted for the previous guideline, and model outcomes when primary research was not available.
3. Apply the **Grading of Recommendations Assessment, Development and Evaluation (GRADE)** methodology to assess the certainty of evidence and to develop recommendations using evidence-to-decision (EtD) tables.

The Guideline Development Group (GDG) for this guideline was formed in early 2019, and the GDG, WHO Secretariat, methodologists and technical groups (see *Annex 1*) met several times to establish the PICO questions, methodology and timeline. The WHO Secretariat led and coordinated the whole process to ensure recommendations were developed in line with the *WHO handbook for guideline development, second edition* (2014). The methods for evidence synthesis and mathematical modelling were used as applied in the previous edition of the guideline, *WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention*. Based on clinical expertise, research and knowledge of tests in development, the Guideline Development Group (GDG) initially identified the screening tests and clinical algorithms for screening and treatment that could be evaluated. The GDG prioritized seven algorithms for evaluation, and these informed the systematic reviews. In 2020, the systematic review teams performed the systematic reviews for each of the PICO questions and, in parallel, the systematic reviews that had been prepared for the International Agency for Research on Cancer's *IARC handbooks of cancer prevention: cervical cancer screening, Vol. 18* (2021) were integrated for the development of these recommendations.

When relevant evidence was not available in primary research, a mathematical model was used to estimate the risk of important outcomes (e.g. recurrence of high-grade cervical intraepithelial neoplasia [CIN], cervical cancer) associated with the use of different screening and treatment strategies. In addition, a modelling group was created to evaluate the impact and cost–effectiveness of the different screening and treatment algorithms. Furthermore, we searched the published literature for studies providing information on acceptability, feasibility and costing aspects of these algorithms, and conducted a survey on feasibility and values and preferences of people using these services. GDG meetings took place on a weekly basis between August 2020 and November 2020 to review and assess the evidence and agree on the final new and updated recommendations and good practice statements presented in this guideline.

Screening and treatment approaches

- In the **"screen-and-treat approach"**, the decision to treat is based on a positive primary screening test only.
- In the **"screen, triage and treat approach"**, the decision to treat is based on a positive primary screening test followed by a positive second test (a "triage" test), with or without histologically confirmed diagnosis.

Summary of screening and treatment recommendations to prevent cervical cancer

In this present publication, there is a total of 23 recommendations and 7 good practice statements.

- Among the 23 recommendations, 6 are identical for both the general population of women and for women living with HIV and 12 are different and specific for each population.
- Among the 7 good practice statements, 3 are identical for both the general population of women and for women living with HIV and 2 are different and specific for each population.

In Table 1 below we have grouped the recommendations and good practice statements in two columns for the general population of women (left column, nos. 1–14) and for women living with HIV (right column, nos. 21–34), while in Table 2, the populations are not separated (nos. 41 and 42).[1]

There are currently 11 recommendations and 3 good practice statements for each population in Table 1, and an additional recommendation and good practice statement for both populations in Table 2.

[1] There are gaps in these numbers because WHO intends to issue additional recommendations soon on screening tests and implementation, which will be numbered as needed (expected to be 15–20 for the general population of women and 35–40 for women living with HIV).

Table 1. Screening and treatment recommendations and good practice statements for the general population of women and women living with HIV

Recommendations for the general population of women[a]	***Strength of recommendation and level of evidence***	**Recommendations for women living with HIV**[a]	***Strength of recommendation and level of evidence***
1. WHO recommends using HPV DNA detection as the primary screening test rather than VIA or cytology in screening and treatment approaches among both the general population of women and women living with HIV. *Remarks: Existing programmes with quality-assured cytology as the primary screening test should be continued until HPV DNA testing is operational; existing programmes using VIA as the primary screening test should transition rapidly because of the inherent challenges with quality assurance.*	Strong recommendation, moderate-certainty evidence	21. WHO recommends using HPV DNA detection as the primary screening test rather than VIA or cytology in screening and treatment approaches among both the general population of women and women living with HIV. *Remarks: Existing programmes with quality-assured cytology as the primary screening test should be continued until HPV DNA testing is operational; existing programmes using VIA as the primary screening test should transition rapidly because of the inherent challenges with quality assurance.*	Strong recommendation, moderate certainty of evidence
2. WHO suggests using an HPV DNA primary screening test either **with triage or without triage** to prevent cervical cancer among the general population of women.	Conditional recommendation, moderate-certainty evidence	22. WHO suggests using an HPV DNA primary screening test **with triage** rather than without triage to prevent cervical cancer among women living with HIV.	Conditional recommendation, moderate certainty of evidence

[a] Rows shaded in blue indicate that the recommendation or good practice statement is identical for both the general population of women (left column) and women living with HIV (right column). In other rows, the wording of the recommendations differs for each population.

Recommendations for the general population of women[a]	*Strength of recommendation and level of evidence*	Recommendations for women living with HIV[a]	*Strength of recommendation and level of evidence*
3a. **In a screen-and-treat approach** using HPV DNA detection as the primary screening test, WHO suggests treating women who test positive for HPV DNA among the general population of women. 3b. **In a screen, triage and treat approach** using HPV DNA detection as the primary screening test among the general population of women, WHO suggests using partial genotyping, colposcopy, VIA or cytology to triage women after a positive HPV DNA test (*Annex 4*). *Remarks: The benefits, harms and programmatic costs of the triage options are similar; therefore, the choice of triage method will be dependent on feasibility, training, programme quality assurance and resources in countries. HPV16/18 genotyping could be integrated into the HPV DNA test (refer to Annex 4 for specific details of the algorithms).*	Conditional recommendation, moderate-certainty evidence	23. **In a screen, triage and treat approach** using HPV DNA detection as the primary screening test among women living with HIV, WHO suggests using partial genotyping, colposcopy, VIA or cytology to triage women after a positive HPV DNA test (*Annex 4*). *Remarks: The benefits, harms and programmatic costs of the triage options are similar; therefore, the choice of triage method will be dependent on feasibility, training, programme quality assurance and resources in countries. HPV16/18 genotyping could be integrated into the HPV DNA test (refer to Annex 4 for specific details of the algorithms).*	Conditional recommendation, moderate-certainty evidence
4. When providing HPV DNA testing, WHO suggests using either samples taken by a health-care provider or self-collected samples among both the general population of women and women living with HIV.	Conditional recommendation, low-certainty evidence	24. When providing HPV DNA testing, WHO suggests using either samples taken by a health-care provider or self-collected samples among both the general population of women and women living with HIV.	Conditional recommendation, low-certainty evidence
5. WHO recommends starting regular cervical cancer screening at the **age of 30 years** among the general population of women.	Strong recommendation, moderate-certainty evidence	25. WHO suggests starting regular cervical cancer screening at the **age of 25 years** among women living with HIV. *Remarks: Low-certainty evidence found that there are likely to be small numbers of women living with HIV with cervical cancer who are below the age of 25. This recommendation applies to women living with HIV regardless of when they first tested positive for HIV.*	Conditional recommendation, low-certainty evidence

Recommendations for the general population of women[a]	***Strength of recommendation and level of evidence***	**Recommendations for women living with HIV[a]**	***Strength of recommendation and level of evidence***
6. After the age of 50 years, WHO suggests screening is stopped after two consecutive negative screening results consistent with the recommended regular screening intervals among both the general population of women and women living with HIV. *Remarks: Neither VIA nor ablative treatment are suitable for screening or treatment of women in whom the transformation zone is not visible. Inadequate visualization is typical after the menopause.*	Conditional recommendation, low-certainty evidence	26. After the age of 50 years, WHO suggests screening is stopped after two consecutive negative screening results consistent with the recommended regular screening intervals among both the general population of women and women living with HIV. *Remarks: Neither VIA nor ablative treatment are suitable for screening or treatment of women in whom the transformation zone is not visible. Inadequate visualization is typical after the menopause.*	Conditional recommendation, very low-certainty evidence
7. Priority should be given to screening women **aged 30–49 years** in the general population of women. When tools are available to manage women aged 50–65 years, those in that age bracket who have never been screened should also be prioritized.	Good practice statement	27. Priority should be given to screening women living with HIV **aged 25–49 years**. When tools are available to manage women living with HIV aged 50–65 years, those in that age bracket who have never been screened should also be prioritized.	Good practice statement
8. WHO suggests a regular screening interval of **every 5 to 10 years** when using HPV DNA detection as the primary screening test among the general population of women.	Conditional recommendation, low-certainty evidence	28. WHO suggests a regular screening interval of **every 3 to 5 years** when using HPV DNA detection as the primary screening test among women living with HIV.	Conditional recommendation, low-certainty evidence
9. Where HPV DNA testing is not yet operational, WHO suggests a regular screening interval of every 3 years when using VIA or cytology as the primary screening test, among both the general population of women and women living with HIV.	Conditional recommendation, low-certainty evidence	29. Where HPV DNA testing is not yet operational, WHO suggests a regular screening interval of every 3 years when using VIA or cytology as the primary screening test, among both the general population of women and women living with HIV.	Conditional recommendation, low-certainty evidence

[a] Rows shaded in blue indicate that the recommendation or good practice statement is identical for both the general population of women (left column) and women living with HIV (right column). In other rows, the wording of the recommendations differs for each population.

Recommendations for the general population of women[a]	***Strength of recommendation and level of evidence***	**Recommendations for women living with HIV[a]**	***Strength of recommendation and level of evidence***
10. While transitioning to a programme with a recommended regular screening interval, screening even just twice in a lifetime is beneficial among both the general population of women and women living with HIV.	Good practice statement	30. While transitioning to a programme with a recommended regular screening interval, screening even just twice in a lifetime is beneficial among both the general population of women and women living with HIV.	Good practice statement
11. WHO suggests that the general population of women who have screened positive on an HPV DNA primary screening test and then negative on a triage test are retested with HPV DNA testing **at 24 months** and, if negative, move to the recommended regular screening interval.	Conditional recommendation, low-certainty evidence	31. WHO suggests that women living with HIV who have screened positive on an HPV DNA primary screening test and then negative on a triage test, are retested with HPV DNA testing **at 12 months** and, if negative, move to the recommended regular screening interval.	Conditional recommendation, low-certainty evidence
12. WHO suggests that women from the general population and women living with HIV who have screened positive on a cytology primary screening test and then have normal results on colposcopy are retested with HPV DNA testing at 12 months and, if negative, move to the recommended regular screening interval.	Conditional recommendation, low-certainty evidence	32. WHO suggests that women from the general population and women living with HIV who have screened positive on a cytology primary screening test and then have normal results on colposcopy are retested with HPV DNA testing at 12 months and, if negative, move to the recommended regular screening interval.	Conditional recommendation, low-certainty evidence
13. WHO suggests that women from the general population who have been treated for histologically confirmed CIN2/3 or adenocarcinoma in situ (AIS), or treated as a result of a positive screening test are **retested at 12 months** with HPV DNA testing when available, rather than with cytology or VIA or co-testing, and, if negative, move to the recommended regular screening interval.	Conditional recommendation, low-certainty evidence	33. WHO suggests that women living with HIV who have been treated for histologically confirmed CIN2/3 or adenocarcinoma in situ (AIS), or treated as a result of a positive screening test are **retested at 12 months** with HPV DNA testing when available, rather than with cytology or VIA or co-testing, and, if negative, are **retested again at 12 month**s and, if negative again, move to the recommended regular screening interval.	Conditional recommendation, low-certainty evidence

[a] Rows shaded in blue indicate that the recommendation or good practice statement is identical for both the general population of women (left column) and women living with HIV (right column). In other rows, the wording of the recommendations differs for each population.

Recommendations for the general population of women[a]	*Strength of recommendation and level of evidence*	Recommendations for women living with HIV[a]	*Strength of recommendation and level of evidence*
14. As programmes introduce HPV DNA testing, use this test at the woman's next routine screening date regardless of the test that was used at prior screening. In existing programmes with cytology or VIA as the primary screening test, rescreening with the same test should be continued until HPV DNA testing is operational among both the general population of women and women living with HIV.	Good practice statement	34. As programmes introduce HPV DNA testing, use this test at the woman's next routine screening date regardless of the test that was used at prior screening. In existing programmes with cytology or VIA as the primary screening test, rescreening with the same test should be continued until HPV DNA testing is operational among both the general population of women and women living with HIV.	Good practice statement

Table 2. Recommendation and good practice statement for treatment not covered in previous guidelines

For both the general population and women living with HIV	*Strength of recommendation and certainty of evidence*
41. Once a decision to treat a woman is made – whether from the general population of women or women living with HIV – it is good practice to treat as soon as possible within six months to reduce the risk of loss to follow-up. However, in women who are pregnant, good practice includes deferral until after pregnancy. In circumstances when treatment is not provided within this time frame, it is good practice to re-evaluate the woman before treatment.	Good practice statement
42. WHO suggests large-loop excision of the transformation zone (LLETZ) or cold knife conization (CKC) for women from the general population and women living with HIV who have histologically confirmed adenocarcinoma in situ (AIS). *Remarks: Loop excision may be preferred in women of reproductive age, in settings with greater availability of LLETZ and by providers with greater expertise performing LLETZ. CKC may be preferred when interpretation of the margins of the histological specimen is imperative.*	Conditional recommendation, low-certainty evidence

HPV: human papillomavirus; VIA: visual inspection with acetic acid.

[a] Rows shaded in blue indicate that the recommendation or good practice statement is identical for both the general population of women (left column) and women living with HIV (right column). In other rows, the wording of the recommendations differs for each population.

Therapeutic HPV vaccine modelling
Virtual consultation, 18 October 2021
DRAFT Concept Note

Background

The World Health Organization (WHO) has developed a global strategy to eliminate cervical cancer (CxCa) as a public health problem, which could result in more than 62 million lives saved over the course of the next century.[1,2] The strategy includes 2030 coverage targets for scale-up of three efficacious and cost-effective interventions: 90% of adolescent girls receiving prophylactic human papillomavirus (HPV) vaccine, 70% of women receiving twice-lifetime cervical cancer screening (eg. with HPV tests), and 90% of pre-invasive cervical lesions and invasive CxCa treated.

CxCa screening and treatment is crucial to address the gap for women in age cohorts too old to receive prophylactic HPV vaccines. However, the complexity of HPV screening and treatment approaches, which may require several visits for women testing positive for high-risk (hr) HPV, may hamper scale-up, particularly in low- and middle-income countries (LMICs). New simpler approaches are needed for hrHPV-positive women to prevent progression to cervical intraepithelial neoplasia (CIN) and CxCa. Therapeutic HPV vaccines, which could clear persistent hrHPV infection and/or regress CIN2/3 lesions to prevent progression to CxCa, would be highly desirable.

The potential value of therapeutic HPV vaccines will depend on how quickly they can be developed relative to ongoing scale-up of CxCa screening and treatment and aging of cohorts vaccinated with prophylactic HPV vaccines in adolescence. It will also be critical to think about how these vaccines would be used and delivered within broader CxCa prevention programs, and what that means for the vaccine attributes that would optimize their public health impact. The characteristics the vaccines are likely to have may also affect the relative benefits and numbers needed to vaccinate when targeting all women of a certain age versus just those found to be hrHPV-positive in screening.

As part of its mission to promote vaccine development for global public health, WHO is embarking on efforts to understand the potential public health value of therapeutic HPV vaccines, particularly for LMICs, while vaccine candidates are still in early stages of development.[3] This approach parallels efforts to identify, early on, the use case(s) and vaccine attributes that would help optimize the global public health value. WHO develops vaccine preferred product characteristics (PPCs) to describe these preferences, from a LMIC perspective, for characteristics like vaccine indications, target groups, immunization strategies, and important safety and efficacy considerations.[4] PPCs are intended to provide guidance to all those involved in vaccine development, to promote development of vaccines that are most relevant to the global unmet public health need.

Mathematical modelling will play a crucial role in assessing the potential health, societal, and economic value of therapeutic HPV vaccines and in defining PPCs. Modelling work done as part of the Cervical Cancer Elimination Initiative focused on LMICs[2,5] can be built upon to evaluate the potential impact of an HPV therapeutic vaccine within the context of other CxCa interventions, and to understand how the vaccine's characteristics will impact its value.

To facilitate these modelling efforts, WHO is partnering with the Bill and Melinda Gates Foundation to convene a virtual consultation on therapeutic HPV vaccine modelling. The modelling consultation will follow an earlier meeting of HPV and CxCa experts (12-13 Oct 2021), which will outline the public health need for therapeutic HPV vaccines, their possible use cases (how and to whom they would be delivered), and key modelling needs for understanding the value and PPCs of therapeutic HPV vaccines, including important modelling scenarios.

The modelling consultation will bring together experts in mathematical modelling, along with HPV and CxCa epidemiology and program experts, to have a more focused discussion on modelling needs to estimate the potential value and PPCs for therapeutic HPV vaccines.

Objectives of the modelling meeting:

- To review important modelling needs for assessing the potential health, economic, and societal value of therapeutic HPV vaccines and for developing PPCs for these products
- To agree on the crucial set of modelling scenarios that will address the identified needs, and discuss the relevant parameters, assumptions, and data needs
- To determine the overall approach, plan, and timeline for conducting the modelling, considering existing models and roles of potential collaborators

Outcomes of the modelling meeting:

1. Coordinated analysis plan for modelling the impact and optimal characteristics of therapeutic HPV vaccines incorporating key public health considerations, with timelines
2. Table of essential scenarios to be modelled, with relevant parameters and assumptions, for both base case and sensitivity analyses
3. List of essential data needs for carrying out the modelling and plan for obtaining data

References

1. Global strategy to accelerate the elimination of cervical cancer as a public health problem. Geneva: World Health Organization; 2020. https://www.who.int/publications/i/item/9789240014107
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5. Brisson M, Kim JJ, Canfell K, et al. Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet. 2020;395(10224):575-590.

World Health Organization

Session 5

Evaluation of morbidity associated with enteric pathogens

Evaluation of long-term morbidity associated with enteric pathogens.

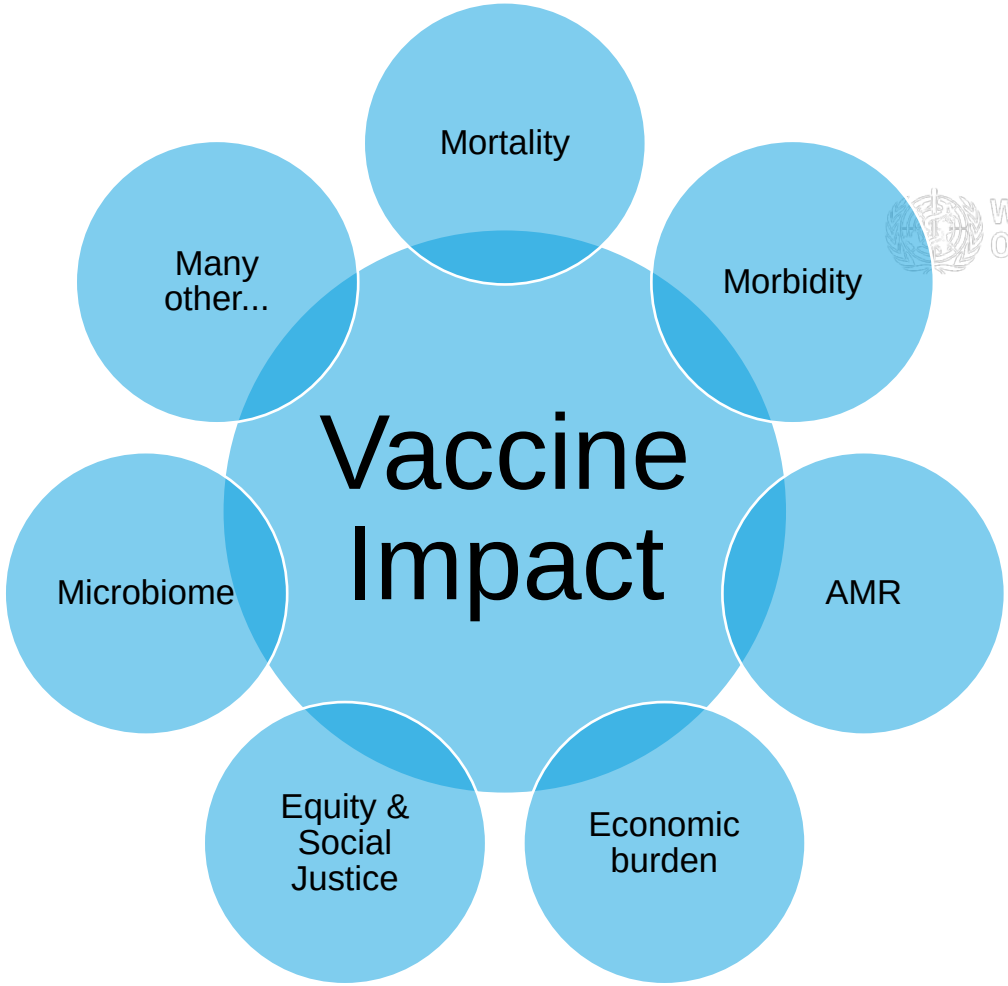
Mateusz Hasso-Agopsowicz, Birgitte Giersing, BoED MWG

The rationale for assessing the full value of vaccines

To prioritise vaccine development, introduction and use, we need to articulate the impact of vaccines in its full capacity.

The impact and value of vaccines can be measured across numerous criteria, beyond mortality.

The appropriate value assessment is needed to **support decision-making across the continuum of vaccine development and uptake**, with a line-of-sight to **sustainable socio-economic and public health impact**.



Assessment of mortality estimates: rationale

* Shift in U5 mortality assessment and divergence between MCEE and IHME in 2016

Study	CHERG/MCEE 2011	MCEE 2017 (Interim Unpublished)	IHME 2010	IHME 2013	IHME 2015	IHME 2016
ETEC deaths (uncertainty range)	42,000 (20,000 – 76,000)	44,078 (32,848 - 58,054)	38,700	23,100 (17,000 – 30,400)	23,600 (9,600 – 44,300)	18,669 (9,800-30,659)
Shigella deaths (uncertainty range)	28,000 (12,000 – 53,000)	25,008 (17,148 - 35,878)	42,600	33,400 (24,900 – 43,500)	54,900 (27,000 – 94,700)	63,713 (41,191-93,611)

PDVAC Recommendation 2018:

"To further investigate understanding and credibility of Burden of Disease estimates, through the formation of a joint IVIRAC/PDVAC independent working group to evaluate diarrheal burden models, and particularly to assess the level of uncertainty regarding ETEC mortality estimates."

Assessment of mortality estimates: outputs

Meeting Report: WHO Workshop on modelling global mortality and aetiology estimates of enteric pathogens in children under five. Cape Town, 28–29th November 2018

H.J. Prudden [a], M. Hasso-Agopsowicz [a], R.E. Black [b], C. Troeger [c], R.C. Reiner [c], R.F. Breiman [d], M. Jit [e, f, g], G. Kang [h], L. Lamberti [i], C.F. Lanata [j, k], B.A. Lopman [d], W. Ndifon [l], V.E. Pitzer [m], J.A. Platts-Mills [n], M.S. Riddle [o], P.G. Smith [c], R. Hutubessy [a], B. Giersing [a]

Association of enteropathogen detection with diarrhoea by age and high versus low child mortality settings: a systematic review and meta-analysis

Julia M Baker, PhD • Mateusz Hasso-Agopsowicz, PhD • Virginia E Pitzer, ScD • James A Platts-Mills, MD • Andre Peralta-Santos, MD • Catherine Troja, MPH • et al. Show all authors

WHO Report

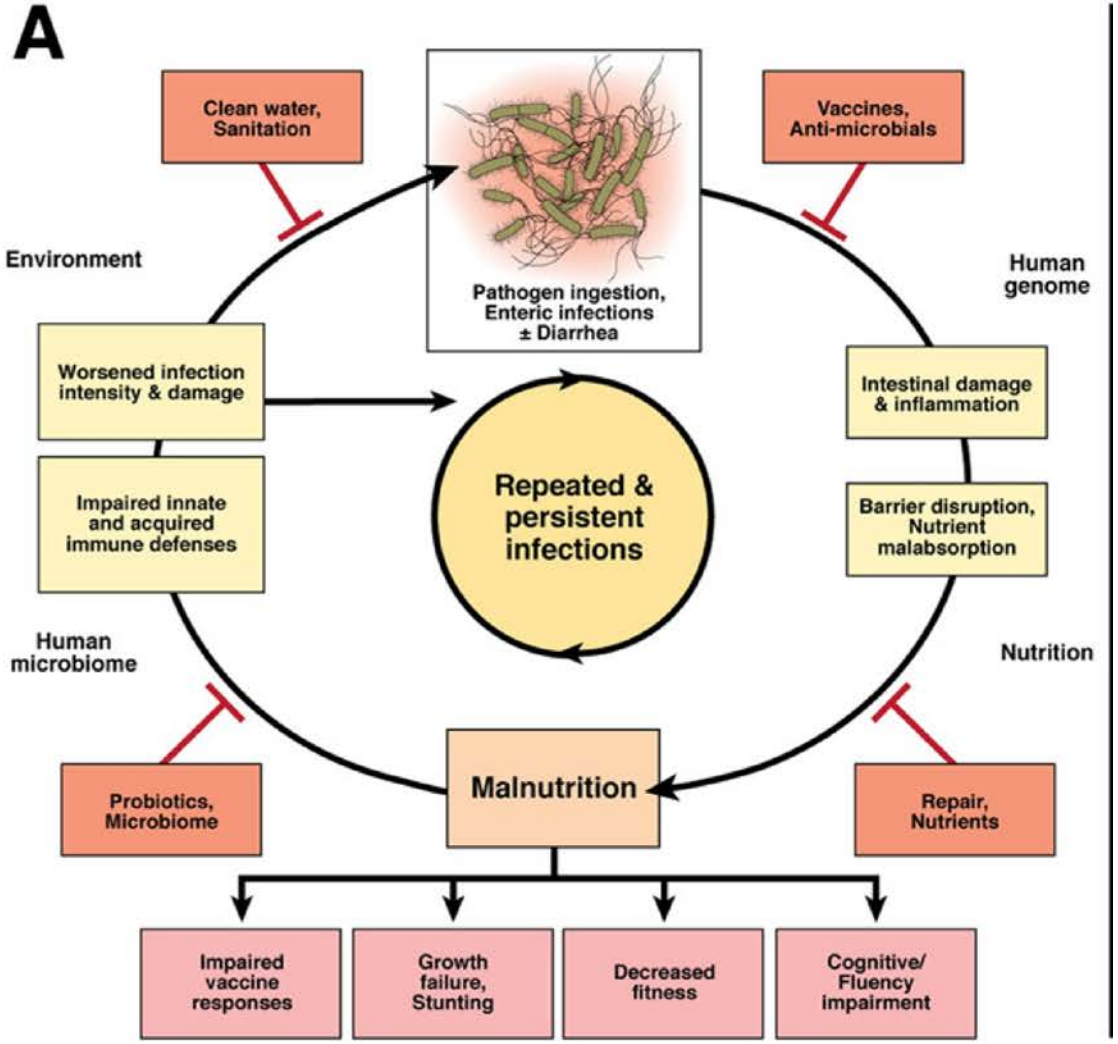
Global diarrhoea-associated mortality estimates and models in children: Recommendations for dataset and study selection

Egle Butkeviciute [a], Holly J. Prudden [b], Mark Jit [c], Peter G. Smith [c], Gagandeep Kang [d], Mark S. Riddle [e], Benjamin A. Lopman [f], Virginia E. Pitzer [g], Claudio F. Lanata [h], James A. Platts-Mills [i], Robert F. Breiman [j], Birgitte K. Giersing [b], Mateusz Hasso-Agopsowicz [b]

Incoming publications:

- A publication (submitted) that summarizes case fatality rates of enteric pathogens stratified by age, mortality strata, setting, and time;
- A publication (in prep) that summarizes the impact of diagnostic adjustments and proposed new methodologies to adjust for different diagnostic methods;
- Revised set of estimates from MCEE and IHME

The “vicious cycle” of enteric disease, enteropathy, and its effects



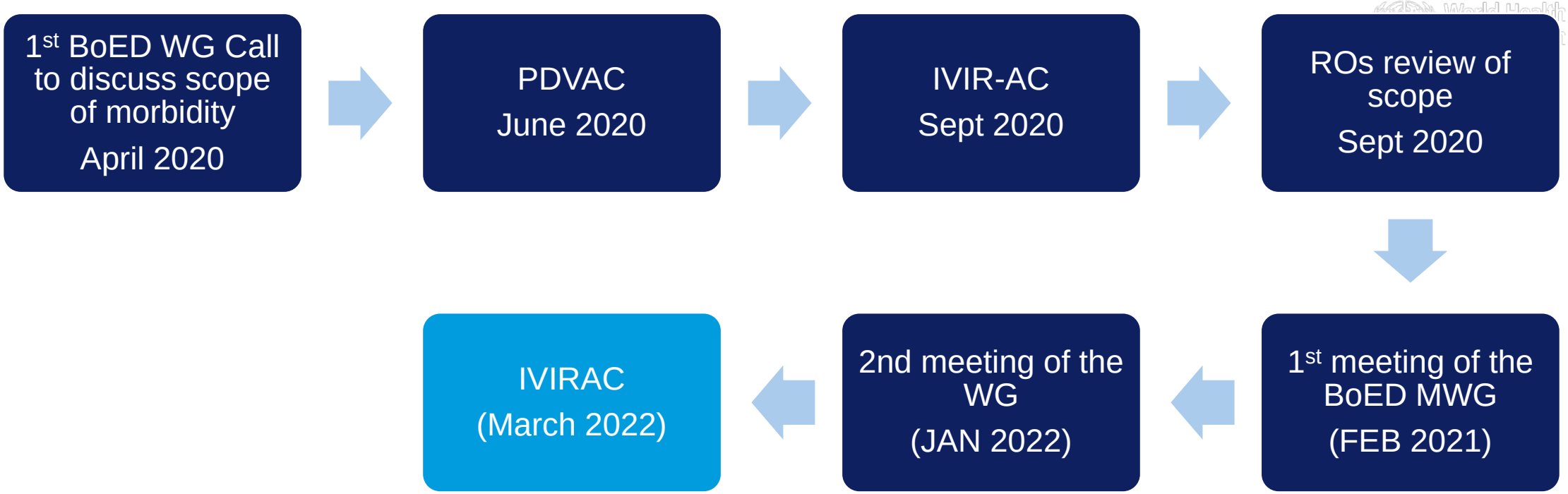
Beyond mortality, repeated enteric infections cause long-term morbidity and can initiate a vicious cycle of enteric disease, entropathy and its effects.

To prioritise vaccine development, introduction and use we need to evaluate vaccines’s full value, including impact on long-term morbidity.

WHO convened Burden of Enteric Diseases Morbidity Working Group (BoED MWG) with a remit to:

- What is the long term morbidity associated with enteric pathogens?
- How can vaccines prevent it?

BoED morbidity: process



IVIR-AC recommendations September 2020

- IVIR-AC fully endorses the focus on long-term morbidity outcomes as the assessment of the full value of vaccine must include its impact on mortality and morbidity and possibly even broader population implications.
- IVIR-AC agrees with prioritizing a systematic review of evidence on impact of enteric pathogens and diarrhea on long-term morbidity together with an assessment of the quality and external validity of that evidence; followed by meta-analysis.
- The assessment of long-term morbidity is challenging given the difficulties of establishing causality.
- Additionally, perhaps in collaboration with the two longitudinal studies (GEMS and MAL-ED), there may be space and need for the use of causal inference models. These can help assess the causal pathways between multiple variables (i.e. exposures of interest and confounders).

Proposed workstreams

Workstream 1: identification and analysis of individual level data from historical datasets to estimate the impact of enteric infections and confounders on long-term morbidity, including growth faltering and cognitive impairment in children.

Workstream 2: a systematic review of evidence on the association of aetiology specific diarrhoea with short- and long- term impact on growth, including stunting, and possibly cognitive impairment in children, while accounting for potential confounders.

Workstream 3: a systematic review of evidence on the association of aetiology specific diarrhoea with short- and long- term impact on health outcomes in adults.

World Health Organization Expert Working Group: Recommendations for assessing morbidity associated with enteric pathogens

Mateusz Hasso-Agopsowicz [a], Benjamin A. Lopman [b], Claudio F. Lanata [c], Elizabeth T. Rogawski McQuade [b], Gagandeep Kang [d], Holly J. Prudden [e], Ibrahim Khalil [f], James A. Platts-Mills [g], Karen Kotloff [h], Mark Jit [i], Mark S. Riddle [j], Patricia B. Pavlinac [f], Paula M. Luz [k], Virginia E. Pitzer [l], Robert F. Breiman [b], Birgitte K. Giersing [a]

Prioritisation of pathogens

We prioritised pathogens for the assessment of morbidity based on the following criteria:

1. Active vaccine candidates in the clinical pipeline
2. Feasibility of developing a vaccine
3. Evidence of association between symptomatic infections and morbidity
4. Evidence of association between non-diarrhoeal infections and morbidity

Prioritised pathogens:

WS1: and WS2*: Campylobacter*, ETEC (LT or ST), norovirus (G1 or G2), and *Shigella (dysenteriae, flexneri, sonnei).*
WS3: *Campylobacter, Shigella*

World Health Organization Expert Working Group: Recommendations for assessing morbidity associated with enteric pathogens

Mateusz Hasso-Agopsowicz [a], Benjamin A. Lopman [b], Claudio F. Lanata [c], Elizabeth T. Rogawski McQuade [b], Gagandeep Kang [d], Holly J. Prudden [e], Ibrahim Khalil [f], James A. Platts-Mills [g], Karen Kotloff [h], Mark Jit [i], Mark S. Riddle [j], Patricia B. Pavlinac [f], Paula M. Luz [k], Virginia E. Pitzer [l], Robert F. Breiman [b], Birgitte K. Giersing [a]

Agenda

Session 6: Evaluation of morbidity associated with enteric pathogens; for review and decision				
13:20 - 13:35 15’	Background	• Evaluation of long-term morbidity associated with enteric pathogens	For decision	M. Hasso-Agopsowicz
13:35 - 14:10 35’	Technical presentation	• Estimating the impact of enteric infections on long-term growth faltering • Mapping the long-term sequelae of *Campylobacter*, Norovirus & ETEC Infections in Children Background reading materials: See SharePoint		E. McQuade Rogawski M. Lalika (recorded)

14:10 - 14:40 40’	Q&A and Discussion	• IVIR-AC discusses presentation, clarifies on content and acknowledges main issues
		• Questions to IVIR-AC:
		  • Does IVIR-AC agree with the proposed analyses to measure the impact of enteric infections on long term morbidity?
		  • What are IVIR-AC’s recommendations on defining post-diarrhoeal shedding and incorporating co-infections into the analyses of the MAL-ED dataset?
		  • Does IVIR-AC agree with the proposed approach to systematic reviews to measure the morbidity burden of enteric infections?
				S Flasche, J Leask, JD Lelievre

Thank you

World Health Organization

WHO

20, Avenue Appia
1211 Geneva

Switzerland

Estimating the impact of enteric infections on long-term growth faltering

Elizabeth Rogawski McQuade

9 March 2022

IVIR-AC Meeting

Proposed workstreams

Workstream 1: identification and analysis of individual level data from historical datasets to estimate the impact of enteric infections and confounders on long-term morbidity, including growth faltering and cognitive impairment in children.

Workstream 2: a systematic review of evidence on the association of aetiology specific diarrhoea with short- and long- term impact on growth, including stunting, and possibly cognitive impairment in children, while accounting for potential confounders.

Workstream 3: a systematic review of evidence on the association of aetiology specific diarrhoea with short- and long- term impact on health outcomes in adults.

World Health Organization Expert Working Group: Recommendations for assessing morbidity associated with enteric pathogens

Mateusz Hasso-Agopsowicz [a], Benjamin A. Lopman [b], Claudio F. Lanata [c], Elizabeth T. Rogawski McQuade [b], Gagandeep Kang [d], Holly J. Prudden [e], Ibrahim Khalil [f], James A. Platts-Mills [g], Karen Kotloff [h], Mark Jit [i], Mark S. Riddle [j], Patricia B. Pavlinac [f], Paula M. Luz [k], Virginia E. Pitzer [l], Robert F. Breiman [b], Birgitte K. Giersing [a]

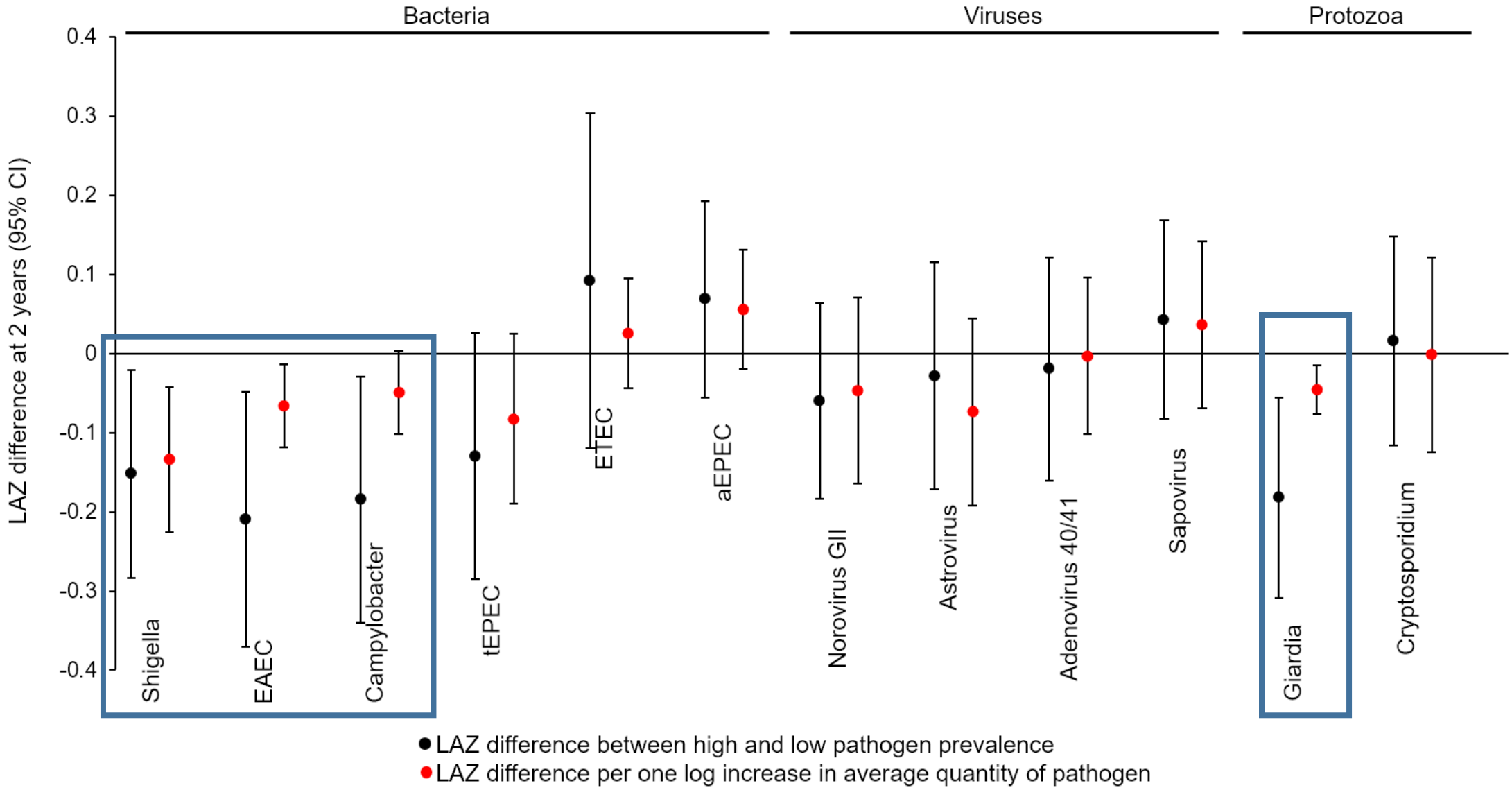
MAL-ED: enteric disease and malnutrition

Do enteric infections contribute to undernutrition by causing environmental enteric dysfunction, and does this lead to growth faltering and deficits in cognitive development?

Observational birth cohort (n=2134)

- Twice-weekly visits from birth to 2 years
- Monthly anthropometry
- Monthly non-diarrheal and diarrhea stool samples tested for 29 enteropathogens using molecular diagnostics (qPCR)

Prior results: Subclinical infections and length



Adjusted for site, enrollment LAZ, sex, SES, exclusive breastfeeding in the first 6 months, and maternal height.

Rogawski *Lancet Global Health* 2018

Rationale for using MAL-ED for WS1

- MAL-ED provides a uniquely rich dataset to understand the impact of specific enteric pathogens on long-term growth outcomes
- Prior work provided evidence of
  - Which pathogens associated with linear growth deficits
  - Importance of subclinical infections (not just etiology-specific diarrhea)

Rationale for using MAL-ED for WS1

- Limitations:
  - Analyses not tailored to specific pathogens of interest
  - Diarrhea was considered separately from subclinical infections
  - Pathogen exposures were highly summarized as the proportion of stools positive
- Questions remain:
  - Directly tease out the importance of subclinical infections versus diarrhea
  - Age-specificity of effects; relevant to age of vaccine administration
  - Relevance of higher burden/severity, persistent infections
    - May define the vaccine preventable subset

Rationale for using MAL-ED for WS1

- MAL-ED remains a unique dataset with opportunities to answer these questions
  - Longitudinal characterization of infection burden (not possible in case-control studies)
  - Detection of subclinical pathogens (not possible in other longitudinal cohorts)
  - Potential confounders well characterized

Objectives

Quantify the morbidity burden attributable to enteric pathogens that could be averted by vaccines

Focus on linear growth

Focus on *Shigella*, *Campylobacter (jejuni/coli* and pan), ETEC, and norovirus

1. Disentangle the relative contributions of subclinical infections versus etiology-specific diarrhea to effects on attained length at 2 and 5 years of age
2. Estimate the age-specific effects of enteric infections and diarrhea
3. Determine whether the effects of enteric infections and diarrhea differ by intensity of infection (defined by quantity, duration/persistence, and severity) and antibiotic treatment

Approach: Disentangle effects of subclinical infections versus etiology-specific diarrhea

1. Identify subclinical detections that represent post-diarrheal shedding
2. Describe the burden of subclinical infections versus diarrhea (including post-diarrheal shedding)
   - Characterize children with subclinical infections and whether these children have been previously exposed and/or had diarrhea
3. Estimate associations between etiology-specific diarrhea (including post-diarrheal shedding) and subclinical infections with LAZ in the same model
   - Assess interaction between diarrhea + subclinical infections
   - Consider days of illness in addition to number of episodes
4. Estimate the impact of vaccines with effectiveness against (i) diarrhea and no impact on subclinical carriage, and (ii) both diarrhea and subclinical carriage

Approach: Estimate the age-specific effects of enteric infections and diarrhea

- Categorize exposures by 0-2 months, 3-5 months, 6-8 months, 9-11 months, 12-14 months, and 15-23 months
- Estimate the independent effects of infections and etiology-specific diarrhea in each age window on length at 2 years of age
- Assess whether there are additional effects of sustained exposure in multiple age windows (interactions between windows)

Approach: Determine whether the effects of enteric infections and diarrhea differ by intensity of infection and antibiotic treatment

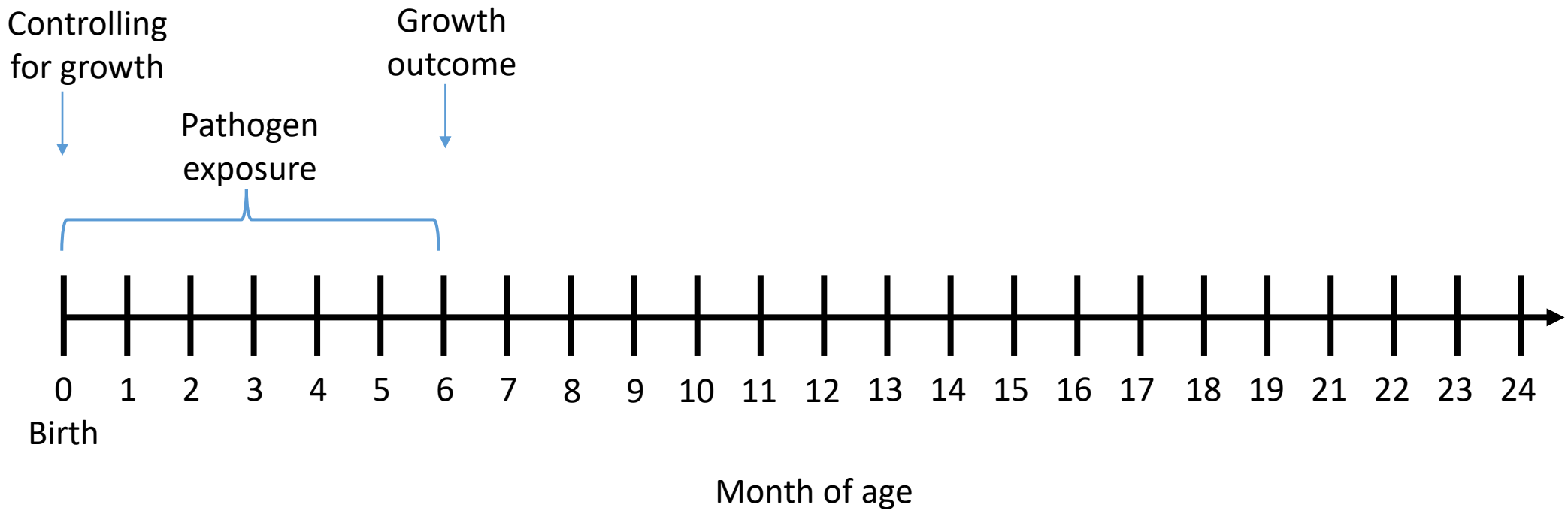
- Identify “high intensity” infections
  - High quantity (low Ct)
  - Culture positive vs. PCR+/culture negative detections
  - Long duration
  - Clinically severe diarrhea episodes (MSD)
  - Persistent carriage following diarrhea
  - Antibiotic treated
- Estimate effects of these subsets

Methods

- Height attainment model
  - Outcome: length at 2 years or height at 5 years
  - Exposures: summarized pathogen burden from 0-2 years
  - Adjusted for baseline and summarized time-varying confounders
    - Simple, relatively precise effects
- Longitudinal model
  - Incorporates growth measurements from 0-2 years; age-specific pathogen exposures
  - Accounts for time-varying confounding, feedback loops
    - Imprecise effects, sensitive to model specification

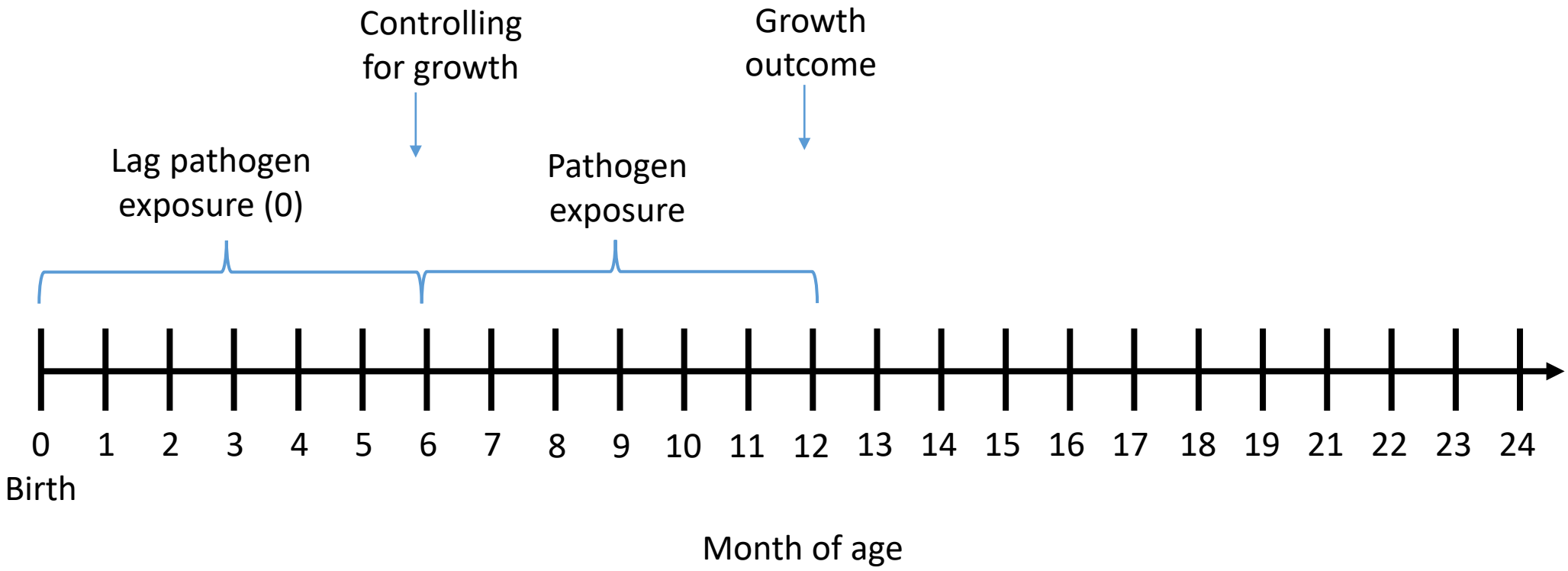
Longitudinal model

- Incorporates lag periods for exposure
- Better control of temporality/reverse causality



Longitudinal model

- Incorporates lag periods for exposure
- Better control of temporality/reverse causality



Longitudinal model

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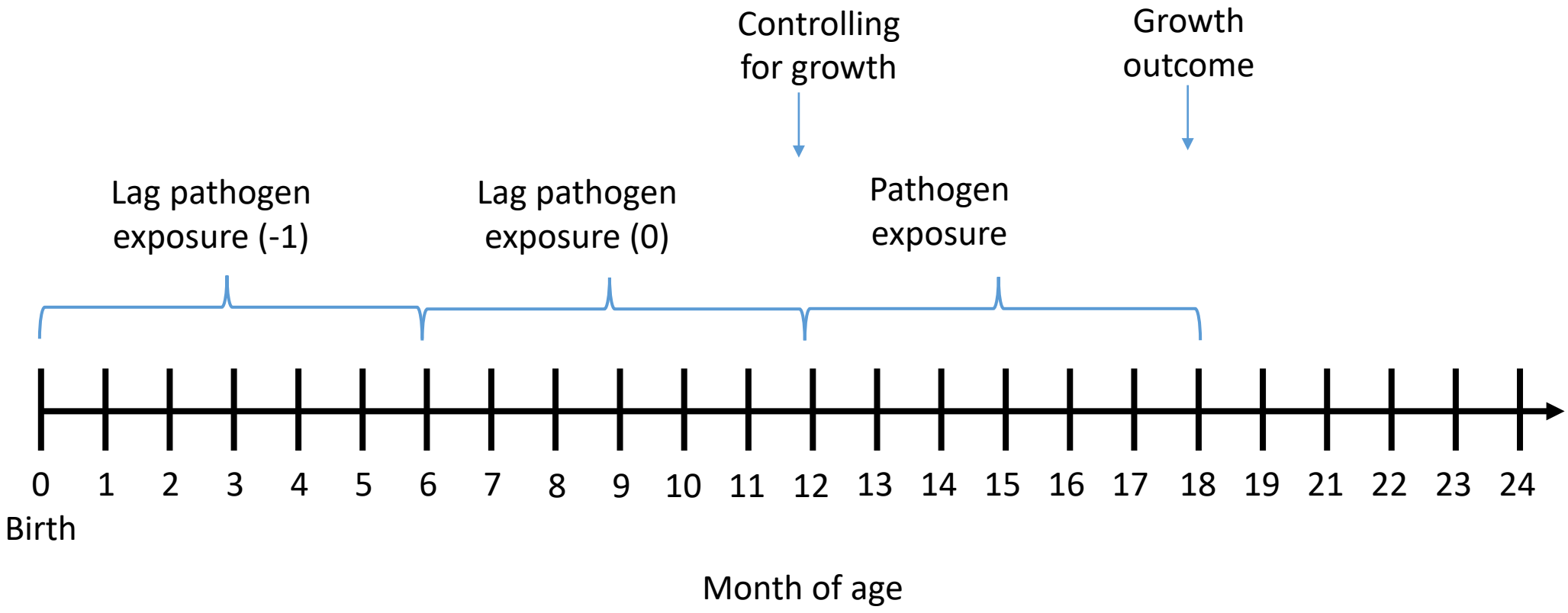

Longitudinal model

- Incorporates lag periods for exposure
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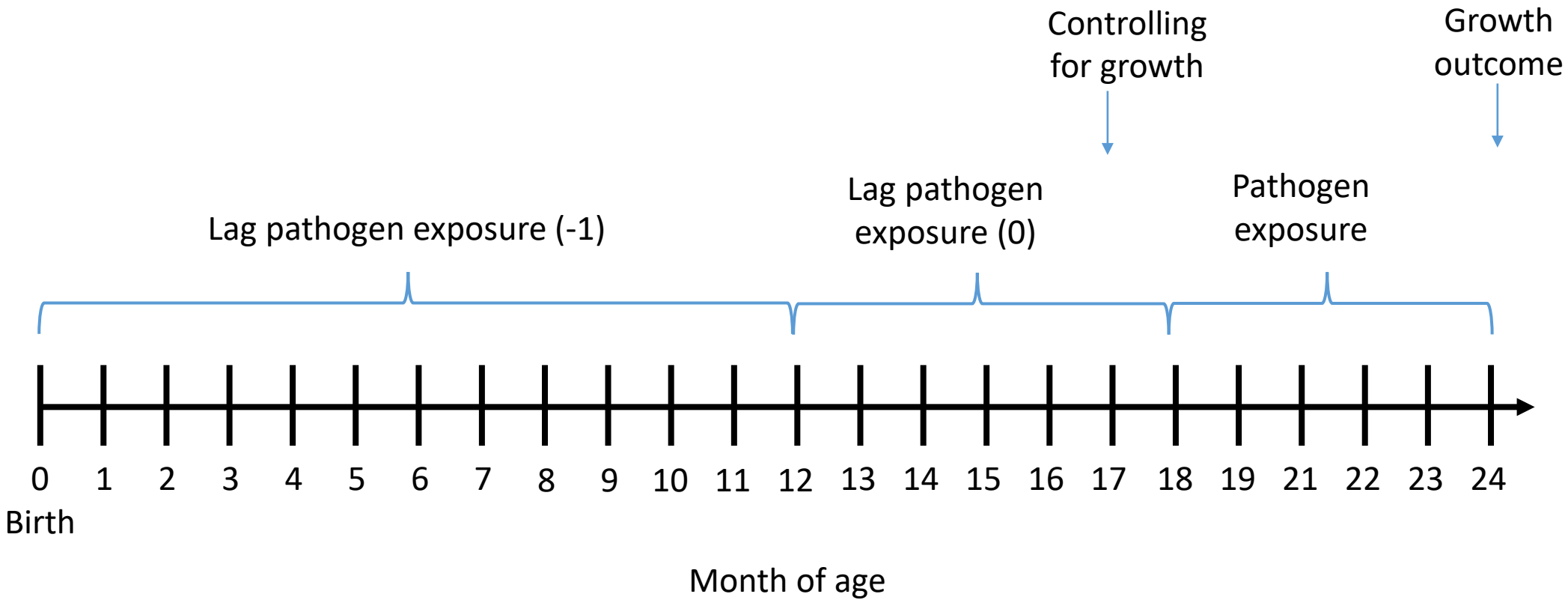


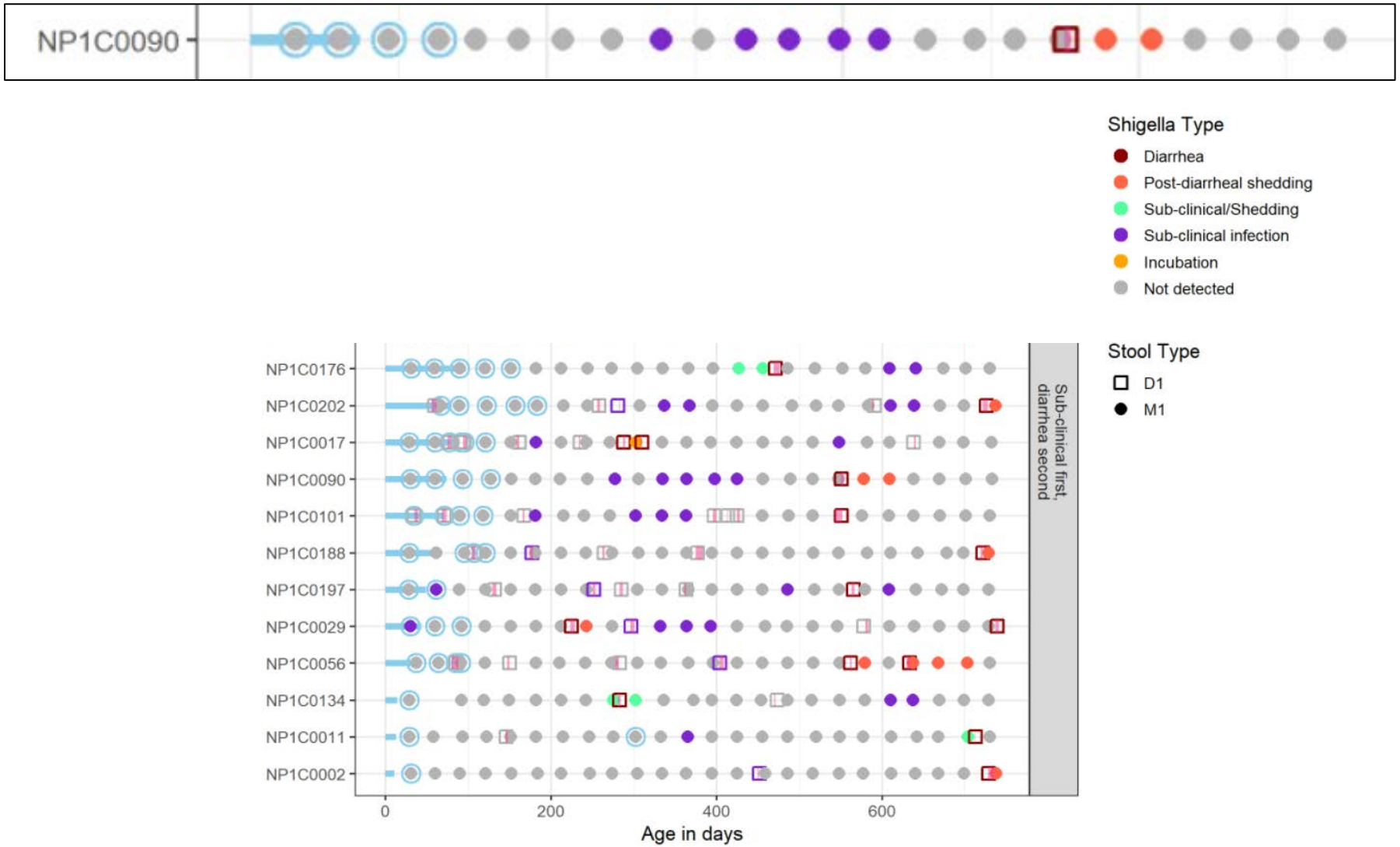
Confounders of interest

- Site
- Other pathogens
- Baseline anthropometry
- SES
- Sex
- Maternal height
- Breastfeeding
- Antibiotic use
- All-cause diarrhea

New:

- Other illnesses (respiratory, fever)
- Feeding?

Preliminary data



Expected outcomes

Inform several key questions related to the potential impact of enteric vaccines

- Vaccines that prevent symptomatic disease but not asymptomatic carriage are likely to impact linear growth outcomes?
- How vaccine impact may differ based on the age administered?
- Whether long-term impacts are disproportionately burdened on a subset of children with persistent or high intensity infections?

Questions for IVIR-AC

1. Does IVIR-AC agree with the proposed analyses to measure the impact of enteric infections on long term morbidity?
2. What are IVIR-AC's recommendations on defining post-diarrhoeal shedding and incorporating co-infections into the analyses of the MAL-ED dataset?

Thank you

Elizabeth Rogawski McQuade

erogaws@emory.edu

Mapping the long-term sequelae of *Campylobacter*, Norovirus & ETEC Infections in Children

Mathias Lalika, Priyanka Shrestha, Gregory Zane, Paul K Drain

March 9, 2022

START CENTER
STRATEGIC ANALYSIS, RESEARCH & TRAINING CENTER
Department of Global Health | University of Washington

PROJECT TEAM

Mathias Lalika, MD

MPH Student in Global Health

Research Assistant | Project Manager

Priyanka Shrestha

PhD Student in Implementation Science

Research Assistant

Gregory Zane, MPH

PhD Student in Epidemiology

Research Assistant

Paul Drain, MD, MPH, FACP

Associate Professor of Medicine & Global Health

Adjunct Associate Professor of Epidemiology

Faculty Lead

START OVERVIEW

Leverages leading content expertise from across the University of Washington

Provides high quality research and analytic support to the Bill & Melinda Gates Foundation and global and public health decision-makers

Provides structured mentorship and training to University of Washington graduate research assistants

Source: Infectious Diseases Hub
https://www.id-hub.com/2017/01/27/foodborne-enterotoxigenic-escherichia-coli-gut-pathogenesis-new-preventive-strategies-involving-probiotics/

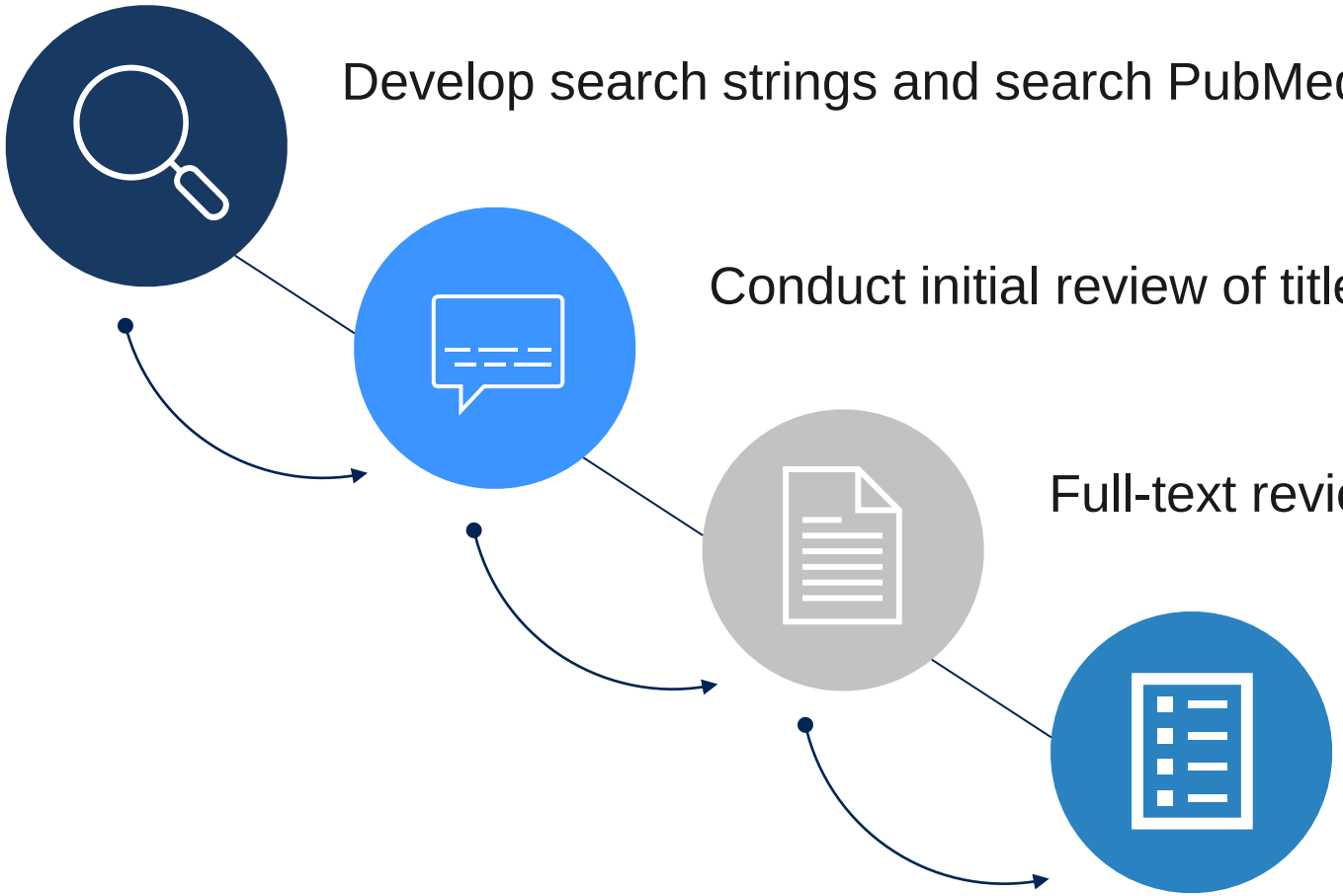
PROJECT REQUEST

Objectives: Synthesize evidence around long-term sequelae of *Campylobacter*, Norovirus & ETEC infections among children < 5 years of age

Methods: Systematic literature review (grey and white) & expert consultation

Rationale: To supplement the recent review of evidence of the impact of Shigella infection on long-term morbidity and to inform ongoing and future vaccine trials

METHODOLOGY



Develop search strings and search PubMed, Embase, LILACS, and SciELO

Conduct initial review of titles and abstracts (double reviewer)

covidence

Full-text review to verify inclusion (double reviewer)

Data extraction of included studies (single reviewer + secondary review of 10% of studies)

REDCap®

SEARCH TERMS IN PUBMED

Sequelae terms: ("Learning Disabilities"[Mesh] OR "Cognition Disorders"[Mesh:NoExp] OR "Cognitive Dysfunction"[Mesh] OR "Learning Disabilit*"[tiab] OR “Cognitive Development”[tiab] OR “Cogniti*”[tiab] OR "Child Development"[Mesh] OR "Growth Disorders"[Mesh] OR "Body Size"[Mesh] OR "child development" OR "postnatal development" OR "post-natal development" OR growth[tiab] OR "Crown Rump Length" OR height OR stunting OR stunted)

AND

Pathogens and disease presentation: ("Campylobacter"[Mesh] OR "Campylobacter Infections"[Mesh] OR Campylobacter*[tiab] OR "Norovirus"[Mesh] OR Norovirus*[tiab] OR "Enterotoxigenic Escherichia coli"[Mesh] OR ETEC[tiab] OR "Enterotoxigenic E*"[tiab] OR "Diarrhea"[Mesh] OR "Diarrhea "[tiab] OR "Diarrhoea"[tiab] OR "Dysentery"[Mesh:NoExp] OR "Dysentery"[tiab] OR "bloody diarrh*"[tiab] OR "bloody stool"[tiab] OR "Vomiting"[Mesh:NoExp] OR "Vomit*"[tiab] OR "Abdominal Pain"[Mesh] OR "Abdominal Pain"[tiab])

AND

Age group terms: ("Child, Preschool"[Mesh] OR "Infant"[Mesh] OR "Child*"[tw] OR "Infant*"[All Fields] OR "Newborn"[All Fields] OR "Baby"[All Fields] OR "Babies"[All Fields] OR "Neonat*"[All Fields] OR "Pediatric"[tw] OR "Paediatric"[tw])

SEARCH TERMS IN PUBMED

AND

Publication date: “1980/01/01”[Date - Publication] : “3000”[Date - Publication]

NOT

Publication type: NOT (“Editorial”[Publication Type] OR “Letter”[Publication Type] OR “Review”[Publication Type] OR “Case Reports”[Publication Type])

Total Results in PubMed: 4,251

- Total results in PubMed with only English: 3,922
- Total results in PubMed with only English, Portuguese, and Spanish: 4,017

Total Results in PubMed without ("Abdominal Pain"[Mesh] OR "Abdominal Pain"[tiab]): 3,912

Total Results in PubMed without “Cogniti*”[tiab]: 4,040

INCLUSION/EXCLUSION CRITERIA

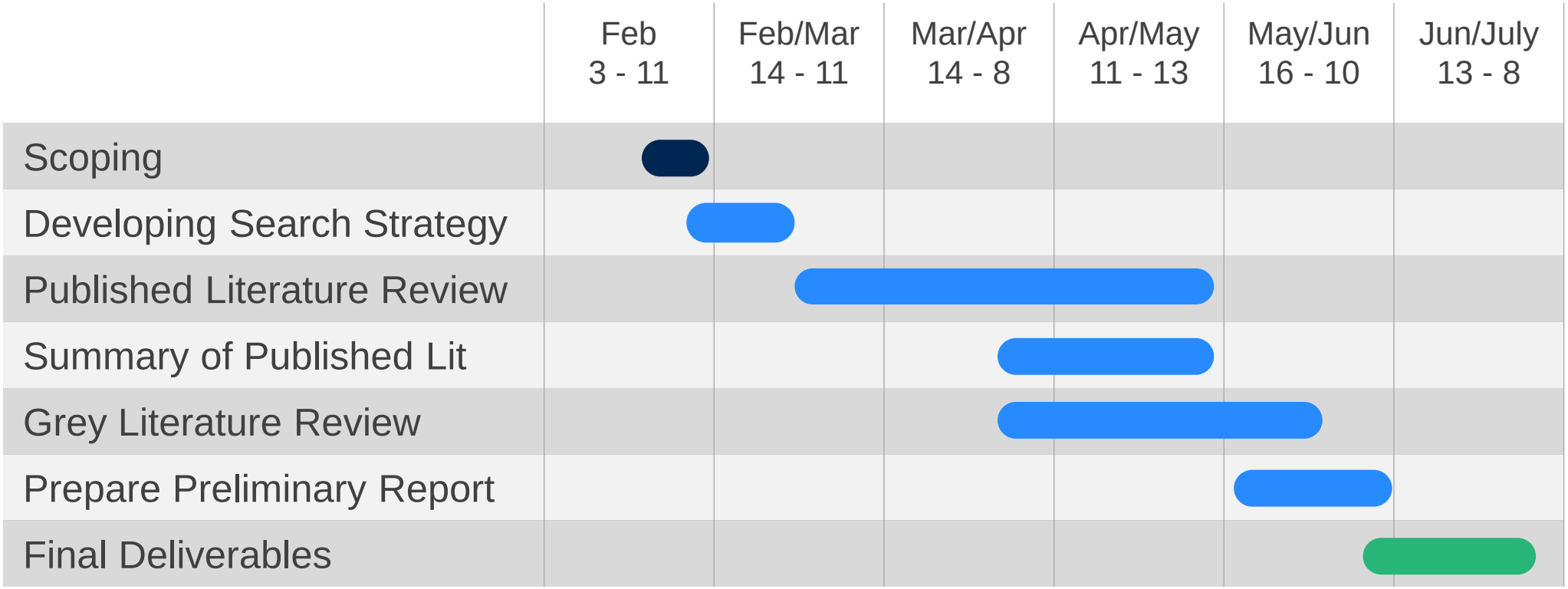
	INCLUDED	EXCLUDED
Language	English, Spanish, Portuguese	Others
Study Population	▪ < 5 years old ▪ With confirmed *Campylobacter,* Norovirus or ETEC (with or without diarrhea)	▪ > 5 years old only ▪ Lack of confirmed *Campylobacter*, Norovirus or ETEC infection
Geography	LMICs & HICs	None*
Year of Publication (if published)	1980 – present	Before 1980
Study Design	▪ Longitudinal (RCTs, Case-control, Cohort) ▪ Reviews (missed articles)	▪ Cross-sectional studies ▪ Case studies ▪ Modeling studies (i.e., GBD) ▪ Non-human studies

*To capture Norovirus data; overwhelmingly from HICs

DATA EXTRACTION

PRIMARY VARIABLES	OUTCOME VARIABLES
▪ Basic publication information (authors, year) ▪ Study design ▪ Study setting/population ▪ Subpopulation (e.g., acute malnutrition, HIV) ▪ Age of participants ▪ Recruitment years ▪ Length of follow up, by outcome ▪ Detection method (e.g., culture, PCR) ▪ Funding source	▪ Stunting/ linear growth faltering ▪ Wasting/ ponderal growth faltering ▪ Underweight/ weight gain ▪ Neurodevelopmental outcomes

PROJECT TIMELINE*



*Subject to change based on the number of obtained search results

QUESTIONS

- Does IVIR-AC agree with the proposed approach to the systematic review to measure the morbidity burden of enteric infections?

THANK YOU

START CENTER
STRATEGIC ANALYSIS,
RESEARCH & TRAINING CENTER

APPENDIX

DETAILED SEARCH TERMS

("Learning Disabilities"[Mesh] OR "Cognition Disorders"[Mesh:NoExp] OR "Cognitive Dysfunction"[Mesh] OR "Learning Disabilities"[tiab] OR “Cognitive Development”[tiab] OR “Cogniti*”[tiab] OR "Child Development"[Mesh] OR "Growth Disorders"[Mesh] OR "Body Size"[Mesh] OR "child development" OR "postnatal development" OR "post-natal development" OR growth[tiab] OR "Crown Rump Length" OR height OR stunting OR stunted)
AND
("Campylobacter"[Mesh] OR "Campylobacter Infections"[Mesh] OR Campylobacter*[tiab] OR "Norovirus"[Mesh] OR Norovirus*[tiab] OR "Enterotoxigenic Escherichia coli"[Mesh] OR ETEC[tiab] OR "Enterotoxigenic E*"[tiab] OR "Diarrhea"[Mesh] OR "Diarrhea "[tiab] OR "Diarrhoea"[tiab] OR "Dysentery"[Mesh:NoExp] OR "Dysentery"[tiab] OR "bloody diarrh*"[tiab] OR "bloody stool"[tiab] OR "Vomiting"[Mesh:NoExp] OR "Vomit*"[tiab] OR "Abdominal Pain"[Mesh] OR "Abdominal Pain"[tiab])
AND
("Child, Preschool"[Mesh] OR "Infant"[Mesh] OR "Child*"[tw] OR "Infant*"[All Fields] OR "Newborn"[All Fields] OR "Baby"[All Fields] OR "Babies"[All Fields] OR "Neonat*"[All Fields] OR "Pediatric"[tw] OR "Paediatric"[tw])
AND
“1980/01/01”[Date - Publication] : “3000”[Date - Publication]
NOT
(“Editorial”[Publication Type] OR “Letter”[Publication Type] OR “Review”[Publication Type] OR “Case Reports”[Publication Type] OR systematic[sb])

APPENDIX

TITLE AND ABSTRACT SCREENING PROTOCOL

MAPPING LONG TERM SEQUELAE OF CAMPYLOBACTER, NOROVIRUS, AND ETEC

TITLE/ABSTRACT SCREENING PROTOCOL IN COVIDENCE

1. Login Covidence and select the Mapping CNTEC review.
    - It will bring you to a dashboard which shows the number of studies you can still screen. That number will be xxx initially and will decrease as you and others screen studies. COVIDENCE automatically limits the # of votes per study to 2, and only displays a single study to two team members at a time.
2. Click on the blue box that says "Continue" to start screening.
3. At the top of your screening page, you can click "Show Highlights" or "Hide Highlights". Highlights have been enabled where words that *might* indicate inclusion are highlighted in green (e.g., Campylobacter, Norovirus, ETEC, height, brain, diarrhea, child, length) and words that *might* indicate exclusion appear in red (e.g., adult, cross-sectional, gastrointestinal).
4. **Exclude** if the article contains one of the following:
    a. **Diagnosis**: Clearly did not study Campylobacter, Norovirus, or ETEC (please include if you cannot tell from Title/Abstract whether patients had Campylobacter, Norovirus, or ETEC infection/detection)
    b. **Study target:** No human subjects (e.g., modeling studies, animal studies)
    c. **Age group:** Only involved adult patients
    d. **Outcomes**: reports on short term outcomes or outcomes other than growth and cognitive development impairment
    e. **Study design:** Cross-sectional studies, single time-point, no follow-up (if uncertain/unclear in abstract, please include)
    f. **Publication year:** Article published before 1980
    g. **Language:** Publication other than in English, French and Spanish
5. **Include** if the article meets all or combination of the following inclusion criteria:
    a. **Diagnosis:** With confirmed Campylobacter, Norovirus or ETEC (with or without diarrhea) detection
    b. **Age group:** children <5 years of age
    c. **Geography:** Conducted either in LMIC or HIC

APPENDIX

TITLE AND ABSTRACT SCREENING PROTOCOL

d. **Study design:** Longitudinal study/follow-up of children with Campylobacter, Norovirus, or ETEC
    i. RCT, Cohort study, Case-control: No minimum duration of follow-up
    ii. Include systematic reviews to check on the references list later (click on the systematic review tags to come back to it later)
e. **Outcomes:** Reports on a longitudinal outcome(s) (except for mortality only)
    i. Growth-related impairments [stunting, Length-weight]
    ii. Cognitive developments [brain..]
f. **Publication year:** Article published between 1980-present
g. **Language:** Publication in English, Portuguese, and Spanish
h. **Grey literature:** Case reports, case studies, or other studies among <5 children with Campylobacter, Norovirus, or ETEC

6. If it's still not clear from the abstract, it's OK to include. Add notes on why you think it might be included or excluded.

7. You can also add tags to track studies that need extra attention such as "reviews", "Conference Abstract", "Non-English". Since we are NOT excluding these, it would be useful to use the tag to track them. [feel free to add more tags]

8. Mistakes: If you make a mistake, you can't "undo," but if the study is still awaiting the second reviewer, you can go find the study and change your vote. Click on "Awaiting other reviewer" and sort by "Most Recent" and the study you just voted on should appear first. If it isn't there, that means someone else already voted on it; if you voted to Exclude, look in "Irrelevant references" and sort by most recent. You can't change your vote, but you can click "move study to screen" and then it will be returned to the screening list again (this would be a good time to add a note).

9. Please don't change any of the Settings and don't click on [Archive].

SUPPLEMENT ARTICLE

The MAL-ED Study: A Multinational and Multidisciplinary Approach to Understand the Relationship Between Enteric Pathogens, Malnutrition, Gut Physiology, Physical Growth, Cognitive Development, and Immune Responses in Infants and Children Up to 2 Years of Age in Resource-Poor Environments

The MAL-ED Network Investigators[a]

Highly prevalent conditions with multiple and complex underlying etiologies are a challenge to public health. Undernutrition, for example, affects 20% of children in the developing world. The cause and consequence of poor nutrition are multifaceted. Undernutrition has been associated with half of all deaths worldwide in children aged <5 years; in addition, its pernicious long-term effects in early childhood have been associated with cognitive and physical growth deficits across multiple generations and have been thought to suppress immunity to further infections and to reduce the efficacy of childhood vaccines. The Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health (MAL-ED) Study, led by the Fogarty International Center of the National Institutes of Health and the Foundation for the National Institutes of Health, has been established at sites in 8 countries with historically high incidence of diarrheal disease and undernutrition. Central to the study is the hypothesis that enteropathogen infection contributes to undernutrition by causing intestinal inflammation and/or by altering intestinal barrier and absorptive function. It is further postulated that this leads to growth faltering and deficits in cognitive development. The effects of repeated enteric infection and undernutrition on the immune response to childhood vaccines is also being examined in the study. MAL-ED uses a prospective longitudinal design that offers a unique opportunity to directly address a complex system of exposures and health outcomes in the community—rather than the relatively rarer circumstances that lead to hospitalization—during the critical period of development of the first 2 years of life. Among the factors being evaluated are enteric infections (with or without diarrhea) and other illness indicators, micronutrient levels, diet, socioeconomic status, gut function, and the environment. MAL-ED aims to describe these factors, their interrelationships, and their overall impact on health outcomes in unprecedented detail, and to make individual, site-specific, and generalized recommendations regarding the nature and timing of possible interventions aimed at improving child health and development in these resource-poor settings.

Keywords. MAL-ED; diarrhea; malnutrition.

[a]MAL-ED Network Investigators are listed in the Appendix.

Correspondence: Mark Miller, MD, Fogarty International Center, 16 Center Drive, MSC 6705, Bethesda, MD 20892-6705 (millemar@mail.nih.gov).

Clinical Infectious Diseases® 2014;59(S4):S193–206

DOI: 10.1093/cid/ciu653

National and multinational investments into public health have greatly reduced child mortality from diarrhea and undernutrition over the past 20 years. Between 1990 and 2013, overall child mortality rates decreased from 87 to 51 per 1000 live births, and the associated

prevalence of children underweight fell from 25% to 16% [1]. The progress in decreasing mortality rates has increased attention on childhood morbidity in low-resource areas and the potential, more insidious consequences of undernutrition and infectious diseases on long-term health outcomes.

Early childhood physical growth and cognitive development may be affected by a multitude of economic, biological, environmental, and possible genetic factors. Exposures to putative pathogens at an early stage of physical, immunologic, and cognitive development may adversely disrupt the trajectory of a child's potential development, resulting in long-lasting consequences. As economic achievement in adulthood has been linked to school performance, which is in turn associated with development during the earliest years of life, such long-lasting consequences are likely to have significantly deleterious effects on both individuals as well as their communities [2].

The causes of poor growth and development in early childhood are complex, with a variety of direct and underlying conditions, including a lack of adequate amounts or quality of food [3]; early termination of or insufficient breastfeeding [4], with possible inadvertent introduction of putative pathogens in weaning foods; inadequate diversity of complementary foods, which may lead to specific micronutrient deficiencies [5–8]; diets that contain inhibitors of micronutrient absorption [9, 10]; catabolic states due to infection [11–13]; the inadequate response of the host and the host's gut microbial community to caloric insufficiency; and/or a configuration of the microbiota that is suboptimal for energy/nutrient harvest [14, 15]. The availability of micro- and macro-nutrients for physical and cognitive development and a healthy immune system are a function of both their input and processing, but few studies have attempted to explore longitudinally the sufficiency of food intake alongside disease and infection history with measures of gut function.

Enteric pathogens and their potential role in developing malnutrition have been a focal point for research. Pathogens may be introduced early in life and may damage the absorptive capacity of the intestine, causing protein-energy and micronutrient malnutrition [16]. Enteric infections can compromise the intestinal barrier, increase inflammation, and lead to decreased function. Both micronutrient deficiencies and chronic immune stimulation have also been found to impair growth and to increase susceptibility to infectious diseases [17].

Pioneering studies in Central America documented the impact of childhood infections and diarrhea on malnutrition [18]. Given the relatively high estimates of the prevalence of malnutrition and diarrhea episodes in much of the developing world, there is a great need for detailed data identifying specific enteric pathogens, age-specific incidence, and their association with growth faltering. Malnutrition also has been shown to increase susceptibility to infections and mortality due to diarrhea and other infectious diseases [19–22]. Repeated enteric infections in adults living in unsanitary conditions damage the intestinal tract, which leads to a condition that has been termed "environmental enteropathy or environmental enteric dysfunction" (EE/EED). A description of the clinical characteristics, possible etiology, and diagnosis of EE/EED is included in this supplement [23].

Although EE/EED is thought to contribute to the development of undernutrition in older populations [24, 25], the histology has not been adequately described in infants or young children living in areas of high exposure to enteric pathogens. Plausible mechanisms for how EE/EED may contribute to undernutrition and to growth faltering have been proposed. Repeated exposure to pathogenic bacteria, viruses, and parasites may impact the nutritional status of an individual by competing for available micronutrients, and/or cause villus blunting and thus impair nutrient absorption [16] and compromise the intestinal barrier, leading to increased intestinal permeability to pathogens, endotoxins, and other macromolecules that can result in the chronic stimulation of the immune system [26, 27]. Serum concentrations of micronutrients have been shown to both increase (iron) and decrease (vitamin A and zinc) in response to infection, inflammation, or tissue injury [28]. Both micronutrient deficiencies and chronic immune stimulation have also been found to impair physical growth and to increase the susceptibility to infectious diseases [19]. Additionally, alterations in the gut microbiota, either as a result of enteropathogen infection or the administration of antimicrobials, may influence the structure and functions of the innate and adaptive arms of the immune system, which in turn may reduce the effectiveness of oral and mucosal vaccines [21, 29–32].

To date, there have been few systematic, longitudinal, prospective studies that help define particular windows of vulnerability in infants and young children when infection by a specific pathogen or combination of pathogens could lead to greater deficits in developmental outcomes [33–35]. Definitive histopathological diagnoses of EE/EED in infants and children in developing countries have yet to be made due to ethical challenges associated with obtaining gut biopsies from vulnerable populations in areas with a high incidence of malnutrition. Furthermore, conclusive studies that define associations of physical growth and cognitive development deficits with repetitive specific enteric infections (controlling for dietary intake, levels of macro- and micronutrient deficiencies, and measures of intermediary indicators such as biomarkers of gut function) have not been conducted. There are also limited studies examining these factors on the immune response in children. To address these gaps in knowledge, the study of Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health (MAL-ED) was established at research sites with a high incidence of diarrheal disease and malnutrition in 8 countries.

MAL-ED Aims

The aim of MAL-ED is to improve scientific understanding of the complex interrelationships between gut microbial ecology, enteropathogen infection, dietary intake, nutritional status, gut physiology, growth, immune function and vaccine response, and cognitive development. Although existing evidence hints at the roles of individual factors, a holistic approach to quantify the interactions between these factors and their potentially synergistic role in multiple and diverse populations has not been explored previously. The primary health outcomes to be evaluated by MAL-ED are physical growth, cognitive development, and immune responses to oral and parenteral vaccines. It is anticipated that knowledge derived from MAL-ED will help the public health community better engineer interventions and their timing to minimize those factors that may contribute to lost lifetime potential.

The central hypotheses of the MAL-ED Network study are as follows:

1. Enteropathogen infection contributes to (*i*) stunting, (*ii*) wasting, and (*iii*) micronutrient deficiencies.
2. Enteropathogen infection causes intestinal inflammation and diminished barrier and adsorptive functions of the gut.
3. In children (≤24 months old), gut dysfunction associated with enteric infections and undernutrition results in (*i*) diminished nutrient absorption from the gut, (*ii*) growth faltering, (*iii*) cognitive impairments, and (*iv*) impaired responses to childhood vaccines.

Each hypothesis is at once superficially simple—with existing evidence—and intractable given the many factors that contribute to the manifestation of the respective health outcomes and the many feedback loops that confound analyses. Underlying these hypotheses is a belief that enteric infections, malnutrition, and gut function interact, rather than act in isolation, to affect physical growth, cognitive development, and immune responses to vaccination (Figure 1).

The MAL-ED Network

Through the MAL-ED study, an international, multidisciplinary collaborative network of researchers was established. Field sites for the study are located in resource-constrained areas (8 countries across 3 continents) and include both urban and rural communities with a history of high incidence of diarrheal disease and malnutrition. The field sites are located in Dhaka, Bangladesh; Fortaleza, Brazil; Vellore, India; Bhaktapur, Nepal; Loreto, Peru; Naushahro Feroze, Pakistan; Venda, South Africa; and Haydom, Tanzania. Collaborating investigators and institutions along with collaborators in the wider MAL-ED Consortium are shown in Table 1.

The Scientific and Administrative Core, based at the Fogarty International Center (National Institutes of Health) and the Foundation for the National Institutes of Health, provides

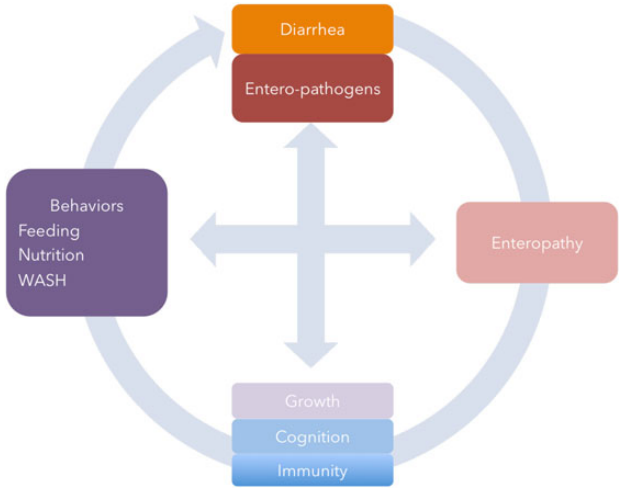


Figure 1. Components of the complex system of interactive relationships of health determinants and outcomes explored by the MAL-ED Study. Abbreviation: WASH, water, sanitary and hygiene interventions.

leadership in coordinating the scientific activities across the network through technical subcommittees (TSCs) for surveillance, microbiology, cognitive development, nutrition, gut function, and vaccine immunogenicity. TSC membership is comprised of subject-matter experts across sites and collaborating institutions and includes epidemiological and statistical support. A common Manual of Procedures containing standardized operating procedures and case report forms used in the study, as well as necessary training and quality assurance/quality control procedures to ensure comparability of results across the sites, was developed following extensive discussion between experts at the field sites and the TSC members. A protocol for real-time data transfer to and from each site to a centralized database was established to collate de-identified data for quality control review and cleaning. The first study subject was enrolled in November 2009 and data and sample collection from study subjects was completed at the end of February 2014.

This supplement describes the MAL-ED study by offering detailed descriptions of each of the 8 field sites [36–43] and specific data collection methodologies for the following categories: surveillance for common infant and childhood illnesses and medication usage, including antibiotics [44], and administered vaccines [45]; growth measurements [46]; breastfeeding and dietary intake assessments [47]; stool collections for microbiological and gut functional assays and antigen detection [48, 49]; blood collections for micronutrients [47] and serological responses to vaccines [45]; urine collections for micronutrients [47] and gut functional assays [50]; and cognitive testing at various ages [51].

Reviews of our current understanding of EE/EED and the scientific tools available to evaluate this condition are also included in the supplement to provide the context in which

Table 1. MAL-ED Consortium, Field Site, Collaborating Institutions, and Companion Project Principal Investigators

Institutions	Principal Investigators
Fogarty International Center	Mark Miller
Foundation for the National Institutes of Health	Michael Gottlieb
Aga Khan University, Karachi, Pakistan[a]	Zulfiqar Bhutta
Christian Medical College Vellore, Vellore, India[a]	Gagandeep Kang and Sushil John
JHSPH Satellite Laboratory, Iquitos, Peru[a]	Margaret Kosek
Federal University of Ceará, Fortaleza, Ceará, Brazil[a,b]	Aldo A. M. Lima and Reinaldo Oria
Walter Reed/AFRIMS Research Unit, Kathmandu, Nepal[a]	Sanjaya Kumar Shrestha
Institute of Medicine, Kathmandu, Nepal[a]	Prakash Sunder Shrestha
University of Venda, Limpopo, South Africa[a]	Pascal Bessong
International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh[a,b]	Tahmeed Ahmed and Rashidul Haque
Haydom Lutheran Hospital, Haydom, Tanzania[a]	Erling Svensen
JHSPH, Baltimore, MD, USA[c]	Laura Caulfield, Laura Murray-Kolb, and Robert Black
UVA, Charlottesville, VA, USA[d,e]	Richard Guerrant, William Petri[f,g], Eric Houpt[h], Patrick Concannon[f], Stephen Rich[f], Rebecca Dillingham[f]
Walter Reed/AFRIMS, Bangkok, Thailand[i]	Carl J. Mason and Ladaporn Bodhidatta
Center for Genome Sciences and Systems Biology, Washington University School of Medicine, St Louis, MO, USA[e]	Jeffrey I. Gordon[j]
University of Colorado at Boulder, Boulder, CO, USA[e]	Rob Knight[j]
University of Michigan, Ann Arbor, MI, USA[e]	Felicia Wu[k]

Abbreviations: AFRIMS, Armed Forces Research Institute of Medical Sciences; CO, Colorado; JHSPH, Johns Hopkins Bloomberg School of Public Health; MD, Maryland; MI, Michigan; MO, Missouri; UVA, University of Virginia; VA, Virginia.

[a] Location of birth cohort study site.

[b] Location of case-control study site.

[c] JHSPH is collaborating with the Peru field site.

[d] UVA is collaborating with the Bangladesh, Brazil, South Africa, and Tanzania field sites.

[e] Location of a companion project.

[f] Genome-wide Association Scans for Undernutrition and Growth Impairment and Molecular Markers of Immunity and the Underperformance of Mucosal Vaccines companion project.

[g] PROVIDE.

[h] Next-Generation Molecular Diagnostic Technologies for Developing Countries diagnostic companion project.

[i] Role of the Gut Microbiome in Nutritional Status companion project.

[j] Aflatoxin Exposure and Its Effect on Growth of Children companion project.

[k] AFRIMS is collaborating with the Nepal field site.

protocols for MAL-ED were established [23, 52]. At present, there are limited choices of noninvasive methods to measure gut integrity appropriate for use in the MAL-ED study. Current methods assess the integrity of the intestinal barrier by measuring markers of inflammatory status [53], permeability [54], and absorptive capacity [55]. The relative balance of lactulose to the nonmetabolized sugar mannitol [56] excreted in urine gives an indication of the gut barrier function for both the absorptive capacity (mannitol) and permeability of the gut (lactulose) [57, 58].

METHODS

Overview of Cohort Study Design

The overall design of the project is described with greater detail in the relevant methods articles contained in this supplement [44–51].

Study Population

The MAL-ED study focuses on birth cohorts followed longitudinally (to 24 months of age) in each of the 8 study sites. Each site performed a census of their local community to obtain an assessment of the number of women of reproductive age and the number of children <5 years of age. Using these data, each site defined a catchment area where it was estimated that >200 infants (the target number of children to be enrolled per site) would be born within the enrollment period lasting 2 years.

The inclusion criteria were as follows:

1. Healthy infants enrolled within 17 days of birth.
2. Caregiver report that they had no plans to move out of the catchment area for at least 6 months following enrollment in the study.
3. Willingness of caregiver to be visited in the home twice weekly.

The exclusion criteria were any of the following:

1. The family had plans to move out of the catchment area for >30 consecutive days during the first 6 months of follow-up.
2. The mother was <16 years of age.
3. The mother had another child already enrolled in the MAL-ED cohort study.
4. The child was not a singleton (ie, twins, triplets).
5. The infant had any of the following indications of serious disease:
   a. Hospitalization for something other than a typical healthy birth;
   b. Severe or chronic condition diagnosed by a medical doctor (eg, neonatal disorder; renal, liver, lung, and/or heart disease; congenital conditions); or
   c. Enteropathies diagnosed by a medical doctor.
6. The child's guardian failed to provide signed informed consent.
7. Weight at birth or enrollment was <1500 g.

Human immunodeficiency virus (HIV) infection of mothers or children was not determined in the study cohort. Although HIV infection is recognized as having impact on nutritional status, it was beyond the scope of the study design. The MAL-ED site descriptive articles in this supplement include information regarding rates of HIV in these populations [36–43].

To elucidate the role of seasonal variation related to pathogen exposure, disease etiology, and food availability, subject enrollment occurred at each site over a 2-year period (the earliest enrollment was initiated in November 2009 and the latest enrollment occurred in February 2012). At least 200 children were enrolled per site and followed for 24 months. All sites received ethical approval, as appropriate, from governmental, local institutional, and collaborating institutional ethical review boards. Signed informed consent was obtained from the guardian of each participating child.

Demographic Characteristics, Socioeconomic Status, and Food Access Insecurity

Prior to enrollment, each site conducted a pilot study in an area representative of the study population to determine household characteristics, socioeconomic status (SES), food access insecurity, and general child health status within the MAL-ED catchment communities. At each site, 100 households were administered a standardized questionnaire about the household demographics (head of household, maternal age, marital status, educational attainment, and maternal parity), household environment, asset ownership, and food access insecurity. The questionnaire was based on questions used by the Demographic and Health Surveys and the Food and Nutrition Technical Assistance project [59] and input from the MAL-ED field sites. Additionally, the height and weight of one child 24–60 months of age was measured. This pilot study guided the development of a standardized questionnaire applicable to the MAL-ED cohorts.

Data Collection

At enrollment, each child's date of birth, sex, birth weight (if available) was recorded; information about initiation of breastfeeding was noted; and the child's length, weight, and head circumference were measured. Active surveillance for infectious diseases, general child health information, and basic dietary intake was undertaken by visiting each home twice per week. Additional visits to each household by trained field staff at various intervals were made to collect data about health, vaccinations, and dietary intake, and to measure anthropometry, perform cognitive tests, and collect blood, urine, and monthly surveillance (nondiarrheal) and diarrheal stool samples. Maternal and household characteristics were also recorded (Table 2).

Table 2. Measurement Collection/Questionnaire and Test Administration/Sample Collection Timeline for MAL-ED Cohort Studies

	Child Age (mo) and Sample Type																
Assessment	0	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24
Gut integrity				U			U			U				U			U
Gut inflammation	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Incidence and prevalence of enteric pathogens	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Diarrhea illness surveillance	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I
Anthropometry	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Nutrition (breastfeeding and dietary intake)	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I
Micronutrients							U	B						B/U			
Cognitive function							T		T					T			T
Household or maternal	I	I	I				I/O/T						I	I	I		I/O
Immunization and vaccine response	I	I	I	I	I	I	I	I/B	I	I	I	I	I	I/B	I	I	I
Other illness surveillance	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I

Abbreviations: B, blood; I, interview; M, measurement; O, observation; S, stool; T, test administration; U, urine.

At enrollment, only the demographics and food access insecurity portions of the SES questionnaire were collected from the households of MAL-ED study children. The complete SES and food access insecurity questionnaire was administered at 6, 12, 18, and 24 months.

Illness Surveillance and Stool Collection

During twice-weekly household visits, caregivers responded to a standardized questionnaire designed to collect a daily record of symptoms of cough, fever, vomiting, diarrhea and medication use. Stool samples were collected during diarrheal episodes (defined as ≥3 loose stools in a 24-hour period and separated by ≥2 diarrhea-free days) and during monthly home visits (nondiarrheal specimens). Subjects experiencing moderate and severe illnesses (including severe diarrhea, dysentery, acute lower respiratory infections, dehydration, and fever) were referred to local health services [44].

Physical Growth

Anthropometric measurements were collected on all children monthly using standardized procedures. The weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length (WLZ) *z* scores are calculated using the World Health Organization (WHO) Multicentre Growth Reference Study Group program [60]. The height and weight of mothers was measured 2 months after delivery.

Microbiology

All stools were analyzed for the presence of bacterial, viral, and parasitic pathogens associated with diarrhea using traditional methods of microscopy, culture, enzyme-linked immunosorbent assay (ELISA), and polymerase chain reaction (PCR) as appropriate to the pathogen [48]. These include *Salmonella*, *Shigella*, *Vibrio*, *Yersinia*, *Aeromonas*, *Campylobacter* and *Plesiomonas*, *Escherichia coli*, rotavirus, norovirus, adenovirus, astrovirus, *Cryptosporidium*, *Giardia*, *Entamoeba histolytica*, *Ascaris*, *Trichuris*, *Strongyloides*, *Cyclospora*, *Isospora*, hookworm, and others. Pathogenic *E. coli* was identified by multiplex PCR amplification of known virulence genes and included enteropathogenic, enterotoxigenic, enteroaggregative, Shiga toxin (1 and 2)–producing, and enteroinvasive strains. Surplus stool samples were archived for use in future studies.

Cognitive Development

The cognitive development of each child was assessed through periodic administration of several validated instruments: the Bayley Scales of Infant Development [61] to assess global capacity (at 6, 15, and 24 months); the Infant Temperament Scale (T. Wachs, personal communication, 2010) to assess infant temperament (at 6 months); and the MacArthur Adapted Communicative Development Inventory: Words and Gestures [62] (at 8, 15, and 24 months) to assess language development [51]. The quality and quantity of stimulation and support available to the child in his or her home environment was assessed with the HOME Inventory [63] (at 6 and 24 months).

Maternal Factors

Maternal factors including mood and reasoning ability, known to be associated with a child's development, were assessed with the Self-Reporting Questionnaire–20 [64] (at 1, 6, 15, and 24 months). Maternal reasoning ability was assessed with the Raven's Combined Progressive Matrices instrument [65] (at 6–8 months) to control for these variables. Information about day and night blindness, and tobacco and alcohol use during pregnancy, was collected at 2 months after delivery.

Nutrition (Breastfeeding Status and Dietary Intake)

Individual nutritional status in the MAL-ED study population was assessed through periodic quantitative and qualitative assessments of the food consumed during the first 2 years of life [47]. Information—organized with a controlled vocabulary—was entered into a searchable database. For the first 8 months, this information was gathered by questioning the caregiver about the extent and duration of exclusive breastfeeding and about the introduction of weaning foods collected during the twice weekly and monthly home visits. When a child was 9 months of age, the caregiver was asked monthly (until 24 months of age is reached) to recall food intake over the past 24 hours to estimate caloric intake of the child and inform assessments of dietary quality and diversity.

Micronutrients

Micronutrient levels were measured in blood samples collected at 7 and 15 months of age. Hemoglobin, ferritin, and plasma transferrin receptor were used to assess levels of iron, lead, zinc, retinol, argentine, and glutamine. Iodine levels were measured in urine collected at 6 and 15 months. Because the acute-phase response to infections are known to affect micronutrient levels, the level of α-1-acid glycoprotein present in blood was measured to serve as a control and enable accurate assessment of micronutrient status in child subjects [28].

Gut Function and Inflammation

The lactulose-mannitol test was administered to study children at 3, 6, 9, 15, and 24 months to evaluate gut permeability and absorptive capacity, respectively. Three additional proteins were also assessed to gauge aspects of gut function: α-1-antitrypsin for gut permeability, neopterin as a marker of T-helper 1 immune activation, and myeloperoxidase, which is indicative of neutrophil activity [66]. Quantitative ELISAs to detect α-1-antitrypsin, myeloperoxidase, and neopterin were performed on all stool samples.

Vaccine Response

During monthly home visits, caregivers provided information about the receipt of childhood vaccinations, including but not limited to those on the schedule of the WHO Expanded Program on Immunization (EPI). Vaccination records were also collected (at 3, 6, 9, 12, 15, 18, 21, and 24 months), and the information source (eg, vaccine card, clinical report) was recorded. The MAL-ED study measured the response to selected parenteral and oral vaccines administered as part of the EPI program in each country. Blood obtained at 7 and 15 months of age was used to evaluate (by ELISA) the level of immune response to pertussis toxin, measles, tetanus toxoid, poliovirus types 1, 2, 3, and rotavirus by ELISA. Poliovirus neutralization titers were also determined.

Case-Control Studies

MAL-ED intensive biweekly household surveillance and efforts to collect clinical specimens and to capture accurate data may create a "Hawthorne effect" that dramatically reduces diarrhea rates and malnutrition [67]. As an adjunct to the cohort study, 2 of the MAL-ED sites (Fortaleza, Brazil [39] and Dhaka, Bangladesh [36]) conducted case-control studies measuring similar variables as described above. In these parallel studies, cases were defined as children from 6 to 18 months of age exhibiting a WAZ score of < -2 compared to community controls. These studies are more fully described in the site-specific articles of this supplement [36, 39].

Data Management and Analysis

The Data Coordinating Center (DCC) of MAL-ED was established at the Fogarty International Center. Members of the DCC contributed to the study design and form development, and developed a double-entry database application, which simultaneously collected and stored MAL-ED data at each site and centrally. In the field and laboratory, data were collected on standardized forms; local data supervisors checked form completeness and accuracy prior to data entry. As an additional quality control measure, forms were double-entered into the local database; discrepancies between first and second entry were resolved by the site data entry supervisor(s).

Data from each site were transferred to a central server at the DCC using data synchronization software. The DCC provided feedback regarding data quality to site investigators through monthly data and quality control reports. In addition, site-specific "issue logs" were maintained in a file sharing Web site that provided real-time, site-specific feedback to identify errors and/or omissions in data entry and to facilitate corrections with minimal time delay. To standardize the definitions of exposure and outcome measures in MAL-ED, the DCC generated datasets that were made available across the MAL-ED Network of investigators. These datasets will serve to uniformly analyze the exposure and outcome relationships of the MAL-ED population.

The MAL-ED Consortium and Companion Projects

The MAL-ED Network provided a scientific and administrative platform from which related projects have leveraged resources including hypothesis-based research and targeted interventional trials. MAL-ED companion projects—together with the cohort and case-control Network studies—constitute the larger MAL-ED Consortium. Companion project institutions and investigators have agreed to abide by the same Research Consortium Agreement (see below), as have all MAL-ED Network investigators. Current MAL-ED companion projects are briefly described below.

Role of the Gut Microbiome in Nutritional Status

Ancillary studies of the human gut microbiome and its role in nutrition are being conducted through a comparative metagenomic study seeking to characterize features of the gut microbiome associated with the development of undernutrition in children identified in the case-control study [36]:

1. Are there identifiable configurations of the gut microbiome associated with undernutrition? If so, the findings may have pathophysiologic and diagnostic implications.
2. How is the microbiome reconfigured with a therapeutic food intervention, and does reconfiguration persist after cessation of the intervention?
3. What is the relationship between diet, the gut microbiome, and environmental enteropathy?
4. Can observations made in one human population be generalized to another?

Answering these questions requires a detailed knowledge of the normal assembly of the microbiome in healthy children in a given cultural setting and an understanding of the variations that exist among these healthy children at given points during their postnatal development.

Genome-wide Association Scans for Undernutrition and Growth Impairment

Genome-wide studies aimed at identifying candidate human genes associated with undernutrition and growth impairment are additionally being conducted. The genetic basis for susceptibility to malnutrition has not been as rigorously studied as the genetic basis for susceptibility to diseases common in the developed world. For obesity, the lipoprotein lipase, β-lactamase, and protein phosphatase 1–like genes have been implicated [68]. In a way, obesity and undernutrition can be considered as extremes of the metabolic spectrum, and it is not unlikely that some of the genetic polymorphisms that predispose to obesity may protect from undernutrition [69]. In addition, genes that influence inflammation and infection may also impact

nutritional state [70, 71]. The adipocytokine leptin not only controls appetite, but also promotes proinflammatory cytokine production, and variation in genes of the immune system can affect susceptibility to infections that contribute to malnutrition [72]. This study aims to narrow the gap in knowledge regarding genetic susceptibility to malnutrition through a genome-wide association scan of malnourished children.

Next-Generation Molecular Diagnostic Technologies for Developing Countries

The Next-Generation Molecular Diagnostic Technologies for Developing Countries project will advance development of enteropathogen target–specific, quantitative, PCR-based assays capable of detecting all of the bacterial, viral, protozoal, and helminthic pathogens being studied in the MAL-ED project. Sample extraction to amplification and detection will be tested on prototype platforms at some of the MAL-ED Network field sites and performance compared with results obtained by more traditional culture, microscopy, ELISA, and biochemical methods. The project deliverables are a series of field-ready protocols for the diagnosis of major enteropathogens that can be deployed efficiently for future epidemiologic projects such as MAL-ED.

Molecular Markers of Immunity and the Underperformance of Mucosal Vaccines

In addition to the vaccine response analyses that will be conducted by MAL-ED for mucosal and parenteral vaccines, the Performance of Rotavirus and Oral Polio Vaccines in Developing Countries (PROVIDE) study is using state-of-the-art immunological methods to assess cellular immunity following vaccination and its association with protection. Additional outcome measures for the study include (*i*) differences in episodes of rotavirus diarrhea between rotavirus vaccinees and nonvaccinees; and (*ii*) change in polio plasma neutralizing antibody titer after immunization. The use of MAL-ED protocols and standardized operating procedures and resources at the MAL-ED Network site in Bangladesh are utilized in this project.

Aflatoxin Exposure and Its Effect on Growth of Children

Aflatoxin exposure has been associated with growth decrements in observational studies. To better assess for this exposure in the context of many other possible growth factors, a subset of blood and urine samples from the MAL-ED study will be assessed for exposures to aflatoxins as an exploratory analysis to investigate the degree of association.

As the data collected from the MAL-ED study populations are explored, associations between factors measured, and health outcomes better defined, it is anticipated that additional opportunities to leverage MAL-ED data and samples and the site's capacities will emerge from diverse research enterprises in the public and private sectors for hypothesis-driven research and intervention studies.

Research Consortium Agreement

A Research Consortium Agreement (RCA) was developed and adopted by all collaborating investigators and their institutions in the MAL-ED Consortium prior to the onset of data collection and/or sharing. The RCA provides the organizational framework for the project including management and authorities, governance structure, methods of dispute resolution, and authority of the Network and its associated advisory committees. The RCA also provides guidance on publication; intellectual property; and data ownership, sharing, and release policies. The intent of these policies is to ensure that the important findings resulting from the study are used to benefit those in low-income countries who are most affected. Clearly delineating these issues, with input from the participating institutions and investigators prior to study initiation, was important to effectively establishing harmonization of the study; having the document in place has helped to facilitate the addition of other studies as companion projects.

DISCUSSION

The multiple interactions of enteric infections, malnutrition, and gut function and their synergistic effect on physical growth, cognitive development, and immune response provide the working hypotheses of MAL-ED. The structural components of this system of relationships and interactions are based on 2 lines of reasoning: (*i*) experiential expert knowledge of biological mechanisms and (*ii*) empirical evidence identifying key components, both risk factors and health outcomes. Together, it is possible to piece together hypothetical ways in which these components interrelate: the components explored by MAL-ED have been described in this introductory article (Figure 1) and are explored in greater detail in the MAL-ED methodological articles of this supplement [44–51].

Empirical evidence to date has usually been derived from studies concentrating on a single outcome. Such a focus ignores the potentially reciprocal and interdependent relationships that we hypothesize exist between the components of this system. The incidence and prevalence of chronic undernutrition manifested as stunting is commonly observed, but the mechanistic causes are poorly understood. Studies to define and quantify the role of particular enteropathogens and their contribution to malnutrition or diminished immune response have been limited by small sample sizes, narrow geographic scope, and/or a lack of robust diagnostic tests [73, 74]. Often they have been predicated on a "one pathogen, one disease" assumption, attributing symptoms to the presence of individual pathogens without consideration for coinfection, timing, or

quantification of pathogens. By definition, pathogens cause damage to their host; however, the ambiguity over the detection, let alone role, of enteric pathogens means that their short- and long-term consequences—especially of chronic and recurrent infections—against the backdrop of this wider system of risks and exposures have not been well characterized to date. Indeed, some enteric pathogens may not cause diarrhea, and therefore are not readily measured or studied in clinical research. Thus the frequency of carriage or infection with these pathogens or their consequences (not associated with diarrhea)—particularly in young children—remains understudied. It is anticipated that the community-based, longitudinal design of MAL-ED will better capture the "average" exposure to enteric pathogens and other factors and more clearly elucidate the consequences of this system of interdependent exposures on child development.

Whether considering single components of this system or the interdependencies, the dilemma with how these components are combined is that the underlying heterogeneity of different populations yields variable rankings of risks and health outcomes [75–89]. Any given case study typically focuses on singular aspects of the system we have described—be that a study of diarrhea, a specific pathogen, socioeconomic status, or growth attainment [90–93]. Between populations, however, the evidence can vary and produce disparate results and expert opinion. Different populations, for example, experience both different pathogens and in different quantities. Add to this a range of diets and behaviors, and the resulting health outcomes of any single population may not be representative of another. In applying a harmonized protocol across 8 geographically, socioeconomically, and culturally diverse populations, MAL-ED expects to identify relationships between health determinants and outcomes that are both uniform across all sites and disparate between sites. Improving the characterization of the similarities and divergence of these relationships would potentially inform decisions about how to most effectively apply as well as adapt interventions to achieve the desired improvements in health outcomes in variable settings. Furthermore, among the important relationships and pathways identified, we expect some to be more or less amenable to intervention. Demographic and socioeconomic characteristics along with general health indicators of each of the 8 MAL-ED research sites are included in the individual papers of this supplement. These papers also contain information about the recruitment and training strategies employed at the sites to implement the MAL-ED protocol [36–43].

As a central objective of MAL-ED, untangling the complicated web of malnutrition and enteric disease is considered a crucial factor in the development of interventions that will improve child health in resource-poor environments. These interventions will ideally account for the multiple and interacting risk factors affecting child development and, given likely limited resources, include consideration of optimal timing and targeting for maximal impact. Improvements in early childhood growth and development can have long-lasting impact, through improved school readiness, educational achievement, and, ultimately, improving the economic potential for individuals and their communities. MAL-ED may provide some insights into targeted interventions at this age.

Notes

Acknowledgments. The authors thank the staff and participants of the MAL-ED Network for their important contributions.

Financial support. The Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development Project (MAL-ED) is carried out as a collaborative project supported by the Bill & Melinda Gates Foundation, the Foundation for the NIH, and the National Institutes of Health, Fogarty International Center.

Supplement sponsorship. This article appeared as part of the supplement "The Malnutrition and Enteric Disease Study (MAL-ED): Understanding the Consequences for Child Health and Development," sponsored by the National Institutes of Health and the Foundation for the National Institutes of Health.

Potential conflicts of interest. No potential conflicts of interest.

Authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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APPENDIX

MAL-ED Network Investigators

Last Name	First Name	Institution	Role in the MAL-ED Network
Acosta	Angel Mendez	A.B. PRISMA, Iquitos, Peru	Data management
Chavez	Cesar Banda	A.B. PRISMA, Iquitos, Peru	Laboratory
Flores	Julian Torres	A.B. PRISMA, Iquitos, Peru	Laboratory
Olotegui	Maribel Paredes	A.B. PRISMA, Iquitos, Peru	Study coordinator
Pinedo	Silvia Rengifo	A.B. PRISMA, Iquitos, Peru	Nutrition
Trigoso	Dixner Rengifo	A.B. PRISMA, Iquitos, Peru	Laboratory
Vasquez	Angel Orbe	A.B. PRISMA, Iquitos, Peru	Psychologist, cognitive development
Ahmed	Imran	Aga Khan University, Naushahro Feroze, Pakistan	Data management
Alam	Didar	Aga Khan University, Naushahro Feroze, Pakistan	Laboratory, nutrition
Ali	Asad	Aga Khan University, Naushahro Feroze, Pakistan	Vaccine response
Bhutta	Zulfiqar A.	Aga Khan University, Naushahro Feroze, Pakistan	Pakistan site PI
Qureshi	Shahida	Aga Khan University, Naushahro Feroze, Pakistan	Laboratory, microbiology
Shakoor'	Sadia	Aga Khan University, Naushahro Feroze, Pakistan	Microbiology
Soofi	Sajid	Aga Khan University, Naushahro Feroze, Pakistan	Operations, surveillance
Turab	Ali	Aga Khan University, Naushahro Feroze, Pakistan	Operations, surveillance, nutrition
Yousafzai	Aisha K.	Aga Khan University, Naushahro Feroze, Pakistan	Cognitive development
Zaidi	Anita K. M.	Aga Khan University, Naushahro Feroze, Pakistan	Pakistan site co-PI, microbiology
Bodhidatta	Ladaporn	AFRIMS, Bangkok, Thailand	Microbiology
Mason	Carl J.	AFRIMS, Bangkok, Thailand	Nepal site PI, vaccine response
Babji	Sudhir	Christian Medical College, Vellore, India	Microbiology supervisor
Bose	Anuradha	Christian Medical College, Vellore, India	Nutrition
John	Sushil	Christian Medical College, Vellore, India	India site co-PI
Kang	Gagandeep	Christian Medical College, Vellore, India	India site PI
Kurien	Beena	Christian Medical College, Vellore, India	Cognitive development supervisor
Muliyil	Jayaprakash	Christian Medical College, Vellore, India	Epidemiology
Raghava	Mohan Venkata	Christian Medical College, Vellore, India	Data management
Ramachandran	Anup	Christian Medical College, Vellore, India	Biochemistry, nutrition
Rose	Anuradha	Christian Medical College, Vellore, India	Epidemiology
Pan	William	Duke University, Durham, NC, USA	DCC, biostatistician
Ambikapathi	Ramya	FIC, NIH, Bethesda, MD, USA	DCC, nutrition
Carreon	Danny	FIC, NIH, Bethesda, MD, USA	DCC, SES, and data management
Charu	Vivek	FIC, NIH, Bethesda, MD, USA	DCC, data management
Dabo	Leyfou	FIC, NIH, Bethesda, MD, USA	DCC, data management
Doan	Viyada	FIC, NIH, Bethesda, MD, USA	DCC, data management
Graham	Jhanelle	FIC, NIH, Bethesda, MD, USA	DCC, data management
Hoest	Christel	FIC, NIH, Bethesda, MD, USA	DCC, vaccine response
Knobler	Stacey	FIC, NIH, Bethesda, MD, USA	Senior scientific program director
Lang	Dennis	FIC, NIH, Bethesda, MD, USA	Senior program coordinator
McCormick	Benjamin	FIC, NIH, Bethesda, MD, USA	DCC, computational biology
McGrath	Monica	FIC, NIH, Bethesda, MD, USA	DCC, QA/QC lead, microbiology, epidemiology
Miller	Mark	FIC, NIH, Bethesda, MD, USA	PI
Mohale	Archana	FIC, NIH, Bethesda, MD, USA	DCC, data management
Nayyar	Gaurvika	FIC, NIH, Bethesda, MD, USA	DCC, data management
Psaki	Stephanie	FIC, NIH, Bethesda, MD, USA	DCC, SES
Rasmussen	Zeba	FIC, NIH, Bethesda, MD, USA	DCC, cognitive development, epidemiology
Richard	Stephanie	FIC, NIH, Bethesda, MD, USA	DCC, surveillance, epidemiology

continued.

Last Name	First Name	Institution	Role in the MAL-ED Network
Seidman	Jessica	FIC, NIH, Bethesda, MD, USA	DCC program manager, gut function, cognitive development, vaccine response
Wang	Vivian	FIC, NIH, Bethesda, MD, USA	DCC, data management
Blank	Rebecca	FNIH, Bethesda, MD, USA	Scientific program manager
Gottlieb	Michael	FNIH, Bethesda, MD, USA	PI
Tountas	Karen	FNIH, Bethesda, MD, USA	Scientific program manager
Amour	Caroline	Haydom Lutheran Hospital, Haydom, Tanzania	Laboratory
Mduma	Estomih	Haydom Lutheran Hospital, Haydom, Tanzania	Tanzania site co-PI, field site manager
Ahmed	Tahmeed	ICDDR-B, Dhaka, Bangladesh	Bangladesh site PI, nutrition
Ahmed	A. M. Shamsir	ICDDR-B, Dhaka, Bangladesh	Field supervisor
Dinesh	Mondol	ICDDR-B, Dhaka, Bangladesh	Microbiology supervisor
Tofail	Fahmida	ICDDR-B, Dhaka, Bangladesh	Cognitive development
Haque	Rashidul	ICDDR-B, Dhaka, Bangladesh	Bangladesh site co-PI
Hossain	Iqbal	ICDDR-B, Dhaka, Bangladesh	Coordinator, case control
Islam	Munirul	ICDDR-B, Dhaka, Bangladesh	Nutrition
Mahfuz	Mustafa	ICDDR-B, Dhaka, Bangladesh	Field supervisor
Chandyo	Ram Krishna	IOM, Tribuhvan University, Kathmandu, Nepal	Field manager, nutrition
Shrestha	Prakash Sunder	IOM, Tribuhvan University, Kathmandu, Nepal	Nepal site co-PI
Shrestha	Rita	IOM, Tribuhvan University, Kathmandu, Nepal	Psychologist
Ulak	Manjeswori	IOM, Tribuhvan University, Kathmandu, Nepal	Clinical supervisor
Black	Robert	JHU, Baltimore, MD, USA	Epidemiology
Caulfield	Laura	JHU, Baltimore, MD, USA	JHU site PI, nutrition
Checkley	William	JHU, Baltimore, MD, USA	DCC, epidemiology, statistician
Chen	Ping	JHU, Baltimore, MD, USA	Data management
Kosek	Margaret	JHU, Baltimore, MD, USA	Peru site PI, gut function
Lee	Gwenyth	JHU, Baltimore, MD, USA	Nutrition, gut function
Yori	Pablo Peñataro	JHU, Baltimore, MD, USA	Data management
Murray-Kolb	Laura	Pennsylvania State University, University Park, PA, USA	Lead, cognitive development
Schaefer	Barbara	Pennsylvania State University, University Park, PA, USA	DCC, cognitive development, psychometrics
Pendergast	Laura	Temple University, Philadelphia, PA, USA	DCC, cognitive development, psychometrics
Abreu	Claudia	Universidade Federal do Ceará, Fortaleza, Brazil	Study coordinator
Bindá	Alexandre	Universidade Federal do Ceará, Fortaleza, Brazil	Laboratory
Costa	Hilda	Universidade Federal do Ceará, Fortaleza, Brazil	Psychologist
Di Moura	Alessandra	Universidade Federal do Ceará, Fortaleza, Brazil	Nurse study coordinator
Filho	Jose Quirino	Universidade Federal do Ceará, Fortaleza, Brazil	DCC, data management
Leite	Álvaro	Universidade Federal do Ceará, Fortaleza, Brazil	Pediatrician
Lima	Aldo	Universidade Federal do Ceará, Fortaleza, Brazil	Brazil site PI
Lima	Noelia	Universidade Federal do Ceará, Fortaleza, Brazil	Pediatrician
Lima	Ila	Universidade Federal do Ceará, Fortaleza, Brazil	Laboratory
Maciel	Bruna	Universidade Federal do Ceará, Fortaleza, Brazil	Nutrition
Moraes	Milena	Universidade Federal do Ceará, Fortaleza, Brazil	Nutrition
Mota	Francisco	Universidade Federal do Ceará, Fortaleza, Brazil	Pediatrician
Oria	Reinaldo	Universidade Federal do Ceará, Fortaleza, Brazil	Brazil site co-PI
Quetz	Josiane	Universidade Federal do Ceará, Fortaleza, Brazil	Laboratory
Soares	Alberto	Universidade Federal do Ceará, Fortaleza, Brazil	Data management
Svensen	Erling	University of Bergen, Norway; Haydom Lutheran Hospital, Haydom, Tanzania	Tanzania site PI, cognitive development
Tor	Strand	University of Bergen, Norway	Consultant, nutrition
Patil	Crystal	University of Illinois, Urbana-Champaign, IL, USA	Nutrition

continued.

Last Name	First Name	Institution	Role in the MAL-ED Network
Bessong	Pascal	University of Venda, Thohoyandou, South Africa	South Africa site PI
Mahopo	Cloupas	University of Venda, Thohoyandou, South Africa	Nutrition
Mapula	Angelina	University of Venda, Thohoyandou, South Africa	Psychology supervisor, cognitive development
Nesamvuni	Cebisa	University of Venda, Thohoyandou, South Africa	Nutrition
Nyathi	Emanuel	University of Venda, Thohoyandou, South Africa	Data management
Samie	Amidou	University of Venda, Thohoyandou, South Africa	Laboratory supervisor
Barrett	Leah	UVA, Charlottesville, VA, USA	Study coordinator
Gratz	Jean	UVA, Charlottesville, VA, USA	Laboratory, Tanzania site
Guerrant	Richard	UVA, Charlottesville, VA, USA	UVA PI, surveillance, cognitive development
Houpt	Eric	UVA, Charlottesville, VA, USA	Microbiology, Tanzania site development
Olmsted	Liz	UVA, Charlottesville, VA, USA	Financial manager
Petri	William	UVA, Charlottesville, VA, USA	UVA co-PI, vaccine response
Platts-Mills	James	UVA, Charlottesville, VA, USA	DCC, microbiology
Scharf	Rebecca	UVA, Charlottesville, VA, USA	Cognitive development
Shrestha	Binob	Walter Reed/AFRIMS Research Unit, Kathmandu, Nepal	Data management
Shrestha	Sanjaya Kumar	Walter Reed/AFRIMS Research Unit, Kathmandu, Nepal	Nepal site co-PI, gut function

Abbreviations: AFRIMS, Armed Forces Research Institute of Medical Sciences; DCC, Data Coordinating Center; FIC, Fogarty International Center; FNIH, Foundation for the National Institutes of Health; ICDDR,B, International Centre for Diarrhoeal Disease Research, Bangladesh; IL, Illinois; IOM, Institute of Medicine; JHU, Johns Hopkins University; MD, Maryland; NC, North Carolina; NIH, National Institutes of Health; PA, Pennsylvania; PI, principal investigator; SES, socioeconomic status; USA, United States of America; UVA, University of Virginia; VA, Virginia.

Pathogen-specific burdens of community diarrhoea in developing countries: a multisite birth cohort study (MAL-ED)

James A Platts-Mills, Sudhir Babji, Ladaporn Bodhidatta*, Jean Gratz*, Rashidul Haque*, Alexandre Havt*, Benjamin J J McCormick*, Monica McGrath*, Maribel Paredes Olortegui*, Amidou Samie*, Sadia Shakoor*, Dinesh Mondal, Ila F N Lima, Dinesh Hariraju, Bishnu B Rayamajhi, Shahida Qureshi, Furqan Kabir, Pablo P Yori, Brenda Mufamadi, Caroline Amour, J Daniel Carreon, Stephanie A Richard, Dennis Lang, Pascal Bessong, Esto Mduma, Tahmeed Ahmed, Aldo A A M Lima, Carl J Mason, Anita K M Zaidi, Zulfiqar A Bhutta, Margaret Kosek, Richard L Guerrant, Michael Gottlieb, Mark Miller, Gagandeep Kang, Eric R Houpt, and The MAL-ED Network Investigators†*

Summary

Background Most studies of the causes of diarrhoea in low-income and middle-income countries have looked at severe disease in people presenting for care, and there are few estimates of pathogen-specific diarrhoea burdens in the community.

Methods We undertook a birth cohort study with not only intensive community surveillance for diarrhoea but also routine collection of non-diarrhoeal stools from eight sites in South America, Africa, and Asia. We enrolled children within 17 days of birth, and diarrhoeal episodes (defined as maternal report of three or more loose stools in 24 h, or one loose stool with visible blood) were identified through twice-weekly home visits by fieldworkers over a follow-up period of 24 months. Non-diarrhoeal stool specimens were also collected for surveillance for months 1–12, 15, 18, 21, and 24. Stools were analysed for a broad range of enteropathogens using culture, enzyme immunoassay, and PCR. We used the adjusted attributable fraction (AF) to estimate pathogen-specific burdens of diarrhoea.

Findings Between Nov 26, 2009, and Feb 25, 2014, we tested 7318 diarrhoeal and 24 310 non-diarrhoeal stools collected from 2145 children aged 0–24 months. Pathogen detection was common in non-diarrhoeal stools but was higher with diarrhoea. Norovirus GII (AF 5·2%, 95% CI 3·0–7·1), rotavirus (4·8%, 4·5–5·0), *Campylobacter* spp (3·5%, 0·4–6·3), astrovirus (2·7%, 2·2–3·1), and *Cryptosporidium* spp (2·0%, 1·3–2·6) exhibited the highest attributable burdens of diarrhoea in the first year of life. The major pathogens associated with diarrhoea in the second year of life were *Campylobacter* spp (7·9%, 3·1–12·1), norovirus GII (5·4%, 2·1–7·8), rotavirus (4·9%, 4·4–5·2), astrovirus (4·2%, 3·5–4·7), and *Shigella* spp (4·0%, 3·6–4·3). Rotavirus had the highest AF for sites without rotavirus vaccination and the fifth highest AF for sites with the vaccination. There was substantial variation in pathogens according to geography, diarrhoea severity, and season. Bloody diarrhoea was primarily associated with *Campylobacter* spp and *Shigella* spp, fever and vomiting with rotavirus, and vomiting with norovirus GII.

Interpretation There was substantial heterogeneity in pathogen-specific burdens of diarrhoea, with important determinants including age, geography, season, rotavirus vaccine usage, and symptoms. These findings suggest that although single-pathogen strategies have an important role in the reduction of the burden of severe diarrhoeal disease, the effect of such interventions on total diarrhoeal incidence at the community level might be limited.

Funding Bill & Melinda Gates Foundation.

Introduction

Infectious diarrhoea is the second most common cause of death in children under 5 years old in developing countries.[1] Studies of the causes of diarrhoea in these settings have usually focused on children who present to health centres and, therefore, best describe pathogens associated with severe diarrhoea.[2,3] However this approach captures only a small subset of diarrhoeal episodes which might show a different hierarchy of pathogens from that associated with mild or moderate episodes of diarrhoea.

Non-severe episodes in the community are of substantial public health importance because of their high prevalence and association with poor growth, impaired cognitive development, environmental enteropathy, and even mortality.[3–8] Estimates of the pathogen-specific burdens of diarrhoea at the community level are, therefore, needed to prioritise interventions. Further, surveillance in the community allows for unbiased estimates of the associations between pathogens and distinct clinical syndromes.

The Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development Project (MAL-ED) is a multisite birth cohort study at eight sites in South America, sub-Saharan Africa, and Asia.[9] We aimed to estimate pathogen-specific burdens of diarrhoea in children aged 0–24 months at these MAL-ED study sites.

Lancet Glob Health 2015; 3: e564–75

Published Online July 20, 2015 http://dx.doi.org/10.1016/S2214-109X(15)00151-5

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*These authors contributed equally to this work

†Listed at end of paper

Division of Infectious Diseases and International Health, University of Virginia, Charlottesville, VA, USA (J A Platts-Mills MD, J Gratz BSc, R L Guerrant MD, E R Houpt MD); **Clinical Research Unit and Institute of Biomedicine, Federal University of Ceara, Fortaleza, Brazil** (A Havt PhD, Ila F N Lima PhD, A M Lima MD); **International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh** (T Ahmed MBBS, D Mondal MD, R Haque MD); **Christian Medical College, Vellore, India** (S Babji MD, D Hariraju MSc, G Kang MD); **Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand** (B Rayamajhi BSc, L Bodhidatta MD, C J Mason MD); **Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA** (P P Yori MPH, M Kosek MD); **Asociación Benéfica PRISMA, Iquitos, Peru** (M P Olortegui BSc, P P Yori MPH, M Kosek MD); **Aga Khan University, Karachi, Pakistan** (S Shakoor MBBS, S Qureshi MSc, F Kabir MSc, A Zaidi MBBS, Zulfiqar Bhutta PhD); **University of Venda, Thohoyandou, South Africa** (A Samie PhD, B Mufamadi BTech, P Bessong PhD); **Haydom Lutheran Hospital, Haydom, Tanzania** (C Amour MSc, J Gratz BSc, E Mduma MPH); **Foundation for the National**

Institutes of Health, Bethesda, MD, USA (D Lang PhD, M Gottlieb PhD); **Fogarty International Center, National Institutes of Health, Bethesda, MD, USA** (B J J McCormick DPhil, M McGrath ScD, J D Carreon MS, S Richard PhD, M Miller MD)

Correspondence to: Dr Eric R Houpt, Division of Infectious Diseases and International Health, University of Virginia, Charlottesville, VA 22908, USA
erh6k@virginia.edu

Research in context

Evidence before this study

We searched PubMed for articles published in any language since 1990 using the terms "diarrhea/diarrhoea" and "etiology/aetiology" and "pediatric/paediatric OR infant*" and "case-control study OR cohort study." We identified 482 publications, including 11 aetiologic studies of diarrhoea which included testing for a broad range of enteropathogens. Of those, eight studied children with more severe diarrhoea presenting to health-care settings. The three remaining studies of community diarrhoea involved a single site.

Added value of this study

Our study provides multisite data on the causes of diarrhoea with longitudinal surveillance and interrogation of a broad range of pathogens, allowing unbiased estimates of pathogen-specific burdens of diarrhoea in the community as well as estimates for specific diarrhoeal syndromes. It documents the broad range of pathogens associated with diarrhoea of any severity, the heterogeneity of the main causes of diarrhoea in low-income and middle-income countries, and the diversity of pathogens associated with seasonal peaks. It also documents the effect of rotavirus vaccine.

Implications of all available evidence

These data suggest that the causes of community diarrhoea are diverse, and single pathogen interventions might not have a substantial impact on total diarrhoeal incidence across multiple populations.

Methods

Study design and participants

A detailed description of the MAL-ED study design is available elsewhere.[9] We enrolled children from the community within 17 days of birth at eight study locations: Dhaka, Bangladesh; Fortaleza, Brazil; Vellore, India; Bhaktapur, Nepal; Loreto, Peru; Naushero Feroze, Pakistan; Venda, South Africa; and Haydom, Tanzania.[10–17]

Inclusion criteria included: a mother aged 16 years or older; intention for the family to stay in the study area for at least 6 months from enrolment; that the child was from a singleton pregnancy and had no other siblings enroled in the study; and birthweight or enrolment weight greater than 1500g. We excluded children with diagnosed congenital disease or severe neontal disease in the newborn.

Enrolment took place between November, 2009, and February, 2012. We aimed to enrol at least 200 children at every site, and we staggered enrolment to capture approximately equal number of births in each calendar month. Follow-up was for 24 months. Length, weight, and head circumference were measured every month, as described previously.[18]

All sites received ethics approval from their respective governmental, local institutional, and collaborating institutional ethics review boards. Written informed consent was obtained from the parent or guardian of every child.

Sample and data collection

Non-diarrhoeal stool specimens were collected for surveillance for months 1–12, 15, 18, 21, and 24. Diarrhoeal episodes were collected from age 0–23 months and were identified at home visits made by fieldworkers twice a week. They were defined as maternal report of three or more loose stools in 24 h, or one loose stool with visible blood.[19] Discrete episodes had at least 2 intervening days without diarrhoea. Diarrhoeal stool specimens had to be collected within 48 h of an episode. When a stool sample was collected between two episodes of diarrhoea that met criteria for collection, we assigned the sample to the episode closest to the time of collection.

A diarrhoea severity score was calculated for every episode using elements derived from the Vesikari score (table 1).[20]

Dehydration was defined as irritability that was difficult to console, increased thirst, loss of skin turgor, sunken eyes, or lethargy.[21] Dysentery was defined as diarrhoea in which visible blood was reported by the child's mother. Diarrhoea associated with fever was defined as diarrhoea with fieldworker-confirmed temperature greater than 37·5°C, and vomiting-associated diarrhoea required vomiting at any point during the episode of diarrhoea.

Diarrhoeal episodes of fewer than 7 days' duration were classified as acute, 7–14 days as prolonged, and more than 14 days as persistent. Stools collected within 1 day of administration of a lactulose-mannitol test were excluded from analysis.[22] Data on rotavirus vaccine administration and antibiotic use were recorded and children were referred to medical care for severe symptoms.[23,24]

Stool testing

All stools were analysed in accordance with a standardised microbiology protocol, which was implemented at all

	1 point	2 points	3 points
Duration	2–4 days	5–7 days	≥8 days
Maximum number of loose stools in 24 h	<5 loose stools	5–7 loose stools	>7 loose stools
Days of vomiting	1 day	2 days	>2 days
Presence of dehydration	..	Some dehydration	Severe dehydration
Fever	Maternal report of fever	..	Temperature >37·5°C confirmed by field worker

Elements derived from the Vesikari score[20]

Table 1: **Scoring system for diarrhoea severity score**

	Children enrolled	Diarrhoea episodes reported	Diarrhoea episode stools collected	Diarrhoeal stools completely tested	Surveillance stools collected	Surveillance stools completely tested	Completely tested diarrhoeal stool samples for specific syndromes							
							Acute (<7 days)	Prolonged (≥7 days)	Mild (score 1–3)	Moderate (score 4–6)	Severe (score >6)	Blood in stool	Associated fever	Associated vomiting
Dhaka, Bangladesh	265	1684	1591	1526 (95·9%)	2937	2910 (99·1%)	1350 (88·5%)	176 (11·5%)	753 (49·3%)	574 (37·6%)	199 (13·0%)	64 (4·2%)	48 (3·2%)	477 (31·3%)
Vellore, India	251	982	749	698 (93·2%)	3215	3181 (98·9%)	611 (87·5%)	87 (12·5%)	406 (58·2%)	218 (31·2%)	74 (10·6%)	49 (7·0%)	13 (1·9%)	164 (23·5%)
Bhaktapur, Nepal	240	1083	976	925 (94·8%)	3105	3071 (98·9%)	684 (74·0%)	241 (26·1%)	266 (28·8%)	525 (56·8%)	134 (14·5%)	43 (4·7%)	58 (6·3%)	179 (19·4%)
Naushero Feroze, Pakistan	277	3255	2272	1836 (80·8%)	2820	2777 (98·5%)	1182 (64·4%)	654 (35·6%)	498 (27·1%)	770 (41·9%)	568 (30·9%)	60 (3·3%)	91 (5·0%)	641 (34·9%)
Venda, South Africa	314	324	200	157 (78·5%)	3720	3617 (97·2%)	149 (94·9%)	8 (5·1%)	122 (77·7%)	32 (20·4%)	3 (1·9%)	4 (2·6%)	4 (2·6%)	28 (17·8%)
Haydom, Tanzania	262	625	206	171 (83·0%)	3295	3252 (98·7%)	158 (92·4%)	13 (7·6%)	95 (55·6%)	63 (36·8%)	13 (7·6%)	27 (15·8%)	0	63 (36·8%)
Fortaleza, Brazil	233	188	129	117 (90·7%)	2519	2425 (96·3%)	99 (84·6%)	18 (15·4%)	73 (62·4%)	34 (29·1%)	10 (8·6%)	2 (1·7%)	12 (10·3%)	34 (29·1%)
Loreto, Peru	303	2131	2047	1888 (92·2%)	3185	3077 (96·6%)	1584 (83·9%)	304 (16·1%)	1038 (55·0%)	650 (34·4%)	200 (10·6%)	108 (5·7%)	120 (6·4%)	347 (18·4%)
Total	2145	10272	8170	7318 (89·6%)	24796	24310 (98·0%)	5817 (79·5%)	1501 (20·5%)	3251 (44·4%)	2866 (39·1%)	1201 (16·4%)	357 (4·9%)	346 (4·7%)	1933 (26·4%)

Table 2: **MAL-ED cohort descriptive statistics and completeness of surveillance and testing**

study sites and has been described in detail previously.[25] We used conventional stool culture to identify bacterial pathogens with the exception of *Campylobacter* spp.

Testing for diarrhoeagenic *Escherichia coli* was done by pooling five lactose-fermenting colonies for multiplex PCR to detect the toxin-encoding genes *stx1*, *stx2*, *eae*, *bfpA*, *ipaH*, *aatA*, and *aaiC*, as well as those encoding heat-labile enterotoxin (LT) and heat-stable enterotoxin (ST).

Enzyme immunoassay was used for detection of *Campylobacter* spp, rotavirus, adenovirus, and astrovirus (ProSpecT, Remel, Lenexa, KS, USA) and *Entamoeba histolytica*, *Giardia* spp, and *Cryptosporidium* spp (TechLab, Blacksburg, VA, USA). Rotavirus detections were considered negative if obtained within 28 days of rotavirus vaccine administration (n=18).

We used PCR to test all diarrhoeal stool samples for norovirus. We also aimed to test all non-diarrhoeal stool samples from a randomly selected 10% subset of participants at each site.

If an additional specimen was available, we did use microscopy for identification of protozoa and helminths; however, microscopy was not required for complete testing, and microscopy results were not included for the analysis of infections for the three protozoal pathogens tested by enzyme immunoassay. If testing was incomplete, recollection was allowed within 48 h.

Statistical analysis

Because pathogens were frequently detected in diarrhoeal and non-diarrhoeal stools, we used the adjusted attributable fraction (AF) to estimate pathogen-specific

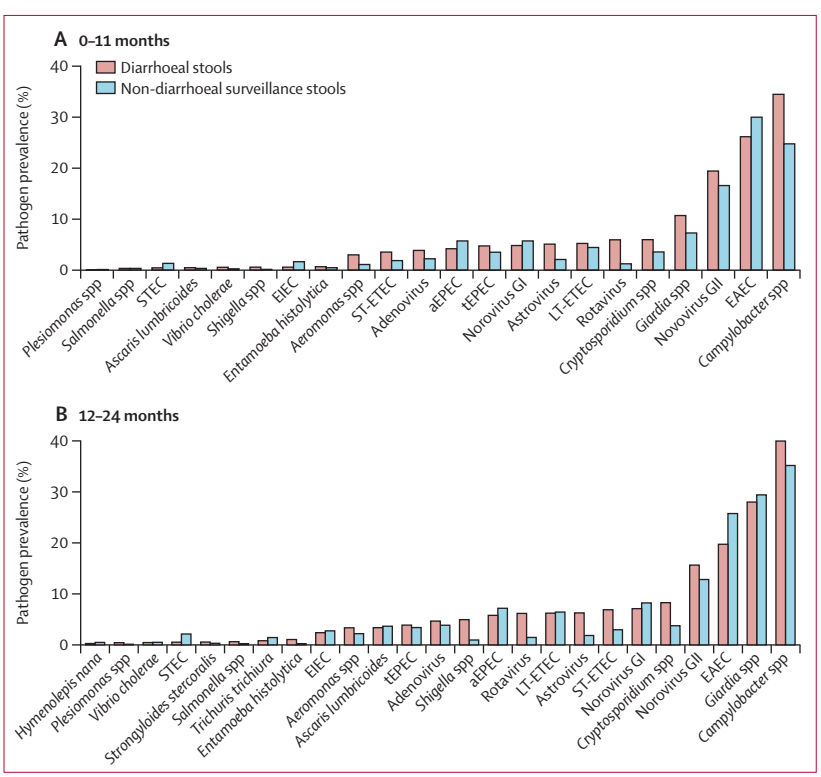

Figure 1: **Pathogens detected in diarrhoeal and non-diarrhoeal stools, 0–11 months and 12–24 months**
EAEC=enteroaggregative *Escherichia coli*; EIEC=enteroinvasive *E coli*; aEPEC=atypical enteropathogenic *E coli*; tEPEC=typical enteropathogenic *E coli*; LT-ETEC=LT-producing enterotoxigenic *E coli*; ST-ETEC=ST-producing enterotoxigenic *E coli*; STEC=Shiga-toxin-producing *E coli*. Pathogens present in less than 0.1% of stool samples are not shown.

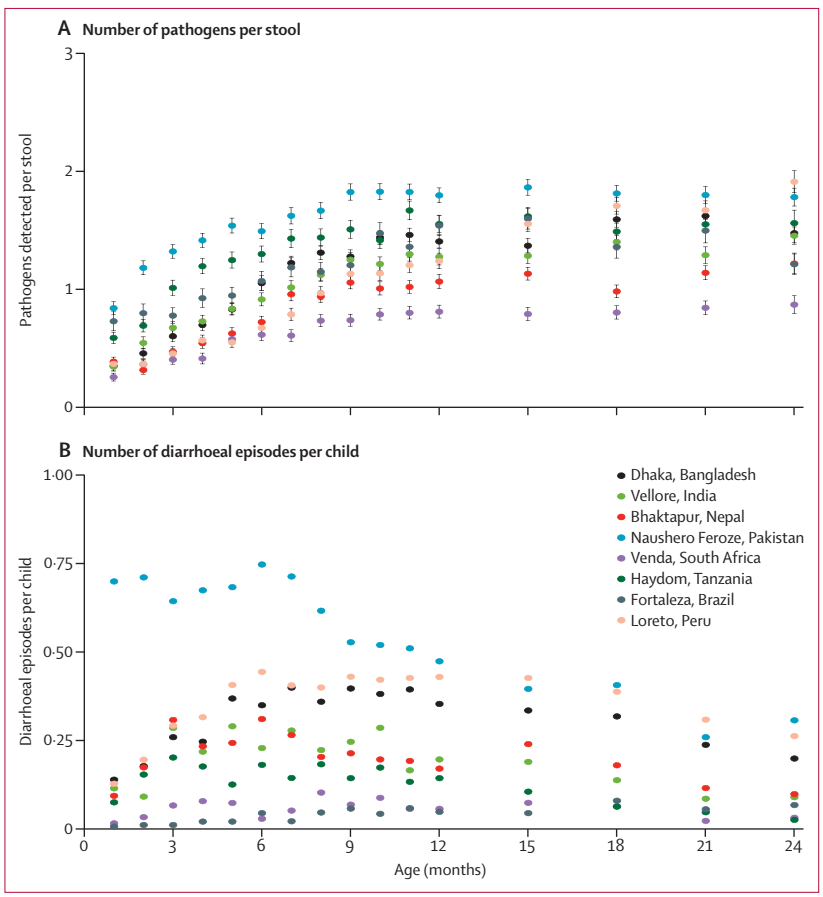

Figure 2: **Pathogen detection and diarrhoeal episodes per child, 0–24 months**
Dots show mean values with standard error bars.

burdens of diarrhoea, a measurement that incorporates the prevalence of detection in diarrhoeal stools and the strength of association with diarrhoea.

To analyse the strength of association between diarrhoea and detection of individual pathogens, we used generalised estimating equations (GEEs) to fit a binary logistic regression model for each site and age group to account for non-independence of stool testing within each participant. All models were adjusted for age (in days), sex, and site. We included all detected pathogens from diarrhoeal stools for each age and site, and we assumed an independent working correlation matrix. We then calculated AFs using the point estimate of the odds ratios derived from the multivariate GEEs[26,27] with 95% CIs estimated using the Delta method.[28]

We determined the pathogen-specific attributable incidence for each calendar month by first calculating the AF using the prevalence of each pathogen in diarrhoea for each calendar month and then multiplying by the number of episodes of diarrhoea during that month. To mitigate the detection of convalescent excretion of pathogens, we excluded from analysis non-diarrhoeal stools collected more than 48 h but fewer than 7 days before or after a diarrhoeal episode. The effect of prolonged excretion of enteric pathogens on AF estimates was evaluated by further restricting non-diarrhoeal specimens to those collected at least 28 days before and after any diarrhoeal episode. Pathogen-specific AFs were calculated for the subset of diarrhoeal episodes that met study definitions of acute, prolonged, persistent, mild, moderate, severe, or dysenteric diarrhoea, or diarrhoea associated with fever or with vomiting.

	Dhaka, Bangladesh	Vellore, India	Bhaktapur, Nepal	Naushero Feroze, Pakistan	Venda, South Africa*	Haydom, Tanzania	Fortaleza, Brazil*	Loreto, Peru*	Overall
Age 0–11 months									
Diarrhoeal stools	819	419	524	1230	84	145	38	1021	4280
Non-diarrhoeal stools	2194	2252	2264	1902	2665	2391	1747	2354	17769
Norovirus GII	..	..	8·4% (5·7–9·7)	..	..	8·2% (0·5–12·9)	..	5·1% (0·2–9·1)	5·2% (3·0–7·1)
Rotavirus	9·6% (8·8–10·1)	6·0% (5·5–6·3)	6·6% (5·9–6·9)	3·2% (2·6–3·5)	..	9·5% (7·6–10·5)	..	1·0% (0·0–1·6)	4·8% (4·5–5·0)
Campylobacter spp	..	..	..	..	16·9% (9·0–21·6)	..	30·9% (22·8–34·3)	5·6% (0·7–9·5)	3·5% (0·4–6·3)
Astrovirus	2·0% (0·3–3·2)	4·2% (3·2–4·9)	..	2·2% (0·9–3·1)	..	..	..	3·6% (2·7–4·3)	2·7% (2·2–3·1)
Cryptosporidium spp	..	..	..	3·6% (1·9–4·8)	..	6·3% (1·2–9·1)	5·5% (0·0–7·2)	2·6% (0·6–4·1)	2·0% (1·3–2·6)
ST–ETEC	4·7% (3·3–5·8)	1·7% (0·6–2·3)	2·0% (1·0–2·5)	1·2% (0·1–1·8)	3·3% (0·9–4·2)	..	..	..	1·9% (1·5–2·2)
Adenovirus	..	2·7% (0·9–3·7)	2·3% (0·7–3·2)	1·1% (0·0–1·9)	..	..	..	1·5% (0·2–2·3)	1·6% (1·0–2·0)
tEPEC	2·2% (0·0–4·1)	..	..	..	..	..	..	..	1·3% (0·7–1·9)
LT–ETEC	2·0% (0·2–3·3)	..	..	..	..	..	16·9% (11·1–19·3)	..	1·3% (0·6–1·9)

(Table 3 continues on next page)

	Dhaka, Bangladesh	Vellore, India	Bhaktapur, Nepal	Naushero Feroze, Pakistan	Venda, South Africa*	Haydom, Tanzania	Fortaleza, Brazil*	Loreto, Peru*	Overall
(Continued from previous page)									
Shigella spp	..	..	0·7% (0·3–0·7)	0·9% (0·6–1·1)	..	..	..	..	0·4% (0·2–0·5)
Age 12–24 months									
Diarrhoeal stools	707	279	401	606	73	26	79	867	3038
Non-diarrhoeal stools	716	929	807	875	952	861	678	723	6541
Campylobacter spp	..	..	8·8% (2·0–13·8)	..	..	..	..	9·9% (3·0–15·5)	7·9% (3·1–12·1)
Norovirus GII	..	..	11·2% (6·4–11·9)	..	19·2% (2·2–26·3)	..	..	11·7% (6·0–15·2)	5·4% (2·1–7·8)
Rotavirus	6·0% (4·8–6·6)	4·8% (4·0–5·2)	8·7% (8·7–8·7)	2·2% (0·7–2·9)	..	14·3% (11·5–15·1)	4·3% (1·7–4·9)	2·9% (0·8–4·2)	4·9% (4·4–5·2)
Astrovirus	2·6% (0·7–3·7)	3·1% (1·7–3·7)	4·6% (3·2–5·3)	..	..	9·7% (1·8–11·2)	4·7% (3·2–5·0)	7·4% (5·5–8·6)	4·2% (3·5–4·7)
Shigella spp	1·5% (0·3–2·0)	9·4% (8·7–9·8)	6·8% (5·8–7·4)	5·1% (3·8–5·9)	..	..	3·7% (2·1–3·8)	2·1% (0·8–2·7)	4·0% (3·6–4·3)
ST–ETEC	8·0% (5·6–9·7)	5·4% (3·6–6·3)	4·6% (2·2–5·9)	..	..	9·1% (2·7–10·9)	..	2·0% (0·5–2·7)	3·9% (3·1–4·5)
Cryptosporidium spp	2·5% (0·0–4·0)	6·9% (5·3–7·7)	3·2% (1·4–4·1)	5·5% (3·5–6·8)	..	13·0% (6·9–14·7)	..	..	3·8% (2·8–4·7)
LT–ETEC	2·4% (0·1–3·8)	..	..	..	..	16·1% (0·0–22·8)	..	..	1·2% (0·0–2·1)
Adenovirus	..	3·6% (0·9–5·0)	3·9% (2·1–4·8)	..	..	..	3·8% (1·1–4·7)	..	0·9% (0·0–1·8)
EIEC	..	..	1·2% (0·0–1·6)	..	..	..	..	..	0·8% (0·1–1·2)
Entamoeba histolytica	..	0·7% (0·7–0·7)	..	0·8% (0·2–1·1)	..	..	..	..	0·7% (0·3–0·9)
Salmonella	..	0·7% (0·7–0·7)	0·5% (0·5–0·5)	..	..	..	..	0·5% (0·5–0·5)	0·3% (0·0–0·5)
Norovirus GI	..	..	1·0% (1·0–1·0)	..	..	..	..	..	..
Aeromonas	..	..	..	..	..	..	..	1·0% (0·1–1·2)	..
Plesiomonas	..	0·7% (0·7–0·7)	..	..	..	..	..	..	..
STEC	..	..	..	..	..	..	..	0·2% (0·2–0·2)	..

EIEC=enteroinvasive *Escherichia coli*; tEPEC=typical enteropathogenic *E coli*; LT-ETEC=LT-producing enterotoxigenic *E coli*; ST-ETEC=ST-producing enterotoxigenic *E coli*; STEC=Shiga-toxin producing *E coli*. Data are n or attributable fractions (95% CI). For cells with ··, the pathogen was either not detected or was not statistically significantly associated with diarrhoea (appendix). *Monovalent rotavirus vaccine was introduced to the national immunisation programme at these sites before the study began.

***Table 3*: Adjusted attributable fraction of diarrhoea for individual pathogens in the first and second year of life**

To analyse the association between pathogen detection and diarrhoea severity, GEEs were used to fit an ordinal regression model which was specified identically to the logistic regression models used for the analysis of diarrhoea association. For all analyses, we constructed models both with and without norovirus because of the differential testing of non-diarrhoeal specimens for this pathogen. The results we report for pathogens other than norovirus, as well as for all analyses involving aggregated pathogen testing, were derived from models that excluded norovirus. We used R version 3.0.3 (Foundation for Statistical Computing, Vienna, Austria) for all statistical analyses, with the geepack package within this program used for GEE analysis.[29]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Nov 3, 2009, and Febm29, 2012, we enrolled 2145 children (range 233–314 per site). The size of the

See Online for appendix

cohort at each site and completeness of stool testing is shown in table 2. We recorded 2 years of follow-up data for 1740 participants (81·1%).

Two fieldworker visits per week were sufficient to collect most diarrhoeal stools within 48 h (79·5% overall; site range 33·0–96·1%). Collection rates were higher for longer episodes (75·5% for acute episodes and 99·3% for prolonged or persistent episodes).

A broad range of pathogens was detected, with 22 pathogens in the first year of life and 25 in the second year of life (we have not included pathogens in analysis if they were present in only very few samples—ie, less than 0·1% of all stools). For certain pathogens, detection in non-diarrhoeal stools approached, and in some cases exceeded, that noted for diarrhoeal stools (figure 1).

Enteropathogen infection began soon after birth and was common at all sites; however, the intensity varied between sites, ranging from an average of about 0·5 pathogens detected per stool by the end of the first year of life (South Africa) to almost two pathogens per stool (Pakistan; figure 2). Both the incidence of diarrhoea and the number of pathogens detected per stool increased markedly during the first year of life. At least one pathogen was detected in 76·9% (n= 15767) of diarrhoeal stools and 64·9% (15767) of non-diarrhoeal stools, and two or more pathogens were identified in 41·0% (2999) and 29·0% (7046) of stools, respectively. The number of pathogens detected was higher in diarrhoeal stools than non-diarrhoeal stools at most time points (appendix).

The presence of pathogens was associated with diarrhoea, in that each additional pathogen increased the odds of diarrhoea (odds ratio (OR) 1·20 per pathogen detection, p<0·0001]). Antibiotics were administered for 4696 (46%) diarrhoeal episodes captured by surveillance with a range between sites of 20 (11%, Brazil) to 1922 (59%, Pakistan).

Overall, 19·1%, (95% CI 16·2–21·8) and 33·1% (29·0–36·7) of diarrhoeal episodes in the first and second year of life, respectively, could be attributed to pathogens. Attributable fractions did not change appreciably when the more restrictive definition of non-diarrhoeal specimens was applied, suggesting that estimates were not biased by convalescent excretion (appendix), nor did they change after controlling for child nutritional status (height-for-age *Z* score).

Across all sites and episodes, the highest AFs were seen for norovirus GII, rotavirus, *Campylobacter* spp, astrovirus, and *Cryptosporidium* spp in the first year of life and *Campylobacter* spp, norovirus GII, rotavirus, astrovirus, and *Shigella* spp in the second year of life (table 3 and appendix).

There was substantial heterogeneity between sites in the individual pathogen most often associated with diarrhoea, with the highest burden of diarrhoea attributed to four unique pathogens in the first year of life (*Campylobacter* spp, *Cryptosporidium* spp, norovirus GII,

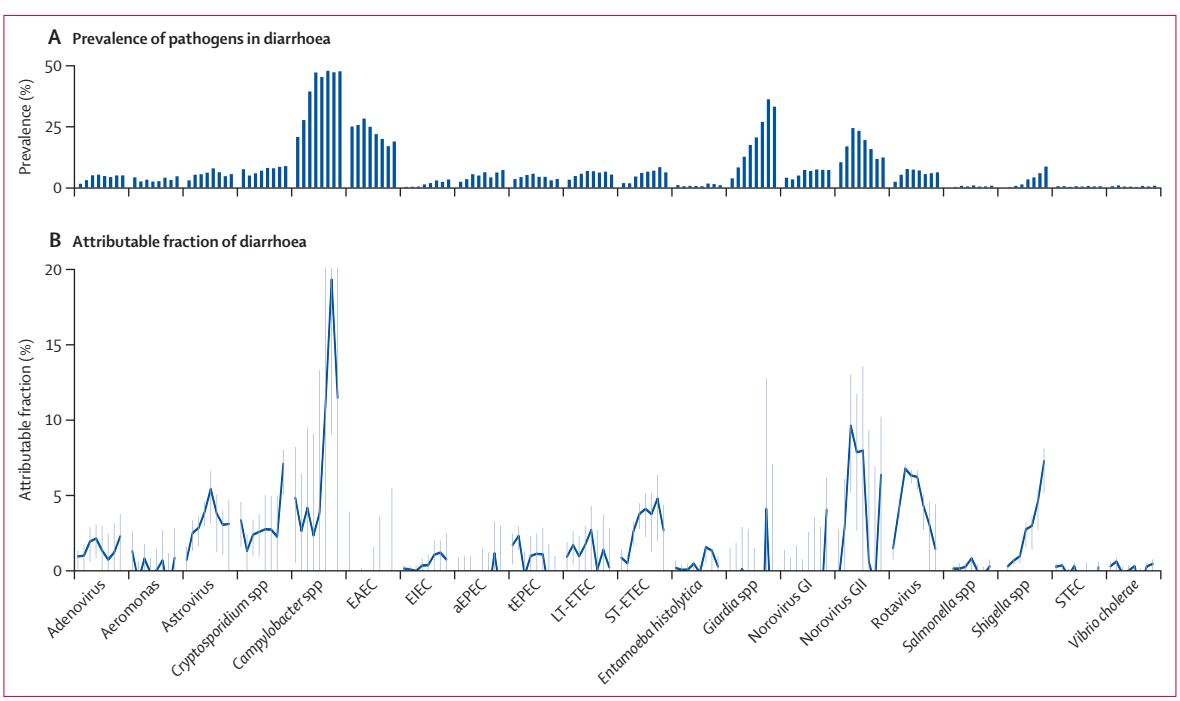

Figure 3: **Prevalence and adjusted attributable fraction of diarrhoea for 3-month intervals, age 0–24 months**
EAEC=enteroaggregative *Escherichia coli*; EIEC=enteroinvasive *E coli*; aEPEC=atypical enteropathogenic *E coli*; tEPEC=typical enteropathogenic *E coli*; LT-ETEC=LT-producing enterotoxigenic *E coli*; ST-ETEC=ST-producing enterotoxigenic *E coli*; STEC=Shiga-toxin producing *E coli*. Data are attributable fractions (95% CI). For each organism, the first data point represents age 0–2 months, the second represents age 3-5 months, then 6–8 months, 9–11 months, 12–14 months, 15-17 months, 18–20 months, and 21–24 months.

and rotavirus) and six across the eight sites in the second year of life (astrovirus, *Cryptosporidium* spp, LT-producing enterotoxigenic *E coli*, norovirus GII, *Shigella* spp, and ST-producing enterotoxigenic *E coli*; table 3) . The monovalent rotavirus vaccine was introduced in three participating countries (South Africa, Brazil, and Peru) before the study began, with 89·4% of enrolled children receiving at least one dose at those sites. The effect of rotavirus vaccine was evident, in that rotavirus had the highest overall AF at sites without rotavirus vaccination (AF 5·8%, 95% CI 5·6–6·0) and the fifth highest overall AF at sites with rotavirus vaccination (1·9%, 1·0–2·6).

Three frequently detected pathogens, namely enteroaggregative *E coli*, *Giardia* spp, and atypical enteropathogenic *E coli*, were not statistically significantly associated with diarrhoea for any age group, site, or diarrhoeal syndrome. Age-related patterns were seen for several pathogens: astrovirus, norovirus GII, and rotavirus diarrhoea burdens peaked during age 6–12 months, whereas *Cryptosporidium* spp, *Shigella* spp, *Campylobacter* spp, and ST-producing enterotoxigenic *E coli* continued to increase through the second year of life (figure 3). First infections were more strongly associated with diarrhoea than were subsequent infections for most pathogens; however, this did not alter AF estimates (data not shown). Helmintic infections were not associated with diarrhoea for any age group, site, or diarrhoeal syndrome.

We next examined whether clinical characteristics or seasonality could aid prediction of the cause of diarrhoea. Total attribution to pathogens for episodes associated with dysentery, dehydration, or admission to hospital was 33·4% (95% CI 27·1–38·6) and 29·1% (26·6–31·0%) in the first and second year of life, respectively, and pathogens most often associated with these events were rotavirus, *Campylobacter* spp, and norovirus GII in the first year and *Shigella* spp, rotavirus, and ST-producing enterotoxigenic *E coli* in the second year of life (appendix). *Campylobacter, Shigella* spp, and enteroinvasive *E coli* were associated with the highest burden of dysentery (table 4). Pathogens associated with fever included rotavirus and *Shigella* spp. Rotavirus and norovirus GII were the pathogens most often associated with vomiting.

Use of the diarrhoea severity score that incorporated vomiting, fever, frequency, and dehydration showed that the following were associated with a higher severity score: rotavirus (OR 2·30 per one unit increase in severity score, 95% CI 1·91–2·77; p<0·0001), *Shigella* spp (1·48, 1·13–1·93; p=0·0043), adenovirus (1·45, 1·19–1·78;

	Acute (<7 days)	Prolonged (≥7 days)	Mild (score 1–3)	Moderate (score 4–6)	Severe (score >6)	Blood in stool	Associated fever	Associated vomiting	Overall
Age 0–11 months									
Diarrhoeal stools (% of diarrhoea)	3249 (75·9%)	1031 (24·1%)	1696 (39·6%)	1762 (41·2%)	820 (19·2%)	198 (4·6%)	204 (4·8%)	1235 (28·9%)	4280
Norovirus GII	5·5% (3·1–7·5)	4·4% (0·9–7·2)	5·2% (2·5–7·6)	4·7% (2·0–7·0)	5·5% (1·8–8·5)	..	..	7·5% (4·5–10·0)	5·2% (3·0–7·1)
Rotavirus	5·6% (5·3–5·8)	2·2% (1·7–2·6)	2·0% (1·5–2·3)	5·2% (4·9–5·5)	9·8% (9·5–10·1)	..	7·2% (6·3–7·7)	11·1% (10·8–11·4)	4·8% (4·5–5·0)
Campylobacter spp	4·4% (1·1–7·3)	..	8·1% (4·3–11·4)	..	..	23·7% (14·2–30·3)	..	..	3·5% (0·4–6·3)
Astrovirus	2·9% (2·4–3·4)	1·8% (0·8–2·5)	2·7% (2·0–3·2)	2·3% (1·6–2·9)	3·4% (2·4–4·1)	..	..	3·9% (3·1–4·5)	2·7% (2·2–3·1)
Cryptosporidium spp	1·7% (0·9–2·4)	3·0% (1·8–4·0)	1·2% (0·0–2·0)	2·3% (1·3–3·1)	3·1% (1·5–4·2)	..	..	2·4% (1·1–3·4)	2·0% (1·3–2·6)
ST-ETEC	2·4% (1·9–2·7)	..	1·8% (1·2–2·3)	2·2% (1·7–2·6)	1·4% (0·5–2·0)	..	..	1·9% (1·2–2·5)	1·9% (1·5–2·2)
Adenovirus	1·4% (0·8–1·9)	2·1% (1·2–2·7)	1·0% (0·3–1·5)	1·6% (0·9–2·2)	3·2% (2·2–3·9)	..	3·0% (0·9–4·1)	3·1% (2·2–3·7)	1·6% (1·0–2·0)
tEPEC	1·2% (0·4–1·8)	1·6% (0·5–2·5)	1·4% (0·4–2·2)	..	2·2% (0·8–3·2)	..	..	1·5% (0·2–2·5)	1·3% (0·7–1·9)
LT-ETEC	0·9% (0·1–1·6)	2·6% (1·4–3·4)	1·0% (0·0–1·8)	1·1% (0·1–1·9)	2·3% (0·9–3·3)	..	..	1·8% (0·6–2·8)	1·3% (0·6–1·9)
Shigella spp	0·3% (0·1–0·4)	0·6% (0·3–0·7)	0·3% (0·1–0·4)	0·4% (0·2–0·5)	..	3·4% (3·1–3·5)	1·2% (0·5–1·4)	..	0·4% (0·2–0·5)
STEC	..	0·5% (0·0–0·7)	..	..	..	..	..	..	..
EIEC	..	..	..	..	0·8% (0·4–1·0)	1·7% (0·4–2·2)	..	..	..
Salmonella spp	..	..	..	..	0·6% (0·1–0·9)	..	1·5% (0·6–1·8)	..	..
Entamoeba histolytica	..	..	..	..	..	..	1·3% (0·0–1·7)	..	..

(Table 4 continues on next page)

	Acute (<7 days)	Prolonged (≥7 days)	Mild (score 1–3)	Moderate (score 4–6)	Severe (score >6)	Blood in stool	Associated fever	Associated vomiting	Overall
(Continued from previous page)									
Age 12–24 months									
Diarrhoeal stools (% of diarrhoea)	2568 (84·5%)	470 (15·5%)	1553 (51·1%)	1104 (36·3%)	381 (12·5%)	159 (5·2%)	142 (4·7%)	698 (23·0%)	3038
Campylobacter spp	8·9% (4·0–13·2)	..	9·7% (3·9–14·7)	8·3% (1·8–13·9)	..	..	..	..	7·9% (3·1–12·1)
Norovirus GII	5·1% (1·8–7·6)	6·9% (1·4–10·4)	4·5% (0·7–7·3)	6·2% (2·3–9·0)	6·9% (1·3–10·4)	..	..	8·9% (4·9–11·7)	5·4% (2·1–7·8)
Rotavirus	5·2% (4·7–5·6)	2·9% (1·9–3·4)	3·8% (3·2–4·3)	5·1% (4·5–5·5)	7·9% (7·2–8·4)	..	4·9% (3·4–5·7)	10·1% (9·6–10·5)	4·9% (4·4–5·2)
Astrovirus	4·5% (3·8–5·0)	2·3% (0·9–3·2)	4·1% (3·2–4·7)	4·7% (3·9–5·3)	2·8% (1·1–3·7)	..	5·4% (3·2–6·6)	4·5% (3·5–5·2)	4·2% (3·5–4·7)
Shigella spp	3·4% (3·0–3·7)	7·0% (6·4–7·4)	2·7% (2·2–3·0)	5·1% (4·6–5·5)	5·7% (5·0–6·1)	17·2% (16·5–17·6)	6·9% (6·0–7·3)	3·1% (2·4–3·4)	4·0% (3·6–4·3)
ST-ETEC	3·6% (2·8–4·3)	5·5% (4·1–6·4)	3·4% (2·5–4·2)	3·9% (2·8–4·8)	5·8% (4·4–6·8)	..	3·6% (0·6–5·0)	5·5% (4·4–6·3)	3·9% (3·1–4·5)
Cryptosporidium spp	3·4% (2·2–4·3)	6·1% (4·1–7·4)	3·0% (1·6–4·2)	4·5% (3·1–5·6)	3·2% (0·5–4·9)	..	..	3·8% (1·8–5·1)	3·8% (2·8–4·7)
LT-ETEC	1·3% (0·1–2·3)	..	..	1·5% (0·0–2·8)	..	..	5·0% (1·2–7·1)	2·2% (0·3–3·4)	1·2% (0·0–2·1)
Adenovirus	1·0% (0·2 –1·9)	..	0·8% (0·1–1·3)	1·9% (0·4–3·0)	..	..	..	1·9% (0·0–3·1)	0·9% (0·0–1·8)
EIEC	0·8% (0·1–1·3)	..	0·9% (0·5–1·1)	1·2% (0·2–1·8)	..	5·0% (3·2–5·8)	..	..	0·8% (0·1–1·2)
E histolytica	0·7% (0·3–0·9)	..	1·1% (0·7–1·3)	..	..	..	..	..	0·7% (0·3–0·9)
Salmonella	0·4% (0·1–0·5)	..	0·4% (0·1–0·5)	..	..	..	1·8% (1·1–2·0)	..	0·3% (0·0–0·5)
Aeromonas spp	..	..	..	..	..	3·3% (1·0–4·3)	..	..	..
Plesiomonas spp	..	..	..	..	..	1·2% (0·0–1·6)	..	..	..

EIEC=enteroinvasive *Escherichia coli*; tEPEC=typical enteropathogenic *E coli*; LT-ETEC=LT-producing enterotoxigenic *E coli*; ST-ETEC=ST-producing enterotoxigenic *E coli*; STEC=Shiga-toxin producing *E coli*. Data are n or attributable fractions (95% CI). The subset of pathogens assayed that were significant in at least one syndrome or age group are shown in descending order of average attributable fraction for study-defined diarrhoea. For cells with a dash, the pathogen was either not detected or was not statistically significantly associated with diarrhoea.

Table 4: **Adjusted attributable fraction of diarrhoea associated with specific diarrhoeal syndromes in the first and second year of life for individual pathogens**

p=0·0003), and *Cryptosporidium* spp (1·26, 1·07–1·49; p=0·0065). *Campylobacter* spp were associated with a lower score (0·85, 0·77–0·94; p=0·0011) .

Persistent diarrhoea represented 4·9% and 1·8% of episodes during the first and second year of life, respectively, and was associated with LT-producing enterotoxigenic *E coli*, astrovirus, *Cryptosporidium* spp, ST-producing enterotoxigenic *E coli*, and *Shigella* spp in the first year of life and *Shigella* and astrovirus in the second (data not shown).

The association between the attributable incidence of specific pathogens and seasonal diarrhoeal incidence varied between sites (figure 4). For many sites, peak diarrhoeal incidence coincided with the peak attributable incidence for some pathogens—for example *Cryptosporidium* spp, ST-producing enterotoxigenic *E coli*, *Shigella* spp, and astrovirus in India and norovirus GII, ST-producing enterotoxigenic *E coli*, and *Shigella* spp in Nepal. Rotavirus incidence was strongly seasonal, and during peak season it dominated all-cause diarrhoea incidence in India, Nepal, Pakistan, and Tanzania. There was little association between rotavirus incidence and seasonality at the three sites where rotavirus vaccine had been introduced.

Discussion

In this multicountry community-based cohort study, pathogen-specific burdens of diarrhoea varied substantially between sites. Although rotavirus diarrhoea burden was substantially decreased at sites where rotavirus vaccine had been introduced, it occupied the overall highest burden of disease at the five sites that do not have vaccination. Nevertheless, it was associated with the highest burden of diarrhoea at only three sites in the first year of life and at none in the second year. *Cryptosporidium* spp, ST-producing enterotoxigenic *E coli*, and *Shigella* spp were also associated with more severe diarrhoea than were other pathogens and are well known to be important pathogens.[2,3] Additionally, however, a substantial number of diarrhoeal episodes were attributable to *Campylobacter* spp, norovirus GII, and

astrovirus—pathogens that have rarely been examined in such a large study with modern diagnostic tools,[2] or have not been noted as important in case-control studies.[2,3,30] The number and diversity of pathogens associated with community diarrhoea suggests that single pathogen interventions, apart from rotavirus vaccination, might not have an effect on the incidence of diarrhoeal episodes across populations.

This multisite longitudinal study design allowed us to uncover an unbiased picture of the association between specific pathogens and specific clinical features, including duration, severity, dysentery, febrile illness, and vomiting.

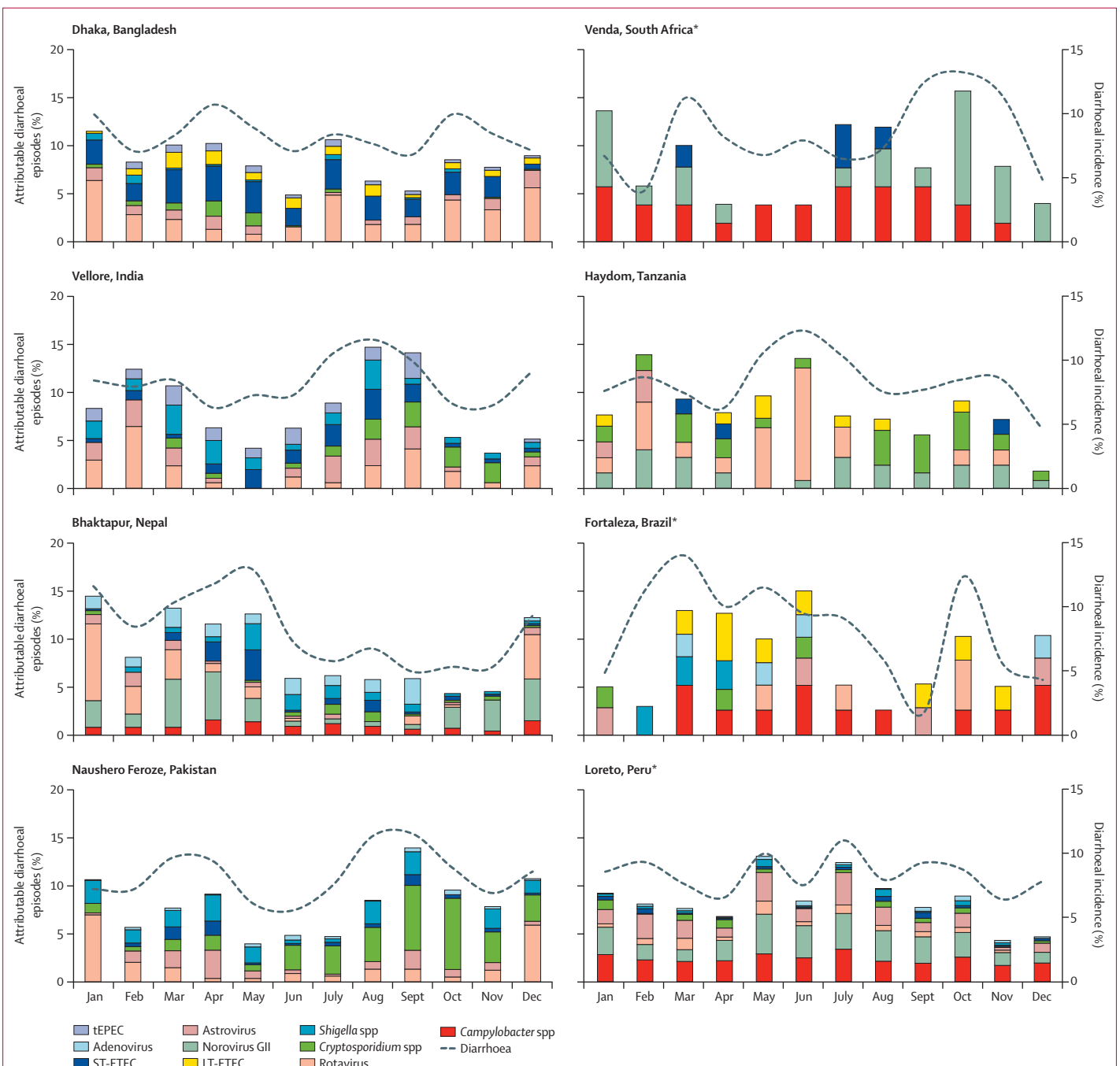

Figure 4: **Association between individual pathogens and seasonal diarrhoeal incidence**
tEPEC=typical enteropathogenic *Escherichia coli*; LT-ETEC=LT-producing enterotoxigenic *E coli*; ST-ETEC=ST-producing enterotoxigenic *E coli*. Primary y-axis shows percent of total attributable incidence of diarrhoea for individual pathogens; secondary y-axis (and dotted line) shows annual diarrhoeal incidence by calendar month. *Monovalent rotavirus vaccine was introduced to the national immunisation programme before the study began.

Dysentery in the first year of life was predominantly associated with *Campylobacter* spp; however, Campylobacter-associated diarrhoea was, otherwise, mild when assessed with a severity score that did not include the presence of blood. By contrast, dysentery associated with *Shigella* spp was often severe and of surprisingly long duration. Rotavirus and norovirus GII were associated with vomiting.

Campylobacter spp were the most frequently detected pathogens and had the highest burden of diarrhoea in Brazil, Peru, and South Africa in the first year of life. Such a high burden of *Campylobacter* spp early in the first year of life, often with dysentery, has been observed in some studies but not others.[2] This pathogen did not show strong seasonal trends. We have previously shown that culture substantially underdetects *Campylobacter*[31] whereas EIA broadly detects *Campylobacter* spp, including species other than *C jejuni* and *C coli*. We expect most of the episodes associated with *Campylobacter* spp to be caused by *C jejuni or C coli*, but culture identification was only done on a subset of stools in our study and further work is needed.

We documented a substantial burden of diarrhoea associated with norovirus GII infection at the sites in Nepal, South Africa, Tanzania, and Peru, as well as in the overall analysis. As in developed countries,[32] norovirus GII appeared to be a significant contributor to overall diarrhoeal incidence at several sites. There has been substantial variation in previous estimates of the global burden of norovirus, in part because detection of norovirus GII is often high in asymptomatic control participants matched for age, community, and season.[30]

Astrovirus is known to be a common cause of sporadic diarrhoea that is less severe than that associated with rotavirus, and astrovirus often exists as a co-infection.[33,34] Our study shows the global importance of astrovirus diarrhoea, with a substantial burden of disease in most sites. Adenovirus had a low overall attributable fraction, but, when present, was associated with diarrhoea classified as "severe" by an adapted Vesikari score. We used a pan-adenovirus ELISA without typing for the major gastrointestinal subtypes 40/41; however, we would not expect the AF for adenovirus to increase significantly given its low prevalence. Helminth infections were rare in this study, except for *Ascaris* in the second year of life, and were not associated with diarrhoea.

This study also documents frequent detection of a wide range of pathogens, including *Campylobacter* spp, enteroaggregative *E coli*, norovirus, *Giardia*, LT-producing enterotoxigenic *E coli*, and typical and atypical enteropathogenic *E coli* in routinely collected non-diarrhoeal stools. Whether the presence of these pathogens is associated with more insidious phenotypes such as poor growth, impaired cognitive development, environmental enteropathy, or impaired mucosal immunity is unclear and further study is warranted in this area.

Our study has some limitations. In light of the variation between sites in diarrhoeal incidence, the study was not powered to identify all associations between pathogens and diarrhoea at individual sites. Furthermore, because short episodes of diarrhoea are more difficult to capture with community-based surveillance than are longer periods of diarrhoea, especially in rural settings, burden estimates might be biased against pathogens associated with a short duration of symptoms. Additionally, we used a modified severity score that only partly recapitulates a score derived from rotavirus studies and may not be generalisable. Therefore, we also looked at the subset of diarrhoea associated with dysentery, dehydration, or hospital admission in addition to looking at specific diarrhoeal syndromes. Finally, the diagnostic approach used a diverse set of detection methods with differing performance characteristics. It is possible, for example, that culture for bacterial pathogens is insensitive and was affected by the frequent use of antibiotics for diarrhoea in these settings, such that the use of culture for detection may have resulted in underestimates of bacterial presence. Molecular testing, in particular quantification of pathogen load and quantitative analysis, could revise estimates of the burden of diarrhoea for these organisms.[35]

The longitudinal nature of this study allowed us to look at causes of diarrhoea in ways that are not possible with other study designs, including use of unbiased estimates of causes of diarrhoea at the community level and evaluation of assumptions about appropriate control specimens.[36] Detection of pathogens in non-diarrhoeal stool samples might represent convalescent excretion of certain pathogens rather than true asymptomatic infection, in which case we may underestimate the burden of diarrhoea associated with these organisms. Malnourished children may be particularly likely to have prolonged excretion of enteropathogens. However, controlling for nutritional status did not appreciably alter AF estimates.

This study documents a diverse range of pathogens associated with community diarrhoea in children in low-income and middle-income countries, which contrasts with the smaller set of pathogens associated with severe diarrhoea. The hierarchy of pathogen-specific diarrhoea varied between sites and high rates of enteropathogens were detected in non-diarrhoeal samples.

Consistent with previous studies,[2,3] a high burden of childhood diarrhoea was attributed to rotavirus, ST-ETEC, *Shigella* spp, and *Cryptosporidium* spp. However, our results suggest that *Campylobacter* spp, norovirus GII, and astrovirus also contribute substantially to the burden of diarrhoea in children.

Contributors

JPM, BJM, MMcGrath, JDC and SR participated in data management and data analysis. SB, LB, JG, RH, AH, MO, AS, SS, DM, IFL, DH, BBR, SQ, FK, PPY, BM, and CA performed and supervised laboratory testing and data collection. PB, EM, TA, AAL, CJM, AZ, ZB, MK, RLG, GK, DL supervised the study. MG and MM organised the project and acquired grant funds. JPM and ERH wrote the report with input from all authors. ERH had final responsibility for the decision to submit for publication. All authors reviewed the draft and approved the decision to submit for publication.

Additional MAL-ED Network Investigators
Cesar Banda Chavez, Dixner Rengifo Trigoso, Julian Torres Flores, Angel Orbe Vasquez, Silvia Rengifo Pinedo, and Angel Mendez Acosta (A.B. PRISMA, Iquitos, Peru). Imran Ahmed, Didar Alam, Asad Ali, Muneera Rasheed, Sajid Soofi, Ali Turab, and Aisha K Yousafzai (Aga Khan University, Naushahro Feroze, Pakistan). Anuradha Bose, M Steffi Jennifer, Sushil John, Shiny Kaki , Beena Koshy, Jayaprakash Muliyil, Mohan Venkata Raghava, Anup Ramachandran, Anuradha Rose, Srujan L Sharma , and Rahul J Thomas (Christian Medical College, Vellore, India). William Pan (Duke University, Durham, NC, USA). Ramya Ambikapathi, Vivek Charu, Leyfou Dabo, Viyada Doan, Jhanelle Graham, Christel Hoest, Stacey Knobler, Archana Mohale, Gaurvika Nayyar, Stephanie Psaki, Zeba Rasmussen, Jessica C Seidman, and Vivian Wang (Fogarty International Center/ National Institutes of Health, Bethesda, MD, USA). Rebecca Blank, Michael Gottlieb, and Karen H Tountas (Foundation for the NIH, Bethesda, MD, USA). Buliga Mujaga Swema, Ladislaus Yarrot, and Rosemary Nshama (Haydom Lutheran Hospital, Haydom, Tanzania). AM Shamsir Ahmed, Fahmida Tofail, Iqbal Hossain, Munirul Islam, and Mustafa Mahfuz (International Centre for Diarrhoeal Research, Bangladesh, Dhaka, Bangladesh). Ram Krishna Chandyo, Prakash Sunder Shrestha, Rita Shrestha, and Manjeswori Ulak (Institute of Medicine, Tribhuvan University, Kathmandu, Nepal). Robert Black, Laura Caulfield, William Checkley, Ping Chen, and Gwenyth Lee (Johns Hopkins University, Baltimore, MD, USA). Laura E Murray-Kolb and Barbara Schaefer (The Pennsylvania State University, University Park, PA, USA). Laura Pendergast (Temple University, Philadelphia, PA, USA). Cláudia Abreu, Hilda Costa, Alessandra Di Moura, Jose Quirino Filho, Álvaro Leite, Noélia Lima, Bruna Maciel, Milena Moraes, Francisco Mota, Reinaldo Oriá, Josiane Quetz, and Alberto Soares (Universidade Federal do Ceara, Fortaleza, Brazil). Crystal L Patil (University of Illinois at Chicago, IL, USA). Cloupas Mahopo, Angelina Mapula, Cebisa Nesamvuni, and Emanuel Nyathi (University of Venda, Thohoyandou, South Africa). Leah Barrett, William A Petri, and Rebecca Scharf (University of Virginia, Charlottesville, VA, USA). Binob Shrestha, and Sanjaya Kumar Shrestha (Walter Reed/AFRIMS Research Unit, Kathmandu, Nepal). Tor Strand (University of Bergen, Norway). Erling Svensen (Haukeland University Hospital, Bergen, Norway).

Declaration of interests
We declare no competing interests.

Acknowledgments
The Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development Project (MAL-ED) is a collaborative project supported by the Bill & Melinda Gates Foundation, the Foundation for the NIH, and the National Institutes of Health, Fogarty International Center. The authors thank the staff and participants of the MAL-ED Network Project for their important contributions.

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Vaccine 39 (2021) 7521–7525

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

World Health Organization Expert Working Group: Recommendations for assessing morbidity associated with enteric pathogens

Mateusz Hasso-Agopsowicz [a,*], Benjamin A. Lopman [b], Claudio F. Lanata [c], Elizabeth T. Rogawski McQuade [b], Gagandeep Kang [d], Holly J. Prudden [e], Ibrahim Khalil [f], James A. Platts-Mills [g], Karen Kotloff [h], Mark Jit [i], Mark S. Riddle [j], Patricia B. Pavlinac [f], Paula M. Luz [k], Virginia E. Pitzer [l], Robert F. Breiman [b], Birgitte K. Giersing [a]

[a] World Health Organization, Geneva, Switzerland
[b] Emory University, Atlanta, United States
[c] Nutritional Research Institute, Lima, Peru
[d] Christian Medical College, Vellore, India
[e] Independent Consultant, United Kingdom
[f] University of Washington, Seattle, United States
[g] University of Virginia, Charlottesville, United States
[h] University of Maryland, College Park, United States
[i] London School of Hygiene and Tropical Medicine, London, United Kingdom
[j] University of Nevada, Reno, United States
[k] Oswaldo Cruz Foundation, Rio de Janeiro, Brazil
[l] Yale University, United States

ARTICLE INFO

Article history:
Received 8 November 2021
Accepted 10 November 2021
Available online 24 November 2021

Keywords:
Enteric infections
Vaccine
Morbidity
ETEC
Shigella
Norovirus
Campylobacter

ABSTRACT

Background: Diarrhoeal infections are one of the leading causes of child's mortality and morbidity. Vaccines against *Shigella*, enterotoxigenic *E. coli* (ETEC), norovirus and invasive non-typhoidal *Salmonella* are in clinical development, however, their full value in terms of short and long-term health and socio-economic burden needs to be evaluated and communicated, to rationalise investment in vaccine development, and deployment. While estimates of mortality of enteric infections exist, the long-term morbidity estimates are scarce and have not been systematically collected.
Methods: The World Health Organization (WHO) has convened a Burden of Enteric Diseases Morbidity Working Group (BoED MWG) who identified key workstreams needed to characterise the morbidity burden of enteric infections. The group also identified four criteria for the prioritisation of pathogens of which impact on long-term morbidity needs to be assessed.
Results: The BoED MWG suggested to identify and analyse the individual level data from historical datasets to estimate the impact of enteric infections and confounders on long-term morbidity, including growth faltering and cognitive impairment in children (workstream 1); to conduct a systematic review of evidence on the association of aetiology specific diarrhoea with short- and long- term impact on growth, including stunting, and possibly cognitive impairment in children, while accounting for potential confounders (workstream 2); and to conduct a systematic review of evidence on the association of aetiology specific diarrhoea with short- and long- term impact on health outcomes in adults. The experts prioritised four pathogens for this work: *Campylobacter jejuni*, ETEC (LT or ST), norovirus (G1 or G2), and *Shigella (dysenteriae, flexneri, sonnei).*
Conclusions: The proposed work will contribute to improving the understanding of the impact of enteric pathogens on long-term morbidity. The timing of this work is critical as all four pathogens have vaccine candidates in the clinical pipeline and decisions about investments in development, manufacturing or vaccine procurement and use are expected to be made soon.

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1. Introduction

Diarrhoeal infections have killed around 500,000 children under five years of age and resulted in an estimated 45.5 million

* Corresponding author at: Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland.
E-mail address: hassoagopsowiczm@who.int (M. Hasso-Agopsowicz).

https://doi.org/10.1016/j.vaccine.2021.11.033
0264-410X/Published by Elsevier Ltd.

disability adjusted life years (DALYs) in 2019 alone, with the majority of the burden occurring in low-income countries [1]. Vaccines are one of the most successful interventions to prevent infections and licensed enteric vaccines against rotavirus, cholera, and typhoid have proven to be safe and effective in preventing diarrhoea episodes and deaths [2]. Vaccines against *Shigella*, enterotoxigenic *E. coli* (ETEC), norovirus and invasive non-typhoidal *Salmonella* are in clinical development. The role of the World Health Organization (WHO) is to consider the use of these vaccines in children under five years old in low- and middle- income countries (LMICs) [3–4]. Other use cases include travellers and military recruits. As such, the full value of vaccines in terms of short and long-term health and socio-economic burden needs to be evaluated and communicated, to rationalise investment in vaccine development, and deployment. The WHO has established an approach to describe the full value of vaccines (FVVA) that are in the early stages of product development [5]. The FVVA approach seeks to understand the perceived burden of disease, to quantify the impact of that burden and the potential benefit of a vaccine, and to drive demand for a vaccine, in particular, from the perspective of LMICs where there is often a lack of epidemiological data to inform decision making and prioritisation of health interventions.

Infections with enteric pathogens, both with and without diarrhoea, can lead to intestinal inflammation and damage, changes in microbiome, nutrient malabsorption, impaired innate and acquired mucosal defences, and worsened clinical presentation of subsequent diarrhoeal infections [6]. Such outcomes can lead to mortality, or potentially to long-term morbidities, such as growth faltering or cognitive impairment, obesity and subsequent metabolic & cardiovascular chronic diseases, as well as socio-economic consequences such as decreased productivity [6]. This extensive burden of enteric infections can have long-lasting effects after the initial infection takes place. To comprehensively assess the FVVA and inform vaccine prioritisation for investment and use, both mortality *and morbidity* need to be explicitly quantified. Modelling groups such as Institute for Health Metrics and Evaluation (IHME) and Maternal Child Epidemiology Estimation (MCEE) have published mortality estimates for enteric diseases, which were recently reviewed by the WHO [7]. These estimates have decreased over the years and the trend is expected to continue. However, the observed morbidity from enteric infections remains high, and there is a lack of consensus on how to measure, analyse and present such morbidity. As such, the full value of enteric vaccines that impact both mortality and morbidity could be underestimated, compounded by the reality that morbidity is often not fully taken into consideration when decisions about vaccine investments are made.

There is evidence showing an association between diarrhoea episodes and growth faltering. The Global Burden of Disease study suggests that each day of diarrhoea is associated with an average loss in length-for-age Z-score (LAZ) of 0.0033, a weight-for-age Z-score loss of (WAZ) 0.0077, and a weight-for-height Z-score loss (WHZ) of 0.0096. The long-term consequences of undernutrition increase the risk of other infectious diseases and increase the total DALY burden associated with enteric infections by 39% [8]. In a large cohort study (MAL-ED), diarrhoea episodes attributed to bacteria or parasites, and high enteropathogen exposure were associated with decreases in growth [10–11]. Aetiology specific analyses suggest that diarrhoeal episodes caused by *Cryptosporidium*, *Campylobacter jejuni/coli*, *Shigella*, enteroinvasive, enteropathogenic or enterotoxigenic *Escherichia coli*, and norovirus impact short or long-term growth in children, albeit inconsistently [9–11]. In addition, non-diarrhoeal infections with *Shigella*, ETEC, *Campylobacter* and *Giardia lamblia* have been associated with substantial decreases in LAZ [11].

Estimating the impact of enteric infections on growth faltering or cognitive impairment is challenging as data are limited, often poorly represent the regions where burden of enteric infections is high, and there is limited consensus on comparison groups, timeframes, and outcome metrics that should be used to measure such impact. The pathway from having an enteric infection to intestinal damage, malabsorption and impact on growth and cognition contains multiple steps, each with a unique set of definitions, indicators and metrics, which are difficult to harmonise across multiple studies or sites. The assessment of morbidity is further complicated by time-varying confounders, which may bias observational associations. Finally, many of the relevant outcomes are highly multifactorial and occur months or years after the infections, making causal inference for often small associations difficult.

WHO has convened a Burden of Enteric Diseases Morbidity Working Group (BoED MWG) with a remit to better understand the morbidity burden of enteric infections and contribute to the characterisation of the full value of enteric vaccines. This article is a summary report of the discussions of the BoED MWG which took place quarter one and two of 2021. The WG identified key workstreams needed to characterise the morbidity burden of enteric infections and prioritised pathogens for such assessment.

2. Summary of discussion and identification of workstreams

The BoED MWG agreed that the understanding of the full value of enteric vaccines is incomplete and analyses of the impact of enteric pathogens on short- and long-term morbidity are critical to ensure rapid vaccine development and deployment. The potential use of enteric vaccines in the travellers' market in high income countries is an opportunity to accelerate the development of enteric vaccines for later use in LMICs. As such, analyses of the impact of enteric pathogens on adults should be a part of the analyses. The experts agreed that the conceptual pathway of diarrhoea to long-term morbidity is well established, and growth, specifically stunting is the most frequent outcome metric used to assess chronic malnutrition in children.

Previous analyses have explored the association between diarrhoea and growth; however, comprehensive analyses of aetiology specific impact of enteric infections on long-term morbidity are scarce. Studies that measure growth such as MAL-ED and GEMS should be explored for datasets that could be combined and re-analysed using systematic and standardised analyses to inform the morbidity work.

Identification, collection and analysis of confounders should be an integral part of the morbidity analyses. Analyses of data at an individual level can help to understand the effect of confounders on long-term morbidity. Analyses should control for the effect of time, consider specific pathogens, and include time-series analyses. Given the growing evidence that asymptomatic enteric infections are associated with malnutrition and stunting, their impact should be included in the assessment of morbidity. As such, the BoED MWG has proposed three workstreams to better understand the impact of enteric infections on morbidity:

1) Workstream 1: identification and analysis of individual level data from historical datasets to estimate the impact of enteric infections and confounders on long-term morbidity, including growth faltering and cognitive impairment in children.
2) Workstream 2: a systematic review of evidence on the association of aetiology specific diarrhoea with short- and long-term impact on growth, including stunting, and possibly cognitive impairment in children, while accounting for potential confounders.

Table 1
Selection of pathogens for the assessment of morbidity.

Pathogen	In clinical development	Source	Vaccine development feasibility	Evidence that symptomatic infections impact growth or cognition	Evidence that non-diarrhoeal infections impact growth or cognition	Included in the analysis?	Reason(s)
Adenovirus	No	Clinicaltrials.gov	NA	Yes [11]	No	No	* No vaccine in clinical development, * No evidence that non-diarrhoeal infections impact growth or cognition
Aeromonas	No	Clinicaltrials.gov	NA	No	No	No	* No vaccine in clinical development, * No evidence that symptomatic infections impact growth or cognition * No evidence that non-diarrhoeal infections impact growth or cognition
Astrovirus	No	Clinicaltrials.gov	NA	No	No	No	* No vaccine in clinical development, * No evidence that symptomatic infections impact growth or cognition * No evidence that non-diarrhoeal infections impact growth or cognition
Clostridium Difficile	Yes	internal pipeline	Moderate	No	No	No	* No evidence that symptomatic infections impact growth or cognition * No evidence that non-diarrhoeal infections impact growth or cognition
Entamoeba	No	Clinicaltrials.gov	NA	No	No	No	* No vaccine in clinical development, * No evidence that symptomatic infections impact growth or cognition * No evidence that non-diarrhoeal infections impact growth or cognition
Rotavirus	Yes	licensed	High	No	No	No	* A vaccine exists and is used in LMICs * No evidence that symptomatic infections impact growth or cognition * No evidence that non-diarrhoeal infections impact growth or cognition
Salmonella enteritidis	Yes	internal pipeline	Moderate	No	No	No	* No evidence that symptomatic infections impact growth or cognition * No evidence that non-diarrhoeal infections impact growth or cognition
Sapovirus	No	Clinicaltrials.gov	NA	No	No	No	* No vaccine in clinical development, * No evidence that symptomatic infections impact growth or cognition * No evidence that non-diarrhoeal infections impact growth or cognition
Vibrio cholerae	Yes	licensed	Moderate-High	No	No	No	* A vaccine exists and is used in LMICs * No evidence that symptomatic infections impact growth or cognition * No evidence that non-diarrhoeal infections impact growth or cognition
Cryptosporidium	No	Clinicaltrials.gov	Low[12]	Yes [11,13]	No	No	* No vaccine in clinical development * Low feasibility of vaccine development * No evidence that non-diarrhoeal infections impact growth or cognition
EPEC	No	Clinicaltrials.gov	Low[14,15]	Yes [16]	Yes [17]	No	* No vaccine in clinical development * Low feasibility of vaccine development
Giardia lamblia	No	Clinicaltrials.gov	Low[18-20]	Yes [17]	Yes [11]	No	* No vaccine in clinical development * Low feasibility of vaccine development
EAEC	No	Clinicaltrials.gov	Low	Yes [10,16–17]	Yes [10–11]	No	* No vaccine in clinical development * Low feasibility of vaccine development
Campylobacter jejuni	Yes	internal pipeline	Moderate	Yes [10,16–17]	Yes [10–11]	Yes	* Vaccine candidates in development * Feasibility of producing a vaccine moderate or higher * Evidence that symptomatic infections impact growth or cognition * Evidence that asymptomatic infections impact growth or cognition
ETEC (LT or ST)	Yes	internal pipeline	Moderate-High	Yes [11,16–17]	No	Yes	* Vaccine candidates in development * Feasibility of producing a vaccine moderate or higher * Evidence that symptomatic infections impact growth or cognition

(*continued on next page*)

Table 1 (*continued*)

Pathogen	In clinical development	Source	Vaccine development feasibility	Evidence that symptomatic infections impact growth or cognition	Evidence that non-diarrhoeal infections impact growth or cognition	Included in the analysis?	Reason(s)
Norovirus GI or GII	Yes	Clinicaltrials.gov	Moderate	Yes [11,16–17]	No	Yes	* Vaccine candidates in development * Feasibility of producing a vaccine moderate or higher * Evidence that symptomatic infections impact growth or cognition
Shigella (dysenteraie, flexneri, sonnei)	Yes	internal pipeline	Moderate	Yes [11,16–17]	Yes [11]	Yes	* Vaccine candidates in development * Feasibility of producing a vaccine moderate or higher * Evidence that symptomatic infections impact growth or cognition * Evidence that asymptomatic infections impact growth or cognition

3) Workstream 3: a systematic review of evidence on the association of aetiology specific diarrhoea with short- and long-term impact on health outcomes in adults.

3. Selection of pathogens for the assessment of morbidity burden

Given the time and workload constraints, the BoED MWG proposed a standardised approach to select pathogens for the assessment of morbidity in children (workstreams 1 and 2). The group identified an initial list of seventeen pathogens (Table 1) for which the mortality burden was previously assessed by IHME or MCEE. A list of the following criteria was identified to prioritise the pathogens for the analyses:

A. **Active vaccine candidates in the clinical pipeline:** the experts gave preference to pathogens for which there are active candidates in the clinical pipeline as the assessment of morbidity should inform the FVVA and drive decisions about future investment in vaccine development, introduction, and use.
B. **Feasibility of developing a vaccine:** preference to pathogens for which there is at least moderate feasibility of developing a vaccine as identified by the WHO feasibility assessment and scientific literature. Vaccines for which FVVA is conducted should be biologically feasible, could be developed, and would likely to be licensed and used.
C. **Evidence of association between symptomatic infections and morbidity**: preference to pathogens for which there is some evidence on the association between symptomatic infections and growth faltering or cognitive outcomes as previous morbidity analyses indicate which pathogens should be analysed in more detail.
D. **Evidence of an association between non-diarrhoeal infections and morbidity:** preference was given to pathogens for which there is evidence that asymptomatic infections are associated with morbidity as asymptomatic infections are not reflected in the acute burden but might impact on growth faltering and cognitive outcomes.

Based on these criteria, the group has prioritised four pathogens to assess their impact on morbidity in children: *Campylobacter jejuni*, ETEC (LT or ST), norovirus (G1 or G2), and *Shigella (dysenteriae, flexneri, sonnei).* The prioritisation process with rationale for exclusion and inclusion is presented in Table 1.

For workstream 3, based on the knowledge of post-infectious sequelae among adults and in alignment with the pathogen list for children, *Campylobacter jejuni* and *Shigella spp*. will be considered and explored for possible association with long-term adult health outcomes globally.

4. Conclusions

There is a need to capture and articulate the full burden of enteric pathogens which are endemic to LMICs and for which vaccine development has a limited commercial attractiveness. For enteric pathogens, there are existing estimates of mortality, however, estimates of morbidity are scarce, and with the exception of data from few cohort studies, have not been systematically evaluated. Analyses that assess the impact of specific enteric pathogens on growth faltering and cognition are lacking. As such, there are major opportunities to analyse individual-level data in existing cohort studies such as MAL-ED, GEMS, VIDA, and identify relevant confounders that may impact the assessment of morbidity (workstream 1). Similarly, there is an opportunity to conduct a systematic review of evidence of the impact of enteric infections on long-term morbidity in children (workstream 2). Lastly, there is a need to assess the evidence of longer-term morbidities in adults, including potential associations with arthritis and functional bowel disorders (workstream 3).

The proposed workstreams should be conducted for at least four pathogens: *Campylobacter jejuni*, ETEC (LT or ST), norovirus (G1 or G2), and *Shigella (dysenteraie, flexneri, sonnei).* All these pathogens have vaccine candidates in clinical pipeline with at least moderate feasibility of vaccine development. As such, decisions about investments in development, manufacturing or vaccine procurement and use are expected to be made soon. There is evidence that symptomatic infections with these pathogens impact growth or cognition. For *Shigella* and *Campylobacter jejuni* there is evidence that asymptomatic infections could impact growth and cognition, further highlighting the need to capture and evaluate morbidity. The specific indicators to evaluate morbidity should be established as part of the analyses and will be guided by the type of data already collected.

The results of the proposed workstreams are expected to be incorporated to the morbidity estimates generated by the modelling groups, and subsequently inform and influence decision making about the development, introduction and use of enteric vaccines. The assessment of morbidity will help funders to decide where to direct their investments; help manufactures to decide which vaccines should be included in their development portfolio;

help international organizations such as Gavi or UNICEF to decide which vaccines to purchase and procure; and help countries to evaluate the role of vaccines in preventing the burden of enteric infections in the context of other interventions.

Once a consensus on the mortality and morbidity burden of enteric pathogens is agreed, additional analyses, beyond the scope of this review, to characterise the full value of vaccines should focus on evaluating the socio-economic impact such as the effect on educational attainment, impact on lifetime productivity and earnings, impact on household costs, poverty, social inequity and economic growth. Research could investigate the impact of morbidity burden on health systems, particularly in LMICs. Additional work could focus on developing a global guidance for metrics and indicators used to measure all components of the pathway from an enteric infection to long-term morbidity, such as environmental enteric dysfunction, malnutrition, growth faltering, and cognition.

5. 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.

6. Data statement

Data can be accessed on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

None.

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World Health Organization

Session 6

VIMC

Vaccine Impact Modelling Consortium

Updates on VIMC

IVIR-Ac meeting March 2022

Dr. Katy Gaythorpe

VACCINE IMPACT MODELLING CONSORTIUM

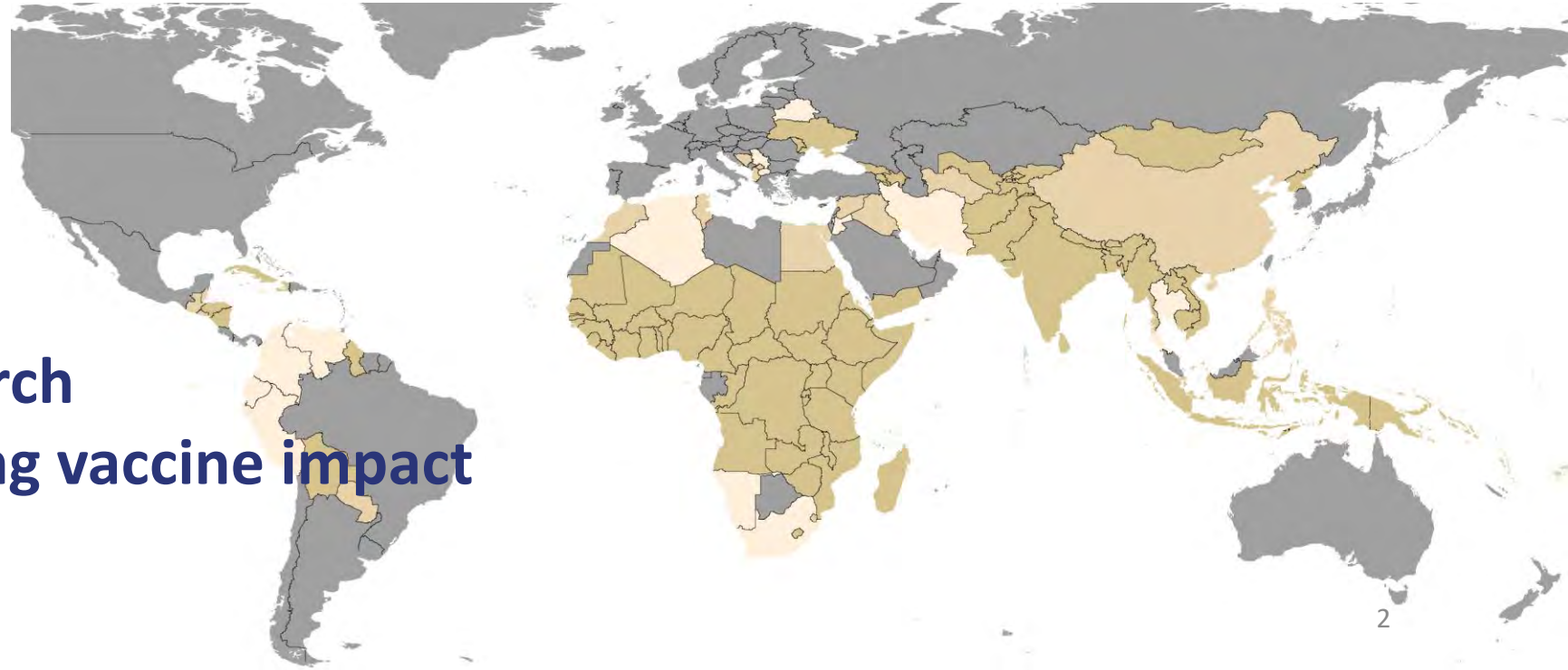
Imperial College London

Gavi The Vaccine Alliance

BILL & MELINDA GATES foundation

VIMC's goals

- **Provide vaccine impact estimates to Gavi and BMGF**
  - 12 diseases (cholera, hepatitis B, Hib, HPV, Japanese encephalitis, measles, meningitis A, pneumococcal disease, rotavirus, rubella, typhoid and yellow fever)
  - 112 countries (shown in light/dark beige on the map)
- Further analyses as required by the funders
- Focus on
  - Consistency
  - Efficiency
  - Quality



- **Advance the research agenda in modelling vaccine impact**

VACCINE IMPACT MODELLING CONSORTIUM

2021 Model runs

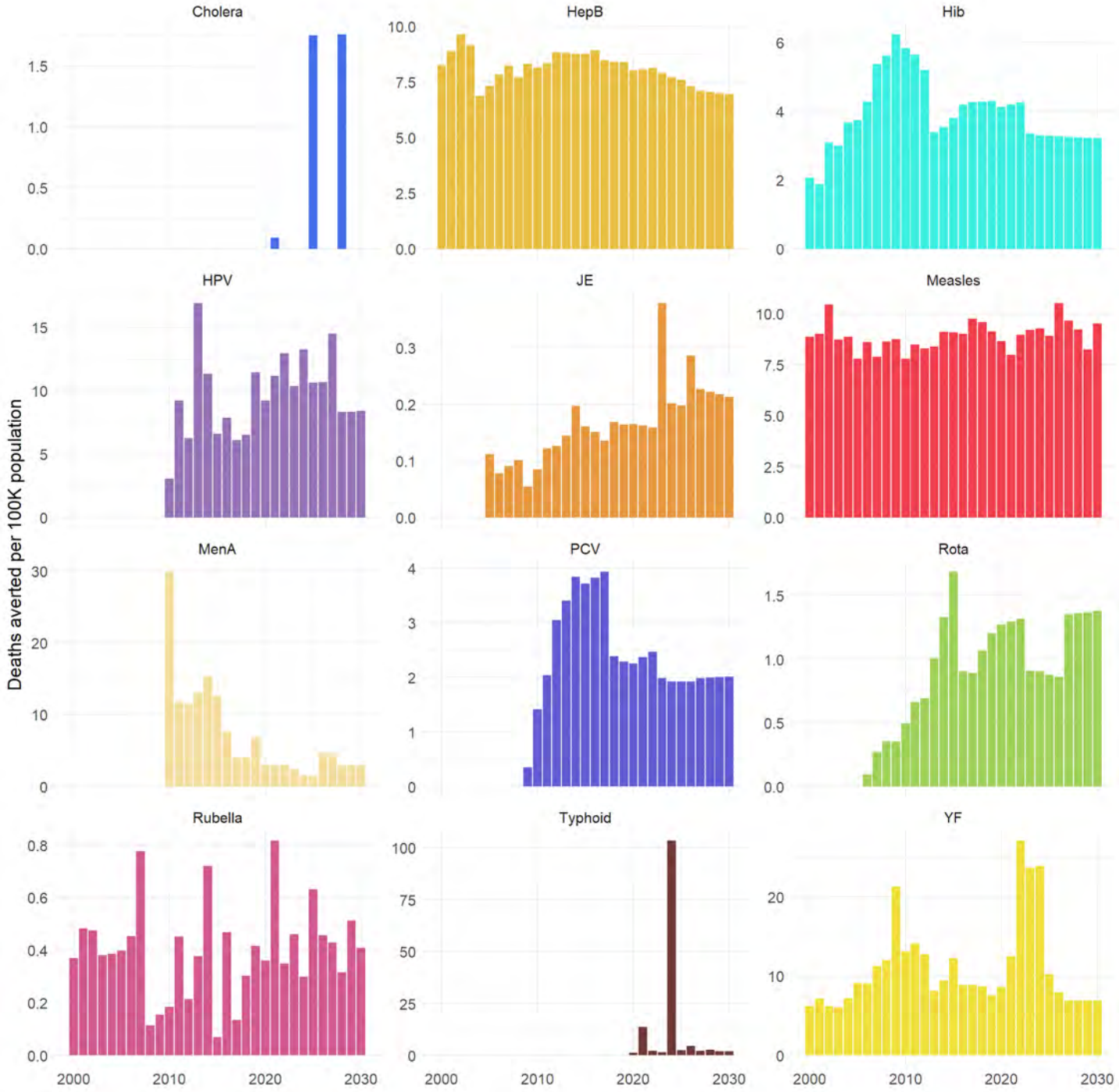
Coverage assumptions

- Two main scenarios: default and aspirational/IA2030.
- Aspirational/IA2030 scenario:
  - Routine coverage relies on WUENIC up to 2020 (inclusive); adjust 2021 levels based on disruption in 2020, then build-up towards the IA2030 coverage endpoints.
  - Campaign coverage is based on the WHO immunisation repo up to 31 Aug 2020 then follows the assumptions for the 2019 VIMC model runs and WHO guidance. Where necessary, campaigns are moved to align with routine introduction in IA2030.
- Default scenario:
  - Routine coverage relies on WUENIC up to 2020 (inclusive); adjust 2021 levels based on disruption in 2020, then build-up towards the IA2030 endpoints, downscaled on a country-by-country basis to be in line with Gavi's most recent operational forecast (OP).
  - Campaign coverage matches coverage in the aspirational/IA2030 scenario.

VACCINE IMPACT MODELLING CONSORTIUM

Overview

Deaths averted per 100,000 population for each disease. Impact is presented by year of vaccination.



VACCINE IMPACT MODELLING CONSORTIUM

Summary and next steps

- We see a drop in deaths averted by vaccination occurring between 2000 and 2030 compared to the 2019 model runs. However these are **preliminary results based on the central estimates and are subject to change.**
- Changes are partly motivated by differences in the number of people vaccinated (FVPs), modelling approaches and parameters such as the case fatality ratio (CFR) (for measles and YF).
- We will continue discussing with modellers to ensure we have the correct interpretation of any difference

Next steps:

- Calculating impact for all stochastic estimates
- Publication of vaccine impact estimates from the 2021 model runs

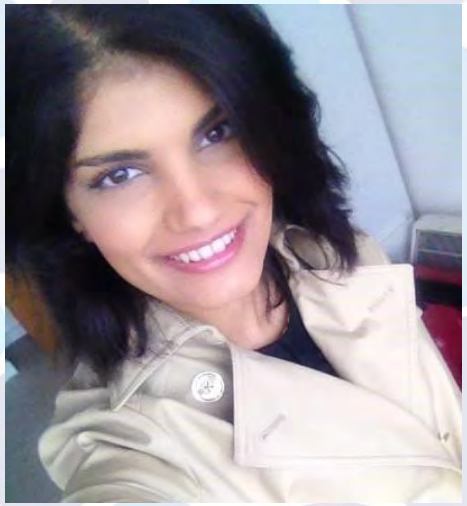
VACCINE IMPACT MODELLING CONSORTIUM

Completed workstreams

Projecting impact post-2021

- Using the VIMC interim update *[Echeverria-Londono et al. 2021]*, project the vaccination impact given drops in coverage in 2020
- Coverage relies on existing VIMC projections (from 2019 model runs) *[Toor et al. 2021]*, IA2030 coverage projections, WUENIC 2020 and IHME estimates of coverage disruption
- Focus is on routine immunisation disruption only
- Investigate the impact of different return strategies
- Three scenarios:
  - One without COVID-19 disruptions
  - Two with different resumptions following COVID-19 disruptions:
    - One reaching IA2030 coverage
    - One with a slower return

Dr. Jaspreet Toor



VACCINE IMPACT MODELLING CONSORTIUM

Projecting impact post-2021

- Preprint available
- Reaching the Immunization Agenda (IA2030) targets leads to 5% fewer fully vaccinated persons (FVPs) and 5.22% more deaths over the years 2020 to 2030 relative to the scenario with no COVID-19-related disruptions, whereas falling short of the IA2030 targets by 10% leads to 11.26% fewer FVPs and 11.34% more deaths.
- The impact of the disruption varies across the vaccine-preventable diseases with those forecasted to have vast expansions in coverage post-2020 able to recover more.

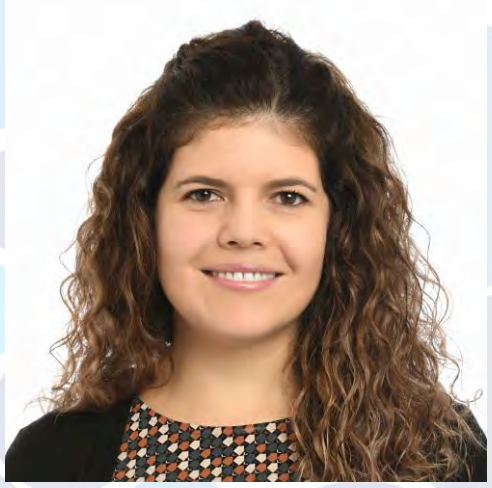
VACCINE IMPACT MODELLING CONSORTIUM

Ongoing workstreams

Subnational heterogeneity in impact

- Using recent estimates of MCV1, DTP1 and DTP3 subnational vaccination coverage *[Sbarra et al. 2021; Mosser et al. 2019]*
- Examine heterogeneity within countries across sub-Saharan Africa over time
- Project vaccine impact given subnational coverage using VIMC interim update approach *[Echeverria-Londono et al. 2021]*
- Compare 3 scenarios:
  - At least national scenario: all districts reach at least national coverage
  - Best performing scenario: all district reach the highest achieved coverage
  - GVAP target threshold: all districts reach at least 80% coverage
- Evaluate how changes in spatial heterogeneity can affect the overall national impact

Dr. Susy Echeverria-Londono



VACCINE IMPACT MODELLING CONSORTIUM

Subnational heterogeneity in impact

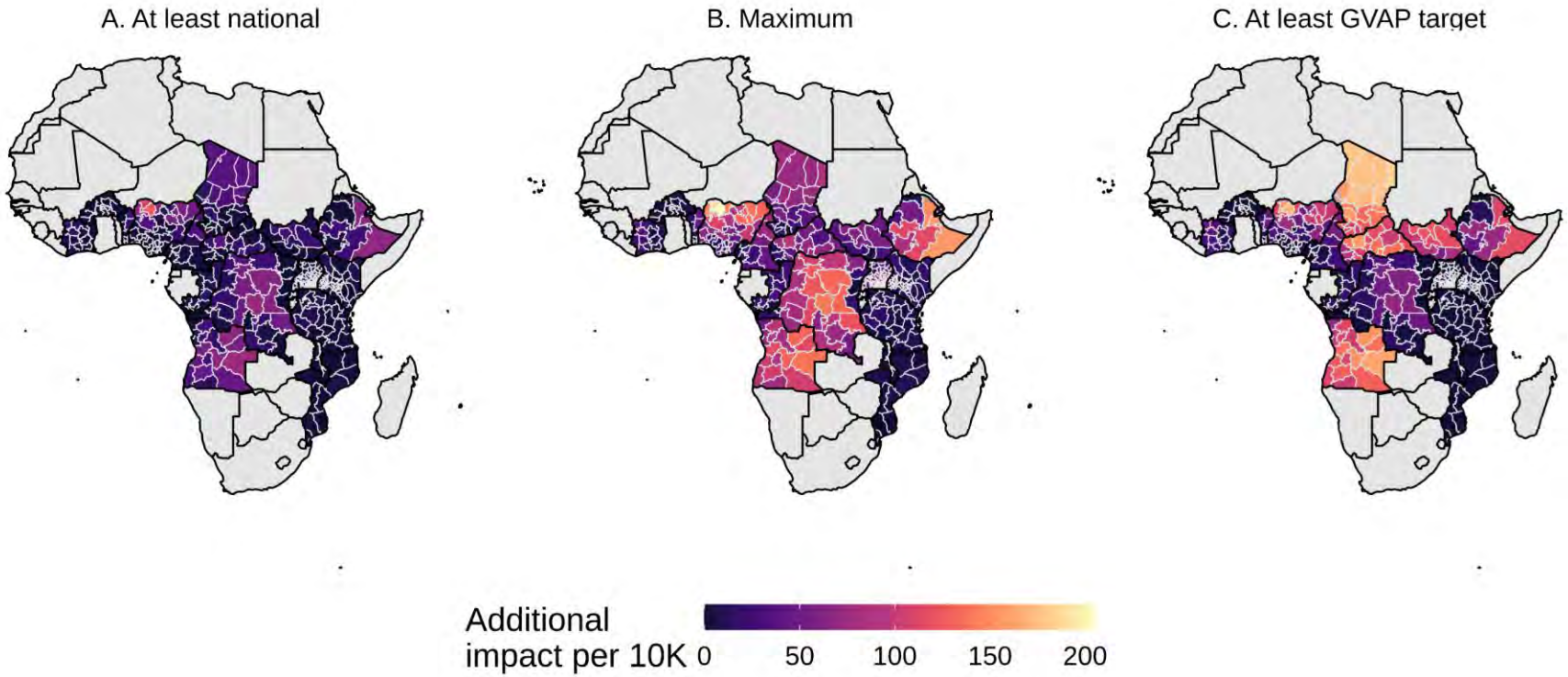


Figure: Change of deaths averted under different scenarios of inequality reduction

A. assuming all districts achieve at least the national coverage in 2019
B. assuming all districts achieve the highest coverage achieved in 2019
C. assuming all districts achieve at least 80% coverage in 2019

VACCINE IMPACT MODELLING CONSORTIUM

The effect of clustering in coverage and indirect benefits

- Partition a population by whether individuals are effectively protected by vaccination against infection
- For each partition, we estimate their probability of survival using the a no-vaccination and a with-vaccination scenarios modelled.
- Comparing survivals in different scenarios results in the attribution of direct vaccine impact and indirect benefits.
- The proposed methodology makes a useful tool for the understanding of vaccine's direct impact and indirect benefits.

Dr. Xiang Li

VACCINE IMPACT MODELLING CONSORTIUM

The effect of clustering in coverage and indirect benefits

- We see gaps between vaccine coverage and the proportion of effectively vaccinated population
- Indirect benefit of measles containing vaccine: 20-25% of total deaths averted (10-18% of total cases averted) in investigated countries between 2000-2018 (vaccine efficacy as effective protection)
- 15-20% total deaths averted (6-13% total cases averted) if vaccine efficacy is defined as reduction in infection

VACCINE IMPACT MODELLING CONSORTIUM

The impact of demographic uncertainty

- UNWPP produce both median and confidence interval projections of population sizes in the future
- We use these to project the range in possible routine immunisation impact due to variation in population size alone
- Initial analysis has focused on understanding the particular sources of uncertainty in their projections, and producing uncertainty estimates targeted to single years and single-year ages that are consistent with the methods and results previously used with five-year age groups and five-year periods

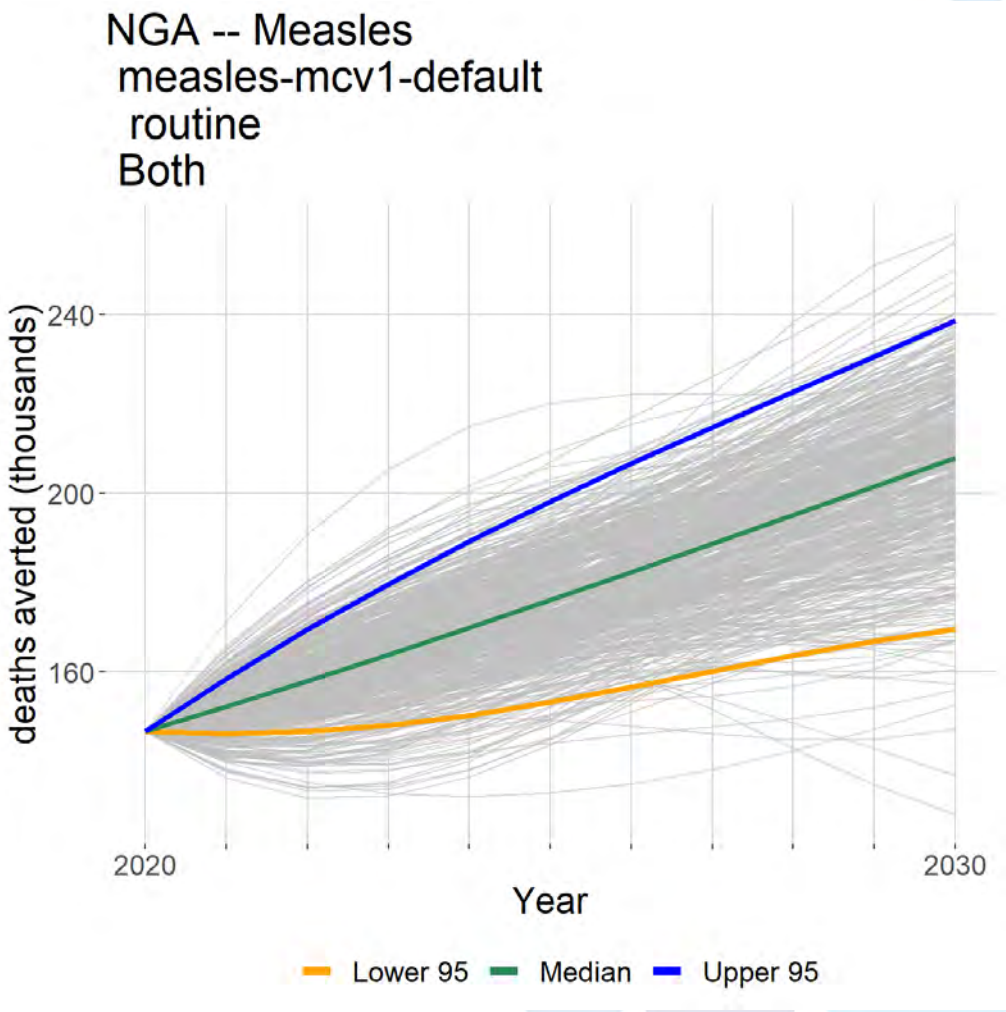
Dr. Jeremy Roth

VACCINE IMPACT MODELLING CONSORTIUM

The impact of demographic uncertainty

Guiding research question: *How sensitive are vaccine impact estimates to changes in projected populations?*

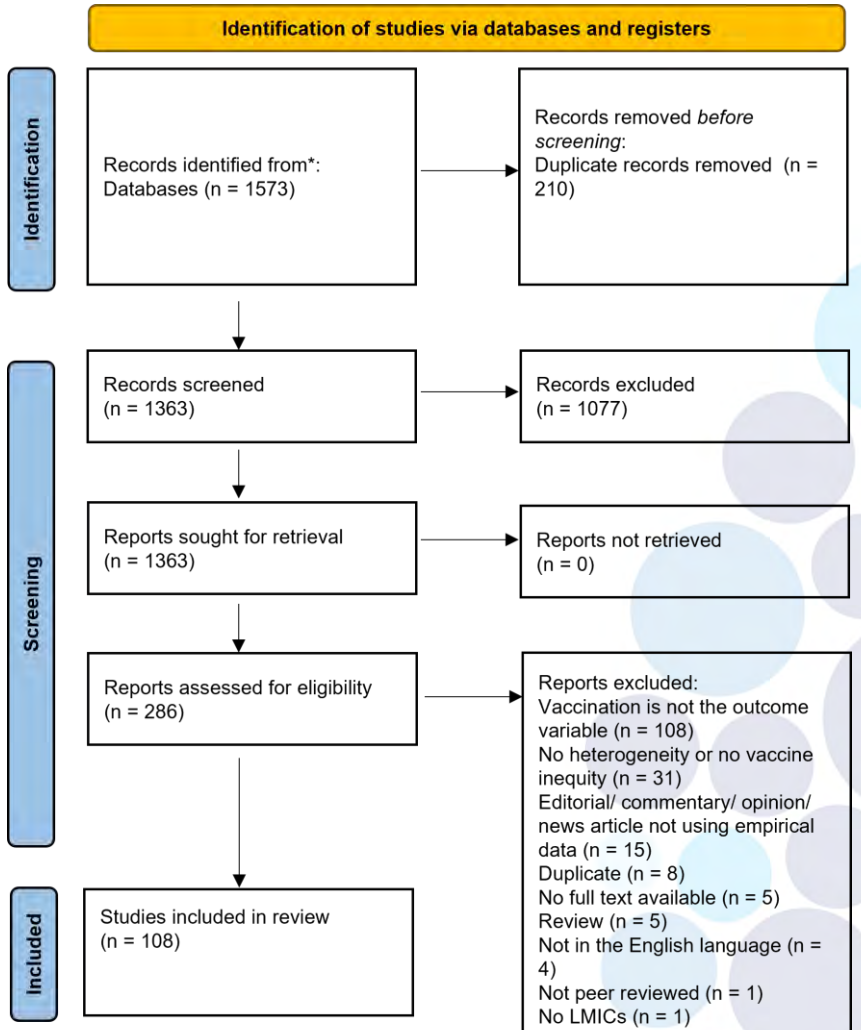
- Visualizations for more combinations of country/vaccine/activity type
- Aggregated estimates
- Relative sensitivity of impact to
  1. Changing population trajectory, holding impact per FVP fixed
  2. Changing impact per FVP, holding population trajectory fixed
- Additional sources of population projections
  - IHME Global Fertility, Mortality, Migration, and Population Forecasts 2017-2100
  - US Census
  - Others?



VACCINE IMPACT MODELLING CONSORTIUM

Vaccine Equity in Low and Middle Income Countries: A Systematic Review and Meta-analysis

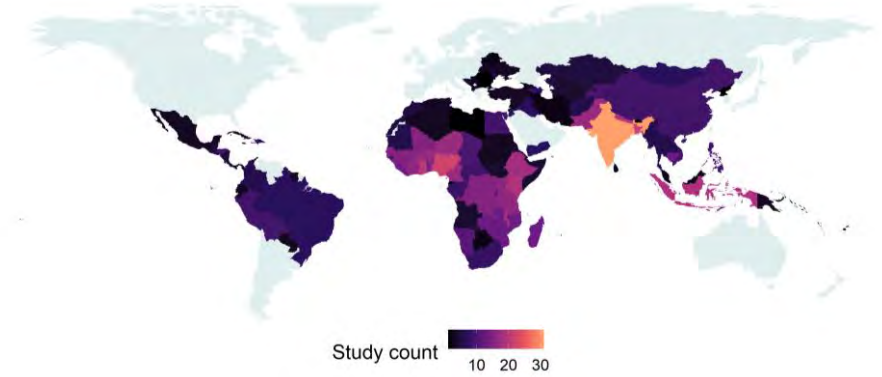
- Review performed on 2 databases as per PRISMA guidelines
- PROSPERO registration: CRD42021261927
- Information collected included thematic and quantitative data on factors associated with heterogeneity in coverage
- Quality assessment was performed using CASP guidelines
- Random effects modelling was used for pooled effects



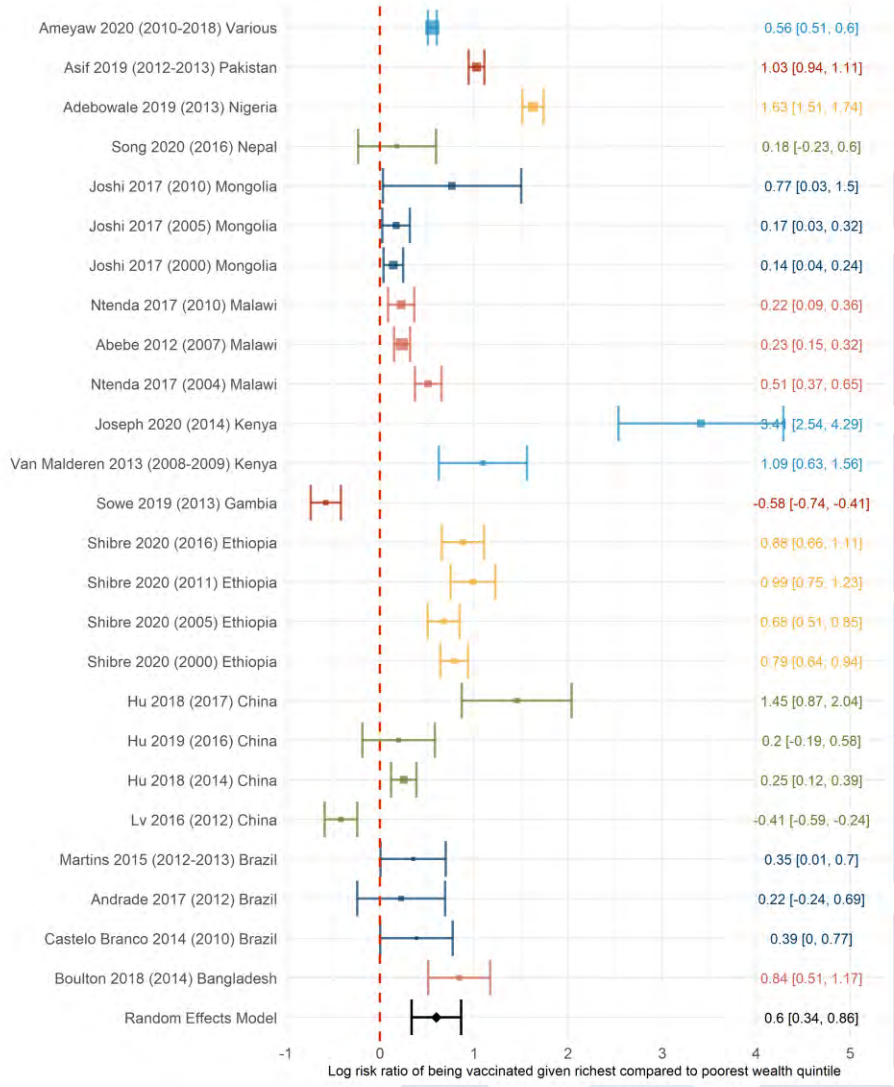
Anna-Maria Hartner

VACCINE IMPACT MODELLING CONSORTIUM

Vaccine Equity in Low and Middle Income Countries: A Systematic Review and Meta-analysis



- Inequities in wealth, education and geographic access can affect vaccine impact and dropout.
- We found that:
  - Females were 3% (95%CI[1%, 5%]) less likely to be fully vaccinated than males
  - Children whose mother had primary level or above education were 28% (95%CI[18%,47%]) more likely to be fully vaccinated but no significant influence of maternal marital status on child immunisation.
  - Individuals in the highest wealth quintiles were 84% (95%[44%,138%]) more likely to be fully vaccinated than those in the poorest.



VACCINE IMPACT MODELLING CONSORTIUM

Thank you to all our members

VACCINE IMPACT MODELLING CONSORTIUM

Imperial College London

Gavi The Vaccine Alliance

BILL & MELINDA GATES foundation

World Health Organization

Session 7

IA2030

World Health Organization

World Health Organization, Analytics

Geneva

Support for IA2030 Vaccine Impact Estimates

Phase 2 Validation and Scoping Exercise

Report on systematic review/literature search to identify existing models for the 14 pathogens

Team members: William Msemburi, Austin Carter, Raymond Hutubessy, Katy Gaythorpe, So Yoon Sim, Maryam Sadeghimehr

March 2022

Table of Contents

Introduction

The first iteration of IA2030 vaccine impact estimates (number of future deaths averted due to immunization from 2021-2030) have been generated for Impact Goal indicator 1.1 of IA2030 Monitoring & Evaluation framework. We plan to validate the estimates and expand the scope of the work to fully capture the impact of vaccination in the coming decade.

Method

As part of the research for validation of High Income Countries (HIC) estimates, the following steps need to be undertaken:

- Data collection by performing a literature search and searching online databases to find relevant studies in HIC and also directly contacting researchers who may have modeled impact in some HIC using the VIMC network.
- Estimation of total deaths averted with vaccination based on these studies/data
- Validation of the predictions of the logistic model with data from the previous step
- Adjustment of the prediction model/approach for HIC accordingly.

In the following sections, we explain steps 1 and 2 in details.

Data collection

Search Strategy

We searched 2 online databases (PubMed and Google Scholar) and used a combination of medical subject headings (MeSH) and text words for the search (see the main document). In addition, we scanned reference lists of included articles and relevant reviews.

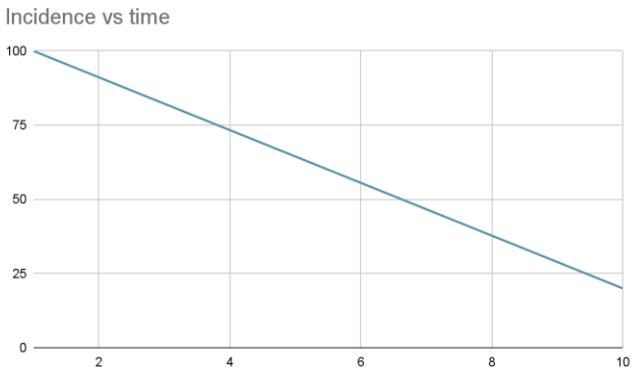
Our search identified 865 abstracts from PubMed and Google Scholar Library. After filtering, we selected 289 potentially relevant articles for full text assessment.

We also contacted the researchers who studied the impact of vaccination in HIC to collect the relevant information. The details are presented in the Supplementary document (see the main document).

Approaches to estimate the number of deaths averted due to vaccination

Depending on the availability and type of output data presented in the studies, we propose using different approaches to translate the studies output to the number of deaths averted due to the vaccination. Some of these approaches are presented in Table 1.

Table 1: Approaches to estimate the number of deaths averted with vaccination

	Approaches
1	**Number of deaths averted directly provided by the studies**: Still quite some post analysis needed, and some challenges exist: For instance: 1. Some studies present the number of deaths averted over lifetime 2. Some studies miss the target population number 3. Extensions to other high-income countries need some post analysis. 4. There are discrepancies between different studies 5. ...
2	**Number of cases averted directly provided by the studies**: Besides the challenges of approach 1, we need to first convert the number of cases averted to the number of deaths averted. Number of deaths averted = Number of cases averted * Case Fatality Ratio (CFR) This estimation, however, might be an underestimation of the number of deaths averted because in a general scenario there exist cases where the vaccine is effective in preventing deaths but not as effective in preventing occurrence of the disease. In other words, Vaccine_effectiveness_case_aversion (85%) < Vaccine_effectiveness_death_aversion (99%)
3	**Incidence reduction in a certain period directly provided by the studies:** We first estimate the number of cases averted assuming a linear fit to the incidence reduction:  Example of linear fit to incidence reduction With the assumption of linearity, we can estimate the number of cases averted as follows: (initial_incidence - final_incidence) / 2 * time_period

4	**Only the prevalence of the disease is known:** In this scenario, normally, a modeling approach is required, however, given the extensive number of pathogens and lack of modelling studies, we can adopt the following simplified approach: Death averted due to the vaccination = Prevalence before intro of vaccine * vaccine coverage * vaccine effectiveness * mortality rate of the pathogen without vaccine
5	**Quality-Adjusted Life-Year (QALY):** QALY will be directly used for validation
6	**Disability-Adjusted Life Year (DALY):** DALY will be directly used for validation

To illustrate further, in Table 2 we present some examples of the second approach listed in Table 1. That is, we show how we can convert the number of cases averted with vaccination to the number of deaths averted by vaccination. We used a study that provided us with both the number of deaths and the number of cases averted due to vaccination in order to estimate the accuracy of this approach. The value of CFR for different pathogens can be found in the supplementary document. Based on the observed number of deaths and the estimated number of deaths we can estimate the CFR value. Then we can validate the value of CFR by using it with the data from other studies (Table 3).

Table 2: Example of verifying approach 2 (using data from [241]).

Pathogen	Approach	Number of deaths averted (estimation)	Number of deaths averted (based on studies)	Estimated CFR (based on studies)
Diphtheria	1) Number of cases averted: 275,028 CFR: [2.3%-12%]	6,326-33,003	27,503	10%
Hib	1) Number of cases averted: 19,606 CFR: 3.1%	608	741	3.7%
Measles	1) Number of cases averted: 3,835,825 CFR: 0.14%-0.64%	5,370-24,549	3,106	0.08%
Pertussis	1) Number of cases averted: 2950836 CFR: 0-0.18%	0-5,311.5	1,062	0.0359%
Hepatitis B	1) Number of cases averted: 239,993 CFR: 0.4%	960	3,514	1.46%
Pneumococcus-related diseases	1) Number of cases averted: 2,323,952 CFR:0.0201%-0.05%	467-1,162	5,056	0.2%

Rotavirus	1) Number of cases averted: 1,582,940 CFR: -		19	0.0012%
Rubella	1) Number of cases averted: 1,981,066 CFR: -	-	15	0.0007%

Table 3: Example of verifying the estimated value for CFR (using data from [240]).

Pathogen	Approach	Number of deaths averted (estimation)	Number of deaths averted (based on studies)	Error
Diphtheria	1) Number of cases averted: 5,073 CFR: 10%	507.3	507.3	0.00%
Hib	1) Number of cases averted: 361 CFR: 3.7%	13.357	13.7	2.5%
Measles	1) Number of cases averted: 70,748 CFR: 0.08%	56.59	57.3	1.2%
Pertussis	1) Number of cases averted: 54,406 CFR: 0.0359%	19.04	20.3	6.2%
Hepatitis B	1) Number of cases averted: 4,007 CFR: 1.46%	58.5	59.7	2%
Pneumococcus-related diseases	1) Number of cases averted: 26,578 CFR:0.2%	53.156	55.0	3.3%
Rotavirus	1) Number of cases averted: 11,968 CFR: 0.0012%	0.14	0.1	40%
Rubella	1) Number of cases averted: 36,540 CFR: 0.0007%	0.25	0.3	15%

Results

In this section, we present a summary of the literature search results for each of the following pathogens in HIC:

Hepatitis B virus, Haemophilus influenzae type B, human papillomavirus, Japanese encephalitis, measles, Neisseria meningitidis serogroup A, Streptococcus pneumoniae, rotavirus, rubella, yellow fever, diphtheria, tetanus, pertussis, tuberculosis.

For each of these pathogens, we also estimate the number of deaths averted due to the vaccination using a few studies.

1. Pneumococcal Conjugate Vaccine (PCV)

We found the interested outcomes for PCV for the following countries:
U.S., Switzerland, Netherlands, Ireland, Canada, Sweden, Australia, Singapore, Poland, U.K., Germany, Greece, Finland, Colombia, France, Italy, Norway, Belgium, Japan.

The target population of these studies are mainly children (mainly at birth or younger than 2 years old) or adults aged ≥65 years.

The following outcomes have been found through our research:

- Number of deaths averted
- Number of cases (IPD, AOM cases) averted
- Number of life-years saved for different vaccination scenarios
- QALY
- Reduction in the number of cases
- Reduction in IPD incidence

Deaths averted	Target population	Source
8 deaths for infants born in 2001 per 100,000	cohort of ~200,000 infants (source: Central Bureau of Statistics) born in the Netherlands in 2001 (per year)	[123]
2.3 deaths for infants per 100,000	a birth cohort of 61,000 infants	[126]
7.5 deaths for infants born in 2006 per 100,00	80 000 births per year	[127]

2. Human papillomavirus (HPV)

Human papillomavirus (HPV) infection, usually a sexually transmitted disease, is a risk factor for cervical cancer. We found the interested outcomes for HPV for the following countries:
Belgium, Japan, U.S., Canada, New Zealand, U.K., Norway, Germany, Netherlands, Denmark, Austria

The target population for the majority of these studies was adolescents (mainly girls). As HPV is a risk factor for cervical cancer, the focus of many of these studies was the number of cases or deaths due to cervical cancer.

In summary, we found the following outcomes through our research:

- Reduction in cervical cancer cases
- Reduction in the head and neck cancer
- Reduction in death
- Cumulative reduction in incidence
- The number of cervical cancer deaths
- QALY
- Number of cases (deaths) prevented over the cohort's lifetime
- Reduction in the incidence of genital warts
- Life-year gained

Deaths averted	Target population	Source
149-214 per 100,000 vaccinated girls over lifetime[1]	unvaccinated and vaccinated cohort of 100,000 12-year-old girls over their lifetime.	[264]
Vaccination averts >224,255 cases of HPV, 112,710 cases of SIL, 3,317 cases of cervical cancer, and 1,340 cervical-cancer deaths over the cohort's lifetime.	Vaccinating the present U.S. cohort of 12-year-old girls (population approximately 1,988,600)	[266]

3. Haemophilus influenzae type B (Hib)

We found potentially relevant studies for Haemophilus influenzae type B in the U.S., Netherlands and Spain. We also found studies in influenza A (H1N1).

The following outcomes have been found through our research:

- The relative risk for invasive Hib disease
- The number of deaths averted
- The number of cases averted

[1] Adding vaccination to current (2008) screening for a cohort of 12-year-old females was predicted to reduce the lifetime number of abnormal cytology test results by 15–24%, treated CIN lesions by 24–56%, and cervical cancer cases and deaths by 71–77%

- The number of deaths with and without vaccination
- Reduction in annual morbidity

Deaths averted	Target population	Source
741 deaths averted over lifetime (17.38 deaths averted per 100,000 target population)	A hypothetical 2009 U.S. birth cohort of 4261494 infant	[241]
13,700 (16.96 deaths averted per 100,000 target population)	birth cohorts born in all years during 1994–2013 in the U.S.	[240]

4. Tuberculosis (TB)

We found potentially relevant studies for Tuberculosis for the following countries: Norway, Ireland, Hong Kong, England, Finland, France, Norway, Slovakia, and the U.K., and Denmark.

However, after filtering, only a handful of these studies/countries had the outcome of interest. These studies estimated the following outcomes:

- Number of cases averted
- Number of identified cases (annual TB notification rates)
- Relative risk of TB
- Incidence in different years

Cases averted	CFR	Deaths averted	Target population	Source
46.8 over 15 years	0.8	0.51 deaths averted per 100,000 individuals over 15 years	a birth cohort of 72,410 infants (2011)	[284]

5. Japanese Encephalitis

We found potentially relevant studies for Japanese encephalitis in Japan, Korea and Australia. Also, we contacted the modelers from VIMC who have modeled the impact of vaccination in

some HIC and we collected the data about the number of deaths/cases with and without vaccination.
The following outcomes have been found through our research:

- Number of cases averted
- Number of confirmed cases (with the history of vaccination)
- Incidence rate and incidence reduction

Deaths averted	Target population	Source
307,774 JE cases (95% CI: 167,442–509,583) were averted due to vaccination globally.[2]	between 2000 and 2015 (globally)	[63]

6. Streptococcus pneumoniae (pneumococcus)

We found potentially relevant studies for Japanese encephalitis in the U.S, Germany and high-income countries in general.

The following outcomes have been found through our research:

- Number of deaths averted
- Number of cases
- QALY
- Reduction in the number of cases

Deaths averted	Target population	Source
8.6 deaths per 100,000 target population	The U.S. population younger than 5 years	[244]

7. Measles, Mumps, and Rubella (MMR)

The interested outcomes for MMR (Measles, Mumps, and Rubella) were found for the following countries:
Denmark, Netherlands, U.S., Australia, Germany, Canada, Korea, Japan

Also, information about the impact of Varicella vaccination (and MMRV (Measles, Mumps, Rubella and Varicella)) can be found in the supplementary document.

We found the following outcomes through our research:

[2] The author kindly provided the data (cases/deaths with and without vaccination) for Japan and Korea.

- Reduction in rate of RSV hospital contact in compare to DTa-IPV-HIb vaccination
- Risk of hospitalization due to any infectious disease in compare to the children who received DTa-IPV-HIb vaccination
- Number of cases reported in different time periods
- Number of deaths averted
- Number of cases averted
- QALY

Pathogen	Deaths averted	Target population	Source
Measles	3106 deaths averted over lifetime (72.8 deaths averted per 100,000 target population)	A hypothetical 2009 U.S. birth cohort of 4261494 infant	[241]
	57.3 (in thousands) deaths averted over lifetime (70.9 deaths averted per 100,000 target population)	birth cohorts born in all years during 1994–2013 in the U.S[3].	[240]
Mumps	12 deaths averted over lifetime (0.28 deaths averted per 100,000 target population)	A hypothetical 2009 U.S. birth cohort of 4261494 infant	[241]
	0.2 (in thousands) deaths averted over lifetime (0.24 deaths averted per 100,000 target population)	birth cohorts born in all years during 1994–2013 in the U.S[4].	[240]
Rubella	15 deaths averted over lifetime (0.35 deaths averted per 100,000 target population)	A hypothetical 2009 U.S. birth cohort of 4261494 infant	[241]
	0.3 (in thousands) deaths averted over lifetime (0.37 deaths averted per 100,000 target population)	birth cohorts born in all years during 1994–2013 in the U.S[5].	[240]

8. Tetanus, diphtheria, and pertussis

Tetanus/diphtheria

[3] About 80.77 million based on https://www.statista.com/statistics/195908/number-of-births-in-the-united-states-since-1990/
[4] About 80.77 million based on https://www.statista.com/statistics/195908/number-of-births-in-the-united-states-since-1990/
[5] About 80.77 million based on https://www.statista.com/statistics/195908/number-of-births-in-the-united-states-since-1990/

Four kinds of vaccines used today protect against tetanus/ diphtheria: Diphtheria and tetanus (DT) vaccines, Diphtheria, tetanus, and pertussis (DTaP) vaccines, Tetanus and diphtheria (Td) vaccines, Tetanus, diphtheria, and pertussis (Tdap) vaccines. We searched literature to get the information about the effectiveness of vaccination for Tetanus as well as diphtheria and pertussis.
We found potentially relevant studies for tetanus mainly in the U.S, and high-income countries in general. A few studies had the outcome of interest. These studies estimated the following outcomes:

- Number of deaths averted
- Number of cases
- QALY
- Reduction in the lifetime

Deaths averted	Target population	Source
25 deaths averted over lifetime (0.58 deaths averted per 100,000 target population)	A hypothetical 2009 U.S. birth cohort of 4261494 infant	[241]
0.5 deaths averted over lifetime (0.61 deaths averted per 100,000 target population)	birth cohorts born in all years during 1994–2013 in the U. S[6].	[240]

We found relevant studies for diphtheria for the following countries:
U.S., Netherlands, Canada.
The following outcomes were found through the literature search for diphtheria:

- The number of deaths averted
- The number of cases averted
- The number of cases
- Mortality reduction
- Reduction in the lifetime

Deaths averted	Target population	Source
27,503 deaths averted over lifetime (645 deaths averted per 100,000 target population)	A hypothetical 2009 U.S. birth cohort of 4261494 infant	[241]
507,300 deaths averted over lifetime (628 deaths averted per 100,000 target population)	birth cohorts born in all years during 1994–2013 in the U.S.	[240]

[6] About 80.77 million based on https://www.statista.com/statistics/195908/number-of-births-in-the-united-states-since-1990/

Pertussis

Deaths averted	Target population	Source
1,062 deaths averted over lifetime (25 deaths averted per 100,000 target population)	A hypothetical 2009 U.S. birth cohort of 4261494 infant	[241]
20,300 deaths averted over lifetime (25 deaths averted per 100,000 target population)	birth cohorts born in all years during 1994–2013 in the U.S.	[240]

9. Rotavirus

We found the interested outcome for Rotavirus for the following countries: Netherlands, Oman, U.S., England and Wales, U.K., Austria, Spain, Belgium, France and Finland.

Neonates and young infants (children aged <5 years) are at particular risk of severe Rotavirus, and they are found to be the target population of the majority of these studies. The following outcomes were found during the literature search:

- The number of cases prevented
- The number of cases prevented
- Reduction in hospitalization, ED visits and office visit
- Reduction in incidence of rotavirus
- QALY

Deaths averted	Target population	Source
19 deaths averted over lifetime (0.44 deaths averted per 100,000 target population)	A hypothetical 2009 U.S. birth cohort of 4261494 infant	[241]
0.1 (in thousands) deaths averted over lifetime (0.123 deaths averted per 100,000 target population)	birth cohorts born in all years during 1994–2013 in the U.S.	[240]

10. Meningococcal Conjugate A (Neisseria meningitidis serogroup A)

The majority of meningococcal disease occurs in developing countries. In the developed world, the incidence of meningococcal disease has decreased to less than one to three cases per 100,000 population per year; cases occur sporadically and most IMD is caused by serogroups B and C [248].
Neisseria meningitidis, is responsible for causing invasive meningococcal disease (IMD). We searched for both IMD and Neisseria meningitidis serogroup A and found the potential relevant studies in the U.S., and Chile. However, after filtering, only a few studies had the outcomes of interest for meningitidis serogroup A, and the majority of studies focused on meningitidis serogroup B.

Deaths averted	Target population	Source
36 deaths prevented in Adolescent strategy, 33 deaths prevented in Toddler strategy and 36 deaths prevented in Infant strategy (all over 22 years)	A hypothetical 2003 US population cohort) (n = 4238672) of children 11 years of age and a 2003 US birth cohort (n = 4026538) (MCV-4) [7].	[223]

11. Hepatitis B Virus (HBV)

We found the following outcomes for HBV in the U.S., Oman, Canada and Netherlands:

- Number of deaths averted
- Number of cases averted
- Percentage of averted the following clinical outcomes: acute and fulminant hepatitis, acute liver death, new chronic
- QALY

Deaths averted	Target population	Source
3514 deaths averted over lifetime (82.4 deaths averted per 100,000 target population)	A hypothetical 2009 U.S. birth cohort of 4261494 infant	[241]

[7] meningococcal conjugate A/C/Y/W-135 vaccine

59.7 (in thousands) deaths averted over lifetime (73.9 deaths averted per 100,000 target population)	birth cohorts born in all years during 1994–2013 in the U.S.	[240]

12. Yellow fever (YF)

We could not find any relevant studies in HIC for yellow fever, however, we found relevant studies for the following middle-income countries: Brazil and Colombia.

We also used the MeSH tree in PubMed (or Cochrane library) and searched the parent node, and other branches of parent nodes in the MeSH tree (see the supplementary document for more information). We only found potentially relevant information for the Dengue virus.

The following outcomes were found:

- Total number of deaths or serious adverse events with the different vaccination coverage
- Number of deaths averted
- Number of cases averted
- DALY averted

Deaths averted	Target population	Source
6 deaths averted	1 million people vaccinated in 2009 outbreak in the region of Botucatu	[206]
During the interepidemic period (1980-2002), routine YF vaccination of 1-year-olds in Colombia might have averted 2223 nonfatal cases of YF and 65 deaths, leading to an overall reduction of 1365 disability-adjusted life-years (DALYs).	vaccination of 1-year-olds in Colombia (total population: 48203405, number of people fully vaccinated: 669137)	[208]

Conclusion

We conducted an extensive literature review with the goal of estimation of the number of deaths averted due to vaccination for certain pathogens. Overall around 290 articles were selected for full text assessment. We presented the summary of the results of the output data of the articles

and proposed different approaches to estimate the number of deaths averted due to vaccination depending on the availability and type of the output data of the relevant studies.
We note that in order to translate the output data of the studies to the number of deaths averted due to vaccination, an extensive post analysis is required. The next steps include extension to other HIC not included in relevant studies, dealing with discrepancies among different studies, and converting the results to the metrics of interest for model validation.

Acknowledgments

We thank Quan Tran and his group for providing data for this research.

IA 2030 Uncertainty Analysis

Problem statement

In our initial approach to estimating averted burden, we generated uncertainty intervals by propagating only a single dimension of input uncertainty and did not include uncertainty coming from our modeled parameter estimates. To more accurately capture uncertainty in our vaccine impact estimates, we transitioned to stratifying our analyses by draw from start to finish, as well as sampling from the estimated joint distribution of our relative-risk model parameters. The result is uncertainty intervals that better reflect the expanding uncertainty associated with extrapolating VIMC results to new locations and separately modeling new pathogens with GBD inputs.

Motivation for Latin hypercube sampling of inputs

Latin hypercube sampling (LHS) is a generalization of the Latin square concept in which samples are spread evenly throughout each dimension so that there is only one sample in each row and each column. Relative to simply sampling randomly from each dimension, the LHS approach leads to better coverage of the joint distribution inputs with fewer samples, especially as the number of dimensions grows. We employ LHS to generate sets of input draws from the distributions of our indepedent and dependent variables that reduce the overall computational requirements of our analysis.

Steps for IA2030 uncertainty analysis

1. Generate draws for uncertain inputs that report ranges (e.g. IQR, 95% UI)
2. Set up location-specific LHS sampling for HAQi, GBD deaths, VIMC deaths, vaccine efficacy for input to regression
3. Perform the regression for each draw combination
4. Take a single draw from the prediction interval of the relative-risk model
5. Execute the VIMC calibration step using the mean of the draws and multiplicatively scale the full draw-level distributions

Input uncertainty

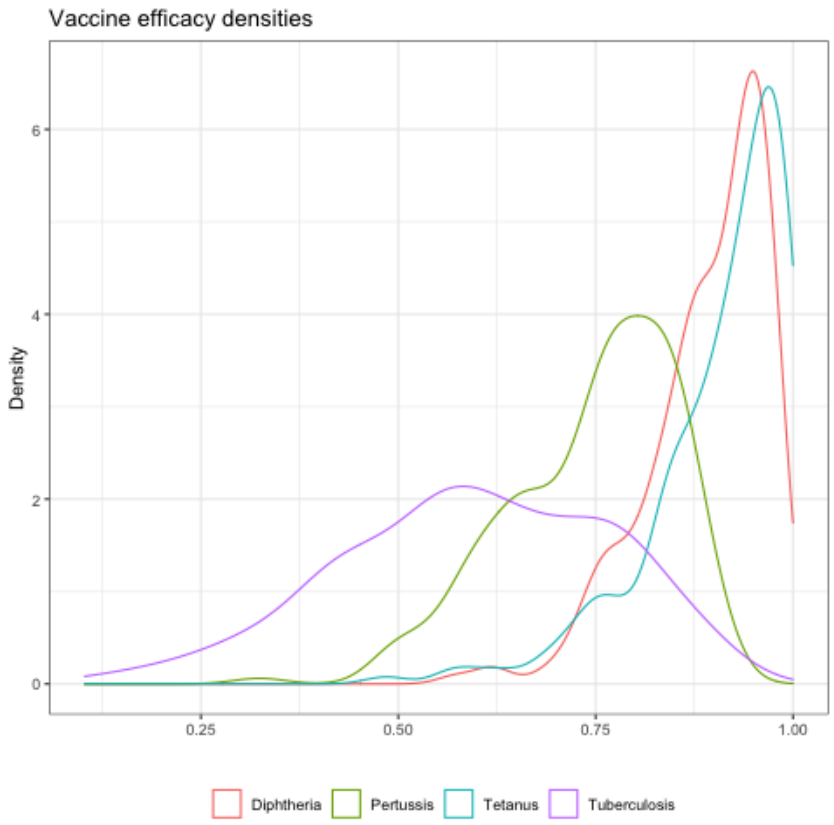
Vaccine efficacy

Method:

- Fit a beta distribution (domain of zero to one) for each disease to the reported mean, lower CI, and upper CI, by minimizing the total absolute difference between the reported summary statistics and the summary statistics associated with the parameterized beta distribution
- Extra weight was given to the mean difference in the objective function to ensure prioritization of alignment in the mean over alignment in the confidence intervals

Limitations:

- Difficult to achieve alignment between all three summary statistics, especially when the mean efficacy is very close to one



Vaccine efficacy data

Disease	Vaccine	Mean	Lower	Upper	Source
D	DTP3	0.969	0.943	0.984	https://apps.who.int/iris/bitstream/handle/10665/258681/WER9231.pdf?sequence=1
T	DTP3	0.99	0.8	1	https://apps.who.int/iris/bitstream/handle/10665/233093/WER8120_198-208.PDF
P	DTP3	0.8	0.71	0.86	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5088088/
TB	BCG	0.66	0.08	0.88	https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-016-0685-4

VIMC deaths averted uncertainty

Method:

- Calculate the normal standard deviation that aligns with the reported IQR
- Sample from a normal distribution with estimated mean and calculated standard devation for each location, disease, vaccine, activity-type, age

Limitations:

- We are assuming a normal distribution for inputs that are not necessarily normally distributed
- We do not retain temporal correlation for a given location/disease combination

GBD deaths observed and HAQi uncertainty

Method:

- Calculate the normal standard deviation that aligns with the reported 95% prediction interval

Limitations:

- Again, we are assuming a normal distribution for inputs that are not necessarily normally distributed and are failing to retain temporal correlation for a given location/disease combination

Inputs currently missing uncertainty

- SDI and all-cause mortality

Location-specific Latin hypercube sampling (LHS)

Method:

- We need to rank draws before indexing with the LHS indices so that the sampling approach effectively spans the input distributions
    - This seems odd, but we believe that without doing this we would simply be mirroring random sampling, as there would be no meaning to the index value for each distribution. Looking forward to feedback on this.
- We generate the LHS draw indices at the location-specific level to avoid draw-level correlation across locations, which would arbitrarily inflate uncertainty during aggregation

Sampling draws from fit models and VIMC calibration

Method:

- For each set of input draws, fit our regression model and generate a single random sample from the poster multivariate normal distibution using the estimated beta coefficients and the variance-covariance matrix
    - Using the `mvrnorm` function from the MASS package in R
- Calculate the mean across draws and compare to the VIMC estimated mean to generate scalars for multiplicatively shifting full distributions of estimated draws so that IA2030 agrees with VIMC at the mean level in countries for which VIMC generates estimates.

Remaining steps

- Finish up full uncertainty analysis and compare to previous uncertainty estimates for different aggregates (e.g. disease, income group)
- Repeat analysis while leaving out uncertainty from individual inputs to determine the contributions of each input to overall uncertainty