World Health Organization

Department of Immunization, Vaccines and Biologicals (IVB)

IVIR-AC – September 2022

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

MICROSOFT TEAMS - VIRTUAL MEETING

WHO HEADQUARTERS, GENEVA, SWITZERLAND

12-14 September 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)
12-14 September 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

World Health Organization

Table of Contents – IVIR-AC meeting

Documents	Page
1. Administrative Documents	
List of IVIR-AC Members	5
IVIR-AC Terms of References	7
DOI for WHO experts and Confidentiality undertakings	8
2. Agenda and List of Participants	
Agenda	23
List of Participants	35
3. **WER summary of last IVIRAC**	44
4. **Background information to the sessions**	
Session 1: COVID 19 vaccine impact modelling	58
Session 2: Full Value of improved Influenza Vaccine Assessment	136
Session 3: Influenza Vaccine Global Demand Forecasting tool	282
Session 4: Pneumococcal Conjugate Vaccine use in humanitarian crises	296
Session 5: Measles Case Fatality Ratio estimation	431
Session 6: TB Full Value of Vaccine Assessment (FVVA)	468
Session 7: MR-MAP initial Full Value of Vaccine Assessment (MR-MAP iFVVA)	713
Session 8: IA2030 vaccine impact estimates	821
Session 9: VIMC	845

World Health Organization

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**
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**
Paula M. Luz, Professor, Evandro Chagas Clinical Research Institute (IPEC/ FIOCRUZ), Av. Brasil 4365, Manguinhos, 21040-360 Rio de Janeiro, **Brazil**

World Health Organization

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, Centre for Tropical Medicine and Global Health, Oxford, **United Kingdom of Great Britain and Northern Ireland**

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**

World Health Organization

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.

- -

* *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 - Hybrid Meeting
Hotel Intercontinental, Geneva, Switzerland
12 September -14 September 2022

Background reading materials **available at:**
IVIR-AC September 2022 - Home (sharepoint.com)

Chair: Walt Orenstein

12 September

Duration	Title	Content	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 - 13:15 10’	Introduction/ Objectives of the meeting	• Administrative issues • Objectives of IVIR-AC meeting and outline of the 1st day		P Lambach W Orenstein

World Health Organization

COVID 19 vaccine impact modelling				
13:15 - 13:30 15’	Background	• Priority questions of the WHO SAGE WG on Covid-19 vaccines currently include (a full list is provided in the background material) o Shifting vaccination priorities with high infection derived immunity, o Cost effectiveness of COVID-19 vaccines (compared to other vaccines) and o Impact of VoC (Variants of Concern) on vaccination priorities • This session serves to discuss the modelling efforts that have been made in follow up to last IVIR-AC meeting’s session on COVID 19 vaccine modelling and that have been funded by WHO to address a subset of the strategic priorities • Two research groups have been funded and will present their progress and plans	For discussion	S Flasche, A Wilder-Smith, S Bhatia, N Ferguson
13:30 - 13:50 20’	Serological data needed to formulate serology-informed national policy on vaccination	• Evaluation of the impact of serology-informed vaccine strategies at the current stage of the pandemic, in terms of cases- and deaths-averted, using rich sources of vaccine coverage, human contact and seroprevalence data • 10 minutes Q&A		C. Liu B. Lopman
13:50-14:10 20’	Updates on fourth dose of the COVID-19 vaccine, and cost-effectiveness of the Pfizer-BioNTech vaccine for teens and children in the US	• Assessment of the cost-effectiveness of a fourth dose of the COVID-19 vaccine, and the cost-effectiveness of the Pfizer-BioNTech vaccine for teens (12-17 years) and children (5-11 years) in the US • 10 minutes Q&A		L. Zhang
14:10-14:40 30’	Q&A and discussion	Expectations to IVIR-AC: • To provide feedback on each group’s conducted work and their plans		V. Pitzer, S. Silal S. Flasche

		• To provide feedback on key messages to SAGE groups with regards to the priority questions		
14:40-15:00	Tea break			
Full Value of improved Influenza Vaccine Assessment (FVIVA)				
15:00 – 15:10 10’	FVIVA – Rational and background	• Update on overall process of Full Value of improved Influenza Vaccine Assessment (FVIVA) development	For discussion	P Lambach
15:10-15:25 15’	Technical presentation	Analysing the influenza vaccine product research, development, and production landscape: • Review the key technical and scientific characteristics for analysing current seasonal influenza vaccines and improved seasonal influenza vaccines • Review proposed approach to assess feasibility of research, development, and production of improved influenza vaccines among developers and manufacturers, including those in low- and middle-income countries Questions to IVIR-AC: • *Does IVIR-AC agree with the approach for analysing current and improved seasonal influenza vaccines?* • *Does IVIR-AC have additional feedback on how to engage developers and manufacturers?*		Chris Chadwick
15:25-15:40 15’	Technical presentation	Assessing the balance of global influenza vaccine supply and demand • Review of the use cases for seasonal influenza vaccines and the approach to estimate their size, which will be used to support the forecasting of current and future demand for seasonal influenza vaccines. • Review of proposed approach for a global MI4A market study for seasonal influenza vaccines. The study will include a comparison of forecasted demand with forecasted available supply to understand		A Soble

		imbalances and areas of risks, as well as changing market dynamics via new and improved influenza vaccines. Questions to IVIRAC: • *Does IVIR-AC agree with the approach to estimate the size of the use cases for seasonal influenza vaccine?* • *Does IVIR-AC have perspectives on how best to assess current and model future coverage of seasonal influenza vaccines as part a global demand forecast?*		
15:40 – 16:00 20’	Technical presentation	• Impact modelling Question to IVIRAC: • *What does IVIR-AC think about the current modelling work to estimate the health and economic benefit of next-generation influenza vaccines?* • *What does IVIR-AC think of plans to extend this work to inform a value proposition for next-generation influenza vaccines globally?* ***Background reading materials**: See SharePoint*		Mark Jit
16:00 – 16:20 20’	Q&A and Discussion	• IVIR-AC discusses presentation, clarifies on content, and provides feedback/inputs to the use case definitions		D Lyimo, P Luz, J Wu
Influenza Vaccine Global Demand Forecasting tool				
16:20 – 16:25 5’	Background	• Global need for Global Demand Forecasting tool	For information	C Chadwick
16:25 – 16:40 15’	Technical presentation	• Presentation of a long-range demand forecasting tool for influenza vaccines targeted towards LMICs developed by Ready2Respond and PwC *Questions to IVIR-AC:* • *How can access to the current tool be enhanced?* • *How can use by public health managers be strengthened?* • *Regarding the extension of the tool to forecast next generation influenza vaccine demand, what is IVIR-AC’s advice on assumptions to be considered, including the “improved” vaccine features to be considered?*		Marie Mazur

		***Background reading materials**: See SharePoint*		
16:40 – 17:00 20’	Q&A and Discussion	• IVIR-AC discusses presentation, clarifies on content, and provides feedback/inputs to the use case definitions		D Lyimo, J Leask, J Wu
17:00 - 17:10 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
17:10	Reception			

World Health Organization

13 September				
10:25 - 10:30 5’	Introduction	• Recap of previous day and objectives for the day	For information	W Orenstein, Chair
Pneumococcal Conjugate Vaccine use in humanitarian crises				
10:30 - 10:40 10’	Background	• Despite the high prevalence for risk factors for transmission and disease from respiratory pathogens pneumococcal conjugate vaccines (PCV) are hardly used in humanitarian crises • This is in part due to a lack of evidence for optimal use of PCV in such situations • The WHO position paper currently states: “In humanitarian or other emergency situations, age-appropriate schedules of PCV vaccination should be used for children <1 year of age and considered for children ≤5 years of age, as indicated by the situation” • Studies are needed to fill the evidence gap and allow a clearer guidance on the use of PCV in humanitarian crises ***Background reading materials**: See SharePoint*	For discussion	J Walldorf
10:40 - 11:00 20’	Technical presentation	• *Description of the finished Phase I study design: cross sectional carriage, risk factor and contact survey to feed into a mathematical modelling framework that simulates a PCV campaign* • *Results on the optimal age targeting for a PCV campaign in such setting, predicted impact on carriage and invasive disease and demand forecast if scaled up to include in routine NGO support portfolio* • *Description of the recently started Phase II study design: PCV campaign to all <5y olds in a IDP camp in Somaliland with multiple cross-sectional follow up surveys to estimate the impact on pneumococcal carriage* • *Data collection and analysis plan*		K van Zandvoort

		***Background reading materials**: see Sharepoint*		

11:00 - 11:30
30’
	Q&A and discussion to inform IVIR-AC recommendations	• Questions to IVIRAC
		  • *Comment on the robustness of the design and methods for generating evidence on the effects of PCV use in humanitarian crises*
		  • *What, if any, additional information would be needed to collect during the subsequent intervention study?*
				HH Farooqui, DC Lyimo, V Pitzer

Measles Case Fatality Ratio estimation				
13:00 - 13:10 10’	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 (Case Fatality Ratio), with noted limitations in data availability. In 2021, IVIR-AC recommended continued updates of measles CFR estimates with increased transparency and systematic covariate selection. • IVIR-AC has previously advised 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.	For decision	P. O’Connor

13:10 - 13:30
20’
	Update on methodological considerations and resulting estimates	• *Results based on the revised framework*
		  • Update on revised methods and considerations to measles CFR estimation framework per IVIR-AC March 2022 recommendations
		  • Presentation of measles CFR estimate results based on revised framework
		  • Considerations for applying revised framework to examine short- and long-term impact of COVID-19 pandemic on measles mortality burden
				A. Sbarra, A. Portnoy, M. Jit, M. Ferrari

		• Use cases for measles CFR open access framework (i.e., user-friendly R package) ***Background reading materials**: see Sharepoint*		

13:30 - 14:00
30’
	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?*
		  • *What factors should be considered when applying the model framework to examine short- and long-term impact of COVID-19 pandemic on measles mortality burden?*
		  • *Are there additional use cases that should be considered for the open access framework (i.e., user-friendly R package with clear documentation) for both WHO and community use?*
				P. Luz, X. Wang, V. Pitzer

TB Full Value of Vaccine Assessment (FVVA)				
14:00 - 14:05 5’	Background	• *The TB vaccine pipeline has a number of late-stage candidate, targeting both neonate/infant and adult and adolescent populations. WHO promotes the full value of vaccine assessment framework to inform decision-making on TB vaccine investment, introduction and use.* • Using this framework, the health and economic impact of new TB vaccines that meet WHO preferred product characteristics for these priority target populations were estimated in 102 low and middle income countries. This session will present the pipeline, and the outcomes of the FVVA work for new TB vaccines.	For discussion	G Giersing
14:05 - 14:35 30’	The potential health and economic impact of new TB vaccines that meet WHO Preferred Product Characteristics, in low-and-middle income countries	• Topic 1: Potential health impact of new TB vaccines that meet WHO Preferred Product Characteristics (context: LMICs) • Topic 2: Potential economic impact of new TB vaccines that meet WHO Preferred Product Characteristics (context: LMICs) ***Background reading materials***: • see Sharepoint • http://apps.who.int/iris/bitstream/handle/10665/273089/WHO-IVB-18.06-eng.pdf?ua=1		R White N Menzies

14:35 – 15:05 30’	Q&A and Discussion	*Questions to IVIRAC* • IVIR-AC is asked to review and comment upon the approach and outcome of the analysis to assess the health and economic impact of new TB vaccines that meet WHO preferred product characteristics • IVIRAC is asked to comment on/recommend any additional studies that may complement/broaden these initial analyses on the health and economic impact of new TB vaccines.		S. Silal, H. Hasan, S. Flasche
15:05 - 15:25 20’	Tea Break			
MR-MAP initial Full Value of Vaccine Assessment (MR-MAP iFVVA)				
15:25 - 15:35 10’	*Background* **MR-MAP iFVVA background and project set-up**	• In collaboration with the VIPS working group that is co-led by WHO, UNICEF has developed an initial FVVA for MR-MAPs, complementing the previously issued WHO/UNICEF TPP on MR–MAP and leveraging the work that has been led by WHO on MR-MAP demand forecasting • The methodology developed under the MR-MAP is intended to be expanded to a full MR-MAP FVVA as well as to additional FVVAs, for example the TCV-MAPs FVVA funded by Wellcome	For information	G Giersing
15:35- 16:05 30’	*Technical presentation* **The demand estimates, potential health and economic impact of MR-MAPs**	UNICEF and the research groups contracted by UNICEF will present. Overview of the MR-MAP iFVVA – Topic 1: Review of scenarios for demand estimates to assess MR-MAP health impact – Topic 2: Potential health and economic impact of MR-MAPs – Topic 3: Using model data for drafting an initial public investment case and (potential) next steps ***Background reading materials***: – Intro slides to MR-MAP iFVVA – Draft MR-MAP demand forecasting paper (WHO/MMGH) – Draft MR-MAP cost effectiveness analysis paper (UNICEF/LSHTM)		Jean-Pierre Amorij (UNICEF) Topic 1: MMGH Topic 2: LSHTM Topic 3: UNICEF

		– MR-MAP TPP: https://apps.who.int/iris/bitstream/handle/10665/330394/9789240000209-eng.pdf – Draft/final report iFVVA		
16:05 - 16:30 25’	Q&A and Discussion	• UNICEF and WHO are seeking review of this initial MR-MAP FVVA, including the approach and results, and are seeking recommendations on priorities for next steps		P. Luz, X. Wang, J. Leask
IA2030 vaccine impact estimates				
16:30 - 16:40 10’	Background	• The IA2030 vaccine impact estimates were first generated in 2021 and have served as the target estimates for the Impact Goal Indicator 1.1 “Number of future deaths averted through immunization” as part of the IA2030 Monitoring & Evaluation framework. From mid-2021 onwards, the project team took the next steps to improve the first iteration of estimates by conducting an expanded uncertainty analysis, performing literature reviews for validation of estimates from high income countries and identifying target pathogens for inclusion in the coming years. Since the inception of the project, the IVIR-AC has provided independent reviews of models, analytical frameworks and methods to inform the use of estimates for global and regional policy and planning process.	For information	Y Sim
16:40 - 17:00 20’	Technical presentation	• To present the final results from the expanded uncertainty analysis implemented based on previous IVIR-AC recommendations • To present the project work plan and main activities planned for the next phase of the project • ***Background reading materials****: see Sharepoint* • Final reports to be shared 2 weeks before the IVIR-AC meeting		Austin Carter, William Msemburi
17:00 - 17:20 20’	Q&A and Discussion	• The project team requests IVIR-AC: o To review the final results from the uncertainty analysis		S Verguet and J Wu

		○ To provide feedback on approaches to tracking annual progress against targets ○ To provide feedback on the planned next steps for the project • IVIR-AC discusses presentation, clarifies on content and acknowledges main issues		
17:20 - 17:30 10’	Wrap up	• Summarize day’s findings and request any follow up from WHO Secretariat/IVIR-AC FPs for closed session	For information	Y Sim

14 September				
13:00 - 13:05 5’	Introduction	• Recap of previous day and objectives for the day		W Orenstein, Chair
VIMC				
13:05 - 13:15 10’	Background	• The Vaccine Impact Modelling Consortium (VIMC) is a multinational collaboration of 21 research groups funded by Gavi, the Vaccine Alliance and the Bill & Melinda Gates Foundation (BMGF). The consortium aims to deliver a more sustainable, efficient, and transparent approach to generating estimates of disease burden and vaccine impact for 12 vaccine preventable diseases (VPDs). The VIMC	For information	Y Sim

		collaborates with WHO on the Immunization Agenda 2030 (IA 2030) Vaccine Impact Estimates and COVID-19-related projects.		
13:15 - 13:25 10’	Presentation on updates	• To present proposed activities and structure for the next strategic period for VIMC (“VIMC 2.0”) • To provide an update on the third consortium-wide publication on the implications of immunisation disruptions ***Background reading materials***: *See SharePoint*		K Gaythorpe
13:25 - 13:45 20’	Q&A and Discussion	• VIMC invites IVIR-AC to provide feedback on the proposed plan for VIMC 2.0 • Discussion of priority questions for the next period, specifically related to optimising the use of current vaccines or future challenges around vaccine preventable disease control • IVIR-AC discusses presentation, clarifies on content and acknowledges main issues		J Wu and JD Lelièvre
13:45 - 13:55 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
13:55 - 14:20 25’	Tea Break			
Closed session: IVIR-AC members only				
14:20 - 18:30	**IVIR-AC reporting/recommendations**			

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

Hybrid Meeting
Microsoft Teams/Intercontinental Hotel
Geneva, Switzerland
12 to 14 September 2022

Draft list of participants

Advisory Committee Members

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

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

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

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

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**

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

Jean-pierre Amorij, UNICEF, New York, **United States of America**

Thomas Cherian, MMGH Consulting, Zurich, **Switzerland**

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**

Han Fu, London School of Hygiene and Tropical Medicine, **London, United Kingdom of Great Britain and Northern Ireland**

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

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

Ben Lopman, Rollins School of Public Health, Georgia, United States of America

Carsten Mantel, MMGH Consulting, Zurich, **Switzerland**

Stefano Malvolti, MMGH Consulting, Zurich, **Switzerland**

Marie Mazur, The Taskforce for Global Health, Georgia, **United States of America**

Nicolas Menzies, Harvard School of Public Health, Boston, United States of America

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

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**

Adam Soble, MMGH Consulting, Zurich, **Switzerland**

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

Naomi Waterlow, London School of Hygiene and Tropical Medicine, **London, United Kingdom of Great Britain and Northern Ireland**

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

Lei Zhang, Monash University, Melbourne, **Australia**

Kevin van Zanvoort, 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**

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

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

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

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

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

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

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

Professor Wan Chin Chen

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

Zoey Diaz, Bill and Melinda Gates Foundation, Seattle, **United States of America**

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

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

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

Maria Lahuerta, International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), Geneva, **Switzerland**

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

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

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

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

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

Ann Moen, Centers for Disease Control and Prevention, Atlanta, **United States of America**

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**

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

Kate Simms, The Daffodil Centre, Faculty of Medicine and Health, The University of Sydney, Cancer Council Australia, Sydney, **Australia**

Duncan Steele, Bill and Melinda Gates Foundation, Seattle, **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**

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

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

Regional and Country Offices

Sunil Kumar Bahl, Coordinator (COVAX, IVD), World Health Organization, Regional Office for South-East Asia, New Delhi, **India**

Lee Chung-won, World Health Organization, Regional Office for the Western Pacific, Manila, **Philippines**

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**

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

Liudmila Mosina, Technical Officer Vaccine-Preventable Diseases and Immunization, Division of Country Health Programmes, World Health Organization Regional Office for Europe, Copenhagen**, Denmark**

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

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

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

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

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

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

Hardeep Sandhu, World Health Organization, Regional Office for the Western Pacific, Manila, **Philippines**

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

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**

Wang Xiaojun, World Health Organization, Regional Office for the Western Pacific, Manila, **Philippines**

WHO Secretariat

Hiroki Akaba, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

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

Sangeeta Bhatia, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Paul Bloem, 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**

Anindya Sekhar Bose, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

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

Christopher Chadwick, Emergency Preparedness, 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**

Nebiat Gebreselassie, Prevention, Diagnosis, Treatment, Care & Innovation, 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**

Mary Hamel, Immunization, Vaccines & 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**

Anna Minta, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Joshua Adam Mott, Emergency Preparedness, World Health Organization, **Switzerland**

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

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

Lisa Menning, Immunization, Vaccines & Biologicals, 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**

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

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

Heidi Soeters, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

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

Jenny Walldorf, 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**

Matteo Zignol, Prevention, Diagnosis, Treatment, Care & Innovation, 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

6 MAY 2022, 97th YEAR / 6 MAI 2022, 97e ANNÉE
No 18, **2022**, **97**, 173–184
http://www.who.int/wer

Contents

173 Meeting of the Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC), March 2022

Sommaire

173 Réunion du Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC), mars 2022

Meeting of the Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC), March 2022

The IVIR-AC recommendations are based on discussions during a virtual meeting of the IVIR-AC held 7 – 11 March 2022 and 1 April 2022 (COVID-19 Ad-hoc session) (See background information available at: https://terrance.who.int/mediacentre/data/sage/220225-IVIR-AC-Pink-Book-March-2022.pdf, accessed March 2022).

COVID-19 immunity

Delta and Omicron COVID-19 variant waves have reached very high global attack rates, particularly in countries with low vaccine coverage. This alters the immune landscape of SARS-CoV-2 necessitating reevaluation of effective and cost-effective vaccination strategies (e.g. single dose in low-risk adults in settings with high rates of prior infection, vaccination in children). To inform their upcoming presentation to the WHO Strategic Advisory Group of Experts on Immunization (SAGE) on hybrid immunity and to stimulate dialogue on future COVID-19 vaccination policy questions and considerations, the *SAGE working group subgroup on vaccine impact modelling for COVID-19 (SG COVID-19)* presented a summary of the epidemiological context of Omicron, including data and analytical gaps preventing a systematic way to account for naturally acquired and hybrid immunity in vaccine recommendations. IVIR-AC was requested to review and confirm whether the current summary narrative and planned presentations capture and provide a complete and coherent picture of the complex and evolving COVID-19 immunity landscape.

Réunion du Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC), mars 2022

Les recommandations de l'IVIR-AC présentées ici sont fondées sur les discussions qui ont eu lieu lors d'une réunion virtuelle de l'IVIR-AC qui s'est tenue du 7 au 11 mars 2022 et d'une session ad hoc sur la COVID-19 organisée le 1er avril 2022. (Voir la documentation disponible à l'adresse: https://terrance.who.int/mediacentre/data/sage/220225-IVIR-AC-Pink-Book-March-2022.pdf, consulté en mars 2022.)

Immunité contre la COVID-19

Les variants Delta et Omicron qui ont donné lieu à des vagues de COVID-19 ont atteint des taux d'attaque très élevés à l'échelle mondiale, en particulier dans les pays où la couverture vaccinale est faible. Cette situation modifie le paysage de l'immunité contre le SARS-CoV-2 et nécessite une réévaluation des stratégies de vaccination efficaces et d'un bon rapport coût/efficacité (par exemple une seule dose pour les adultes à faible risque dans les milieux où les taux d'infection antérieure sont élevés, la vaccination des enfants). Afin d'étayer sa prochaine présentation sur l'immunité hybride au Groupe stratégique consultatif d'experts (SAGE) de l'OMS sur la vaccination et de stimuler le dialogue sur les questions et considérations futures en matière de politique de vaccination contre la COVID-19, le *sous-groupe chargé de la modélisation de l'impact des vaccins anti-COVID-19 (SG COVID-19)* au sein du groupe de travail du SAGE a présenté un résumé du contexte épidémiologique d'Omicron, y compris les lacunes en matière de données et d'analyses qui empêchent de rendre compte de manière systématique de l'immunité naturellement acquise et de l'immunité hybride dans les recommandations vaccinales. L'IVIR-AC a été invité à examiner l'exposé actuel et les présentations prévues et à déterminer s'ils saisissent et fournissent une image complète et cohérente du paysage complexe et évolutif de l'immunité contre la COVID-19.

Summary of IVIR-AC feedback and recommendations

IVIR-AC agreed with the key considerations and data gaps identified and presented by the SG COVID-19 and highlighted additional considerations with respect to COVID-19 immunity:

- A better understanding of immunity from both previous infection and vaccination (including with different types of vaccines) against infection and severe disease is needed.
- Infection-induced immunity may vary depending on type of infection, variant causing infection and outcome of interest.
- The breadth of immune responses may vary depending on whether boosting is with homologous versus heterologous vaccines.
- "At risk" populations need to be further defined based on their ability to respond to vaccination.
- Further consideration and characterization of T-cell and B-cell memory responses is needed as antibodies may not provide a sufficiently good correlate of immunity against severe disease, and in particular, waning immunity against severe disease.

IVIR-AC highlighted future COVID-19 immunity modelling considerations:

- Modelling variant scenarios should focus on determining thresholds (for immune escape–against infection versus severe disease, transmissibility and/or severity) that would necessitate a change in current health policy approaches (with a focus on vaccine policy) and the data needed to rapidly characterize the properties of new variants.
- The *SG COVID-19* should continue to identify, support and advise modelling groups from different countries, to ensure a variety of modelling approaches and perspectives are included.
- Models should differentiate between infection- and vaccine-derived immunity against infection versus severe disease. Future modelling efforts should focus on prevention of severe disease as the primary outcome of interest.

IVIR-AC noted the importance of simplifying vaccine recommendations to ensure optimal implementation and uptake and noted additional considerations for vaccination strategy development. For example, a recommendation based on age groups would be easier to implement than a recommendation based on the presence of specific conditions/co-morbidities:

- A wider set of vaccination strategies may be needed for different vaccines. More data are needed to compare and parameterize vaccine effectiveness over time for different vaccines currently in use (e.g. Sinovac, CoronaVac, Cansino, Bharat).

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

L'IVIR-AC a souscrit aux principales considérations et à la description des lacunes en matière de données identifiées et présentées par le SG COVID-19 et a souligné d'autres considérations concernant l'immunité contre la COVID-19:

- une meilleure compréhension de l'immunité acquise à la suite d'une infection antérieure et de l'immunité conférée par la vaccination (y compris avec différents types de vaccins) contre l'infection et les formes graves de la maladie est nécessaire;
- l'immunité induite par l'infection peut varier en fonction du type d'infection, du variant à l'origine de l'infection et du résultat d'intérêt;
- l'ampleur des réponses immunitaires peut varier selon que le renforcement de l'immunité est procuré par des vaccins homologues ou hétérologues;
- les populations «à risque» doivent être définies plus précisément en fonction de leur capacité à répondre à la vaccination;
- un examen et une caractérisation plus approfondis des réponses des lymphocytes mémoire T et B sont nécessaires, car les anticorps peuvent ne pas fournir un corrélat suffisamment bon de l'immunité contre les formes graves de la maladie, en particulier en termes de déclin progressif de l'immunité contre les formes graves.

L'IVIR-AC a mis en évidence des considérations pour la modélisation future de l'immunité contre la COVID-19:

- la modélisation fondée sur différents scénarios de variants devrait être axée sur la détermination de seuils (pour l'échappement immunitaire – contre l'infection et contre les formes graves, la transmissibilité et/ou la sévérité) au-delà desquels un changement serait nécessaire dans les politiques de santé actuelles (en mettant l'accent sur la politique vaccinale), et sur les données nécessaires pour caractériser rapidement les propriétés des nouveaux variants;
- le SG COVID-19 devrait continuer d'identifier, de soutenir et de conseiller les groupes de modélisation de différents pays pour faire en sorte d'inclure une variété d'approches et de perspectives en matière de modélisation;
- les modèles doivent faire la distinction entre l'immunité consécutive à une infection et celle conférée par la vaccination contre l'infection et contre les formes graves de la maladie; les futurs travaux de modélisation devraient être axés sur la prévention des formes graves de la maladie en tant que principal résultat d'intérêt.

L'IVIR-AC a souligné l'importance de simplifier les recommandations vaccinales pour assurer une mise en œuvre et une adoption optimales de la vaccination et a relevé d'autres considérations pour l'élaboration des stratégies de vaccination. Par exemple, une recommandation fondée sur des tranches d'âge serait plus facile à mettre en œuvre qu'une recommandation fondée sur la présence d'affections ou de comorbidités particulières:

- un ensemble plus large de stratégies de vaccination peut être nécessaire pour différents vaccins. Davantage de données sont nécessaires pour comparer et paramétrer l'efficacité des vaccins au fil du temps pour différents vaccins actuellement utilisés (par exemple Sinovac, CoronaVac, CanSino, Bharat);

- Future strategies for repeat "booster" vaccination should consider whether the frequency of vaccination be timed to waning of immunity or the reemergence of new variants.

Measles case fatality ratio (CFR) estimation

Measles remains a worldwide infectious disease causing unpredictable and explosive epidemic outbreaks in endemic settings. To ensure that data on measles mortality reflect the current global state of measles, WHO aims to update and improve measles mortality estimates by utilizing reliable, robust, transparent and dynamic age- and country-specific measles case fatality ratios. On behalf of the working group of experts convened to support this aim, the London School of Hygiene and Tropical Medicine (LSHTM) and Harvard School of Public Health presented a conceptual framework of indicators[1] related to measles CFR, and preliminary estimates from a new methodology and expanded literature review. Building on previous recommendations made by IVIR-AC in March 2021,[2] IVIR-AC in March 2022 provided several technical suggestions for the next iteration of model refinement and stressed again the global public health importance of the initiative.

Summary of IVIR-AC feedback and recommendations

- IVIR-AC reinforced its past recommendation to make financial and human resources available to support model development, literature and data reviews, and the generation of CFRs, predictions and projections.

- On the proposed selection of indicators[1] to be used in the meta-regression models, IVIR-AC recommended:
  - to clearly state the statistical criteria for selecting the final list of indicators in each mechanistic modelling group to ensure transparency;
  - to examine the collinearity of proxy indicators that fall within more than 1 mechanistic modelling group; and
  - to ensure that the included indicators, or proxy indicators, have an association with measles CFR supported by evidence in the literature.

- The decomposition analysis should state the metric(s) used to quantify the changes resulting from the updated modelling framework, new data and selected indicators.

- les futures stratégies relatives aux doses de rappel répétées devraient déterminer si la fréquence des rappels doit être fonction de la baisse de l'immunité ou de l'émergence de nouveaux variants.

Estimation du taux de létalité due à la rougeole

La rougeole demeure une maladie infectieuse qui sévit dans le monde entier et qui donne lieu à des épidémies imprévisibles et explosives dans les milieux d'endémie. Pour s'assurer que les données sur la mortalité rougeoleuse reflètent l'état actuel de la rougeole dans le monde, l'OMS vise à actualiser et à améliorer les estimations de la mortalité due à la rougeole en utilisant des taux de létalité fiables, robustes, transparents et dynamiques par âge et par pays. Pour le compte du groupe de travail d'experts réuni pour soutenir cet objectif, la London School of Hygiene and Tropical Medicine et la Harvard School of Public Health ont présenté un cadre conceptuel d'indicateurs[1] liés au taux de létalité due à la rougeole, ainsi que des estimations préliminaires établies à partir d'une nouvelle méthode et d'une revue élargie de la littérature. S'appuyant sur ses précédentes recommandations formulées en mars 2021,[2] l'IVIR-AC a fourni en mars 2022 plusieurs suggestions techniques pour la prochaine itération d'affinement du modèle et a réitéré l'importance de cette initiative pour la santé publique mondiale.

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

- L'IVIR-AC a renforcé sa recommandation antérieure préconisant de mettre à disposition des ressources financières et humaines pour soutenir l'élaboration de modèles, l'examen de la littérature et des données, ainsi que la génération de taux de létalité, de prédictions et de projections.
- En ce qui concerne la sélection proposée d'indicateurs[1] à utiliser dans les modèles de métarégression, l'IVIR-AC a recommandé:
  - d'énoncer clairement les critères statistiques utilisés pour établir la liste définitive des indicateurs dans chaque groupe de modélisation mécaniste afin de garantir la transparence;
  - d'examiner la colinéarité des indicateurs indirects qui relèvent de plus d'un groupe de modélisation mécaniste; et
  - de s'assurer qu'il existe une association des indicateurs qui sont inclus, ou des indicateurs indirects, avec le taux de létalité due à la rougeole, laquelle est étayée par des données probantes dans la littérature.

- L'analyse de décomposition devrait indiquer le ou les paramètres utilisés pour quantifier les changements résultant du cadre de modélisation mis à jour, des nouvelles données et des indicateurs sélectionnés.

[1] Indicators are factors presumed to be related to measles' CFR.

[2] See No. 17, 2021, pp. 133–143.

[1] Les indicateurs sont des facteurs présumés liés au taux de létalité due à la rougeole.

[2] Voir N° 17, 2021, pp. 133-143.

- To increase transparency, IVIR-AC recommended, where applicable, to post project timelines on the online project website to illustrate the process to date and to show forthcoming actions with direct links to the published work, updates (e.g. systematic reviews, conceptual model), modelling codes (e.g. R-packages), data sources, project results and details of the working group.

- Periodically reassess indicators and update the list of indicators selected, as needed, with a particular focus on the potential availability of new data.

- In future iterations of the systematic reviews (for studies reporting measles CFRs and for those assessing the association of indicators with measles CFR), expand the literature search to databases beyond PubMed – i.e. Embase and the Cochrane Library.
- Consider and include study quality and case definitions as part of the meta-regression model development and seek to validate predicted CFRs against unpublished data sources not used for model fitting.

Behavioural and social drivers (BeSD) of vaccination

In 2018, WHO established a global working group called Measuring Behavioural and Social Drivers of Vaccination which contributed to the development of practical tools and guidance that enabled programmes to assess and address reasons for low vaccine uptake for childhood and COVID-19 vaccinations. In October 2021, WHO's Strategic Advisory Group of Experts on Immunization reviewed the related evidence and findings from the tool testing and validation process, leading to SAGE's recommendations to WHO on standardized gathering and use of data on BeSD.[3]

WHO is preparing activities to encourage and accelerate country implementation of the guidance and tools – e.g., supporting integration of indicators into existing surveys, providing digital tools and automated report templates, building capacity, providing technical assistance, disseminating findings and trends and documenting case examples to illustrate the practical use of the tools. IVIR-AC was asked for feedback on global harmonization of BeSD data, the proposed next steps to produce comparable data sets, and ways to encourage and support the standardized use of tools and methods to benefit countries.

Summary of IVIR-AC feedback and recommendations

IVIR-AC acknowledged the importance of BeSD of vaccination, especially in low- and middle-income coun-

[3] See No. 50, 2021, pp. 613–632.

- Afin d'accroître la transparence, il est recommandé, le cas échéant, d'afficher les échéances du projet sur le site Web correspondant pour illustrer le processus à ce jour et montrer les actions à venir, avec des liens directs vers les travaux publiés, les mises à jour (par exemple les revues systématiques, le modèle conceptuel), les codes de modélisation (par exemple les paquets R), les sources de données, les résultats du projet et les informations sur le groupe de travail.
- Il est préconisé de réévaluer périodiquement les indicateurs et de mettre à jour la liste des indicateurs sélectionnés, si besoin, en accordant une attention particulière à la disponibilité potentielle de nouvelles données.
- Dans les futures itérations des revues systématiques (pour les études présentant des taux de létalité due à la rougeole et pour celles évaluant l'association d'indicateurs avec le taux de létalité due la rougeole), la recherche documentaire devrait être élargie à d'autres bases de données que PubMed – c'est-à-dire Embase et la Cochrane Library.
- Il convient de prendre en compte et d'inclure la qualité des études et les définitions de cas dans le cadre du développement du modèle de métarégression et de chercher à valider les taux de létalité prédits par rapport à des sources de données non publiées et non utilisées pour l'ajustement du modèle.

Facteurs comportementaux et sociaux de la vaccination

En 2018, l'OMS a créé un groupe de travail mondial chargé de mesurer les facteurs comportementaux et sociaux de la vaccination ; ce groupe a contribué à l'élaboration d'outils pratiques et d'orientations qui ont permis aux programmes d'évaluer et de s'attaquer aux causes de la faible adoption de vaccins de l'enfant et des vaccins contre la COVID-19. En octobre 2021, le SAGE a examiné les données probantes et les conclusions issues du processus d'essai et de validation des outils, puis formulé des recommandations à l'OMS sur la collecte et l'utilisation normalisées des données sur les facteurs comportementaux et sociaux.[3]

L'OMS prépare des activités visant à encourager et à accélérer la mise en œuvre par les pays de ces orientations et outils – par exemple, en aidant à l'intégration d'indicateurs dans les enquêtes existantes, en fournissant des outils numériques et des modèles de rapport automatisés, en renforçant les capacités, en fournissant une assistance technique, en diffusant les résultats et les tendances et en présentant des exemples de cas pour illustrer l'utilisation de ces outils dans la pratique. Il a été demandé à l'IVIR-AC d'émettre des commentaires sur l'harmonisation des données sur les facteurs comportementaux et sociaux à l'échelle mondiale, sur les prochaines étapes proposées pour produire des ensembles de données comparables et sur les moyens d'encourager et de soutenir l'utilisation standardisée d'outils et de méthodes au profit des pays.

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

L'IVIR-AC a reconnu l'importance des facteurs comportementaux et sociaux de la vaccination, en particulier dans les pays

[3] Voir N° 50, 2021, pp. 613–632.

tries (LMICs) and suggested ways to further minimize any added burden by leveraging existing activities related to gathering and use of immunization programme data. To that end, IVIR-AC recommended the following:

- Ensure that all data-collection tools are friendly/easy to implement at all levels.
- Automate as many processes as possible, including data-handling, cleaning, analysis and dissemination.
- Develop templates for protocols, consent forms, interview scripts and others.
- Embed BeSD priority indicators within epidemiological reviews and other routine assessments/surveys.
- Encourage vaccination sites to add priority indicators as well as other items which are directly relevant to their local setting and which may immediately inform efforts to increase coverage.
- Build the capacity of qualitative researchers who may assist immunization programmes.

- Consider further research on drivers such as political trust.
- Suggest additional demographic information (e.g. education, rurality) which may facilitate policy development or implementation and evaluation of targeted interventions.

IVIR-AC suggested the provision of:

- more case examples of findings from the use of the BeSD tools and subsequent actions;

- a set of minimum requirements for priority questions and data collection methods to facilitate the tracking of comparable data at all levels;
- further clarification of specific influences which are measurable and changeable;
- validation of the conceptual framework and tools by conducting additional analyses (e.g. structural equation modelling) as data using the tool are accumulated;
- guidance on how quantitative and qualitative findings from the tools could be used in a complementary way (i.e. from the perspective of mixed methods).

Developing guidance on methodologies to measure the impact of vaccines in preventing antimicrobial resistance

Antimicrobial resistance (AMR) is considered 1 of the top 10 global public health threats facing humanity.[4] Although vaccines are effective at reducing the incidence of both drug-sensitive and resistant pathogens, thereby limiting AMR, assessing a vaccine's impact on AMR is complex and hard to measure. Impact varies by high- or low-resourced settings, pathogens, vaccine types, clinical trial phases, target population and possibly

à revenu faible ou intermédiaire (PRFI) et a suggéré des moyens pour réduire davantage toute charge supplémentaire en tirant parti des activités existantes liées à la collecte et à l'utilisation des données des programmes de vaccination. À cet effet, l'IVIR-AC a recommandé:

- de s'assurer que tous les outils de collecte de données sont conviviaux/faciles à mettre en œuvre à tous les niveaux;
- d'automatiser autant de processus que possible, notamment le traitement, le nettoyage, l'analyse et la diffusion des données;
- d'élaborer des modèles pour les protocoles, les formulaires de consentement, les scripts d'entretien et autres;
- d'intégrer les indicateurs prioritaires des facteurs comportementaux et sociaux dans les revues épidémiologiques et autres évaluations/enquêtes systématiques;
- d'encourager les sites de vaccination à ajouter des indicateurs prioritaires ainsi que d'autres éléments directement liés à leur contexte local et susceptibles de guider immédiatement les efforts visant à accroître la couverture;
- de renforcer les capacités des spécialistes en recherche qualitative qui peuvent aider les programmes de vaccination;
- d'envisager d'autres travaux de recherche sur des facteurs comme la confiance dans la politique;
- de suggérer des informations démographiques supplémentaires (par exemple l'éducation, la ruralité) qui peuvent faciliter l'élaboration ou la mise en œuvre de politiques et l'évaluation d'interventions ciblées.

L'IVIR-AC a suggéré de fournir:

- davantage d'exemples de constatations tirées de l'utilisation des outils pour les facteurs comportementaux et sociaux et des actions qui en découlent;
- un ensemble d'exigences minimales pour les questions prioritaires et les méthodes de collecte de données afin de faciliter le suivi de données comparables à tous les niveaux;
- une clarification plus précise des éléments d'influence spécifiques qui sont mesurables et modifiables;
- la validation du cadre conceptuel et des outils en effectuant des analyses supplémentaires (par exemple la modélisation par équations structurelles) au fur et à mesure de l'accumulation des données utilisées avec ces outils;
- des conseils sur la façon dont les résultats quantitatifs et qualitatifs obtenus avec ces outils pourraient être utilisés de manière complémentaire (c'est-à-dire dans la perspective de méthodes mixtes).

Élaboration d'orientations sur les méthodes permettant de mesurer l'impact des vaccins pour prévenir la résistance aux antimicrobiens

La résistance aux antimicrobiens (RAM) est considérée comme l'une des 10 plus grandes menaces pour la santé publique mondiale auxquelles l'humanité est confrontée.[4] Bien que les vaccins soient efficaces pour réduire l'incidence des agents pathogènes sensibles mais aussi résistants aux médicaments, limitant ainsi la RAM, évaluer l'impact d'un vaccin sur la RAM est complexe et le mesurer est difficile. L'impact varie selon les ressources des zones considérées, les agents pathogènes, les

[4] See https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance (accessed March 2022).

[4] Voir https://www.who.int/fr/news-room/fact-sheets/detail/antimicrobial-resistance (consulté en mars 2022).

other unknown variables. A global coordinated response to AMR relies on a common understanding, starting with the harmonization of approaches to evaluating vaccine impact on AMR and the ability to compare results. To address this need, WHO is developing guidance on methodologies for measuring vaccine impact on AMR (for both licensed vaccines and those in development), focusing on potential outcome measures for AMR – i.e. vaccine-averted prevalence of AMR,[5] incidence of drug-resistant infections,[6] number of deaths due to drug-resistant infections over time, antibiotic use and economic burden.

The presenters explained the need for such guidance within the context of ongoing work on vaccines and AMR within WHO and outlined their next steps within the proposed approach, methodology and case example – typhoid conjugate vaccines. IVIR-AC was requested to provide feedback on the scope of the project and details on case studies.

Summary of IVIR-AC feedback and recommendations

In response to the proposed vaccine case studies, IVIR-AC recommended:

- expanding the focus to include respiratory pathogens as they are known contributors to AMR;
- choosing pathogens that are representative of the different pathways through which vaccination may have an impact on AMR; and
- including a case study in which vaccine impact on AMR is indirect, such as respiratory syncytial virus (RSV)[7]

IVIR-AC stressed that modelling is essential to understanding vaccine impact on AMR, since this impact varies across space and time. Therefore, IVIR-AC recommended either:

- to expand the scope of the landscape analysis to include modelling studies; or
- to clarify and stress in the resulting guidance document that the landscape analysis covered only primary data collection and that modelling is needed to get a complete assessment of vaccine impact.

To clarify and distinguish the indicators (potential outcome measures) of the burden of AMR, IVIR-AC suggested:

- to define and organize indicators of AMR burden and vaccine impact as those for the vaccine-targeted pathogen (direct effects) and those for

[5] Vaccine-averted prevalence of AMR = % of infections that are resistant to antimicrobials at a given time.

[6] Incidence of drug-resistant infections = the number of resistant infections over time.

[7] RSV has a crowded vaccine pipeline and high annual attack rates in children, which if prevented, would eliminate antibiotic misuse and any opportunity to provide selective pressure for the emergence of AMR.

types de vaccins, les phases d'essais cliniques, la population cible et peut-être d'autres variables inconnues. Une réponse mondiale coordonnée à la RAM repose sur une compréhension commune, à commencer par l'harmonisation des approches d'évaluation de l'impact des vaccins sur la RAM et la capacité de comparer les résultats. Pour répondre à ce besoin, l'OMS élabore des orientations sur les méthodes permettant de mesurer l'impact des vaccins sur la RAM (tant pour les vaccins homologués que pour ceux en cours de développement), en mettant l'accent sur la mesure de résultats potentiels en matière de RAM – c'est-à-dire la prévalence de la RAM évitée par la vaccination,[5] l'incidence des infections pharmacorésistantes, le nombre de décès dus aux infections pharmacorésistantes[6] au fil du temps, l'utilisation d'antibiotiques et la charge économique.

Les intervenants ont expliqué la nécessité de telles orientations dans le contexte des travaux en cours sur les vaccins et la RAM au sein de l'OMS et ont décrit leurs prochaines étapes dans le cadre de l'approche proposée, la méthode employée et un exemple concret – les vaccins conjugués antityphoïdiques. L'IVIR-AC a été invité à émettre des commentaires sur la portée du projet et les informations détaillées des études de cas.

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

En réponse aux études de cas de vaccins proposées, l'IVIR-AC a recommandé:

- d'étendre les travaux aux agents pathogènes respiratoires, car l'on sait qu'ils contribuent à la RAM;
- de choisir des agents pathogènes représentatifs des différentes voies par lesquelles la vaccination peut avoir un impact sur la RAM; et
- d'inclure une étude de cas dans laquelle l'impact de la vaccination sur la RAM est indirect, comme dans le cas du vaccin contre le virus respiratoire syncytial (VRS).[7]

L'IVIR-AC a souligné que la modélisation est essentielle pour comprendre l'impact des vaccins sur la RAM, car cet impact varie dans l'espace et dans le temps. Par conséquent, l'IVIR-AC a recommandé:

- d'élargir la portée de l'analyse du paysage pour inclure les études de modélisation; ou
- de clarifier et de souligner dans le document d'orientation à venir que l'analyse du paysage ne se fonde que sur la collecte de données primaires et que la modélisation est nécessaire pour obtenir une évaluation complète de l'impact des vaccins.

Pour clarifier et distinguer les indicateurs (résultats potentiels mesurés) de la charge de la RAM, l'IVIR-AC a suggéré:

- de définir et d'organiser les indicateurs de la charge de la RAM et de l'impact des vaccins pour les agents pathogènes ciblés par un vaccin (effets directs) et pour ceux qui ne

[5] Prévalence de la RAM évitée par la vaccination = % d'infections résistantes aux antimicrobiens à un moment donné.

[6] Incidence des infections pharmacorésistantes = nombre d'infections résistantes au fil du temps.

[7] De nombreux vaccins sont à l'étude contre le VRS; le taux d'attaque annuel de ce virus est élevé chez les enfants et prévenir ces infections permettrait d'éviter l'usage inadapté d'antibiotiques et d'éliminer toute possibilité de fournir une pression sélective susceptible de donner lieu à l'émergence d'agents pathogènes résistants.

non-focal pathogens (indirect effects[8]) and by threat level; and
- to further differentiate the direct effects based on measures of resistance to specific antibiotics.

IVIR-AC made additional technical suggestions, as follows:

- Add a specific question on potential pitfalls to the "challenges" part of the expert interviews.

- Widen the interview-based needs analysis to include an online consultation.
- Focus primarily on post-licensure studies when measuring changes in antibiotic usage following vaccination, since blinding of study participants and researchers in the context of randomized controlled trials (RCTs) may dampen potential effects.
- Focus on settings with intermediate prevalence of AMR to ensure maximal statistical power to differentiate between elements such as vaccine effectiveness, severity and cost of illness of resistant versus sensitive strains.

- Prepare additional guidance on measuring vaccine impact on AMR (indicators, measurement, standardization) for observational studies.
- Consider that genomic data and analyses may be useful to differentiate and reveal mechanisms by which vaccination may reduce the prevalence of AMR, particularly for *Salmonella Typhi*.

Evaluation of a modelling approach to assess the public health value and preferred product characteristics of a therapeutic vaccine for human papillomavirus

In August 2020, the World Health Assembly adopted the *Global strategy to accelerate the elimination of cervical cancer as a public health problem*,[9] echoing ongoing efforts by WHO since 2018.[10] WHO's global strategy for cervical cancer elimination includes scale-up of prophylactic vaccination against human papillomavirus (HPV), cervical cancer screening and treatment of cervical pre-cancers and cancer. Therapeutic HPV vaccines in early clinical development may be useful in clearing existing HPV infection and/or regressing pre-cancerous lesions, as a complement to existing cervical cancer prevention interventions and as an option for women who did not receive prophylactic vaccine in early adolescence.

The added value of therapeutic HPV vaccination and the *preferred product characteristics* (PPCs) are not well understood. The presenters outlined the rationale for the WHO elimination strategy for cervical cancer and

[8] For instance, decreasing bacterial secondary infections and the need for antibiotics or misuse of antibiotics to treat illnesses for which antibiotics are not indicated

[9] See https://www.who.int/publications/i/item/9789240014107 (accessed March 2022).

[10] See https://www.who.int/publications/i/item/9789240014107 (accessed March 2022).

sont pas ciblés (effets indirects[9]) et pour les différents niveaux de menace; et
- de différencier plus avant les effets directs en fonction des mesures de la résistance à des antibiotiques donnés.

L'IVIR-AC a soumis les suggestions techniques supplémentaires suivantes:

- ajouter une question spécifique sur les écueils potentiels à la partie relative aux «difficultés» dans les entretiens avec les experts;
- élargir l'analyse des besoins fondée sur les entretiens pour inclure une consultation en ligne;
- se concentrer principalement sur les études post-homologation lorsqu'il s'agit de mesurer les changements dans l'utilisation des antibiotiques après la vaccination, car le double insu (participants et chercheurs) dans le contexte des essais contrôlés randomisés (ECR) peut atténuer les effets potentiels;
- se concentrer sur les zones où la prévalence de la RAM est intermédiaire afin d'obtenir une puissance statistique maximale pour différencier des éléments tels que l'efficacité de la vaccination en population, la sévérité et le coût des maladies dues à des souches résistantes par rapport aux souches sensibles;
- préparer des orientations supplémentaires sur la mesure de l'impact des vaccins sur la RAM (indicateurs, mesure, standardisation) pour les études d'observation;
- considérer que les données et les analyses génomiques peuvent être utiles pour différencier et révéler les mécanismes par lesquels la vaccination peut réduire la prévalence de la RAM, en particulier pour *Salmonella Typhi*.

Évaluation d'une approche de modélisation pour évaluer l'utilité pour la santé publique et les caractéristiques à privilégier d'un vaccin thérapeutique contre le papillomavirus humain

En août 2020, l'Assemblée mondiale de la Santé a adopté la *Stratégie mondiale en vue d'accélérer l'élimination du cancer du col de l'utérus en tant que problème de santé publique*,[9] faisant écho aux efforts continus de l'OMS depuis 2018.[10] Cette stratégie comprend l'intensification de la vaccination prophylactique contre le papillomavirus humain (PVH), le dépistage du cancer du col de l'utérus et le traitement des lésions précancéreuses et du cancer du col de l'utérus. Les vaccins thérapeutiques contre l'infection à PVH administrés à un stade clinique précoce peuvent être utiles pour éliminer l'infection existante et/ou faire régresser les lésions précancéreuses, en complément des interventions existantes de prévention du cancer du col de l'utérus et comme option pour les femmes qui n'ont pas reçu de vaccin prophylactique au début de l'adolescence.

La valeur ajoutée de la vaccination thérapeutique contre le PVH et les caractéristiques du produit à privilégier ne sont pas bien comprises. Les intervenants ont exposé la raison d'être de la stratégie d'élimination du cancer du col de l'utérus de l'OMS

[8] Par exemple, la diminution des infections bactériennes secondaires et la nécessité de recourir à des antibiotiques ou l'usage inadapté d'antibiotiques pour traiter des maladies pour lesquelles ils ne sont pas indiqués.

[9] Voir https://www.who.int/publications/i/item/9789240014107 (consulté en mars 2022).

[10] Voir https://www.who.int/publications/i/item/9789240014107 (consulté en mars 2022).

provided a detailed overview of past and planned activities, including PPC determination and modelling,[11] to assess the impact and cost-effectiveness of therapeutic HPV vaccination. IVIR-AC was asked to provide feedback on the suitability of the proposed modelling plan, steps, scenarios and related assumptions for decision-making.

Summary of IVIR-AC feedback and recommendations

- IVIR-AC confirmed the choice of model and approach as suitable to address questions about the impact of therapeutic vaccination, noting the extremely ambitious timeline.
- IVIR-AC acknowledged that the extensive expert consultations support the modelling scenarios, assumptions and use cases and agreed that they reflect our best knowledge at this time.
- IVIR-AC welcomed the acknowledgment by the modelling team that they will track *time in state*[12] in different populations, explore more optimistic baseline coverage scenarios for preventive vaccination and screening and provide further detail on the economic analysis to be conducted when these have been finalized.
- IVIR-AC acknowledged that *Use case 1* (giving therapeutic vaccine to all adult females in a cohort) is not likely to be cost-effective, but that data to that effect may provide additional insight.
- IVIR-AC stressed the need for extensive sensitivity analyses of assumptions in the calibration of HIV effects in *Policy1-Cervix*-HIV to the United Republic of Tanzania data and for the generic model of sexual behaviour applied in the 78-country platform.
- IVIR-AC welcomed the revised thinking on *Staging of analyses* and suggested consideration not only of criteria scenarios for further analysis but also of criteria to re-evaluate a subset of scenarios that were omitted in the early stages of analysis.

Evaluation of morbidity associated with enteric pathogens

Diarrhoeal infections are a leading cause of childhood 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 socioeconomic burden needs to be evaluated and communicated to encourage and justify investment in vaccine development and deployment.

Although global mortality estimates of enteric pathogens exist, there are limited data on the broad, long-

et ont présenté une vue d'ensemble détaillée des activités passées et prévues, y compris la détermination des caractéristiques du produit à privilégier et la modélisation,[11] pour évaluer l'impact et le rapport coût-efficacité de la vaccination thérapeutique contre le PVH. Il a été demandé à l'IVIR-AC d'émettre des commentaires sur la pertinence du plan de modélisation proposé, des étapes, des scénarios et des hypothèses connexes pour la prise de décisions.

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

- L'IVIR-AC a confirmé la pertinence du choix du modèle et de l'approche pour répondre aux questions sur l'impact de la vaccination thérapeutique, en relevant que le calendrier était extrêmement ambitieux.
- L'IVIR-AC a reconnu que les vastes consultations d'experts vont dans le sens des scénarios de modélisation, des hypothèses et des utilisations envisagées et a convenu qu'ils reflétaient nos meilleures connaissances à l'heure actuelle.
- L'IVIR-AC s'est félicité de l'intention de l'équipe de modélisation de suivre le «*time in state*» dans différentes populations, d'étudier des scénarios plus optimistes de couverture de base de la vaccination préventive et du dépistage et de fournir davantage de détails sur l'analyse économique à effectuer lorsque ceux-ci auront été finalisés.[12]
- L'IVIR-AC a reconnu que le rapport coût-efficacité du *scénario d'utilisation 1* (administrer un vaccin thérapeutique à toutes les femmes adultes d'une cohorte) n'est probablement pas satisfaisant, mais que les données à cet effet peuvent fournir des informations supplémentaires.
- L'IVIR-AC a souligné la nécessité d'effectuer des analyses de sensibilité approfondies des hypothèses de calibrage des effets du VIH dans le modèle *Policy1-Cervix*-HIV pour les données de la République Unie de Tanzanie et pour le modèle générique de comportement sexuel appliqué sur la plateforme incluant 78 pays.
- L'IVIR-AC s'est félicité de la réflexion révisée sur le phasage des analyses (*Staging of analysis*) et a suggéré d'envisager non seulement des scénarios basés sur des critères en vue d'une analyse plus approfondie, mais aussi des critères permettant de réévaluer un sous-ensemble de scénarios qui ont été omis dans les premiers stades de l'analyse.

Évaluation de la morbidité associée aux agents pathogènes entériques

Les infections diarrhéiques sont l'une des principales causes de mortalité et de morbidité de l'enfant. Des vaccins contre l'infection à *Shigella, E. coli* entérotoxinogène (ETEC), le norovirus et *Salmonella* non typhique invasive sont en cours de développement clinique; toutefois, leur *pleine valeur* en termes de santé à court et à long terme et de charge socio-économique doit être évaluée et communiquée pour encourager et justifier les investissements dans le développement et le déploiement de vaccins.

Bien qu'il existe des estimations mondiales de la mortalité due aux agents pathogènes entériques, il existe peu de données sur

[11] Utilizing Policy-1 cervix which is an extensively validated dynamic model of HPV transmission, vaccination, precancer, cancer survival, screening, diagnosis and treatment. See https://www.policy1.org/models/cervix (accessed March 2022).

[12] *Time in state* is the time since entering a stage of infection.

[11] Utilisant Policy1-Cervix, un modèle dynamique largement validé de la transmission du PVH, de la vaccination, des lésions précancéreuses, de la survie au cancer, du dépistage, du diagnostic et du traitement. Voir https://www.policy1.org/models/cervix (consulté en mars 2022).

[12] *«Time in state»* est le temps écoulé depuis l'infection.

term impact of these pathogens (e.g., growth retardation, mental status impairment, etc.). WHO and the Burden of Enteric Diseases Morbidity Working Group (BoED MWG)[13] aim to assess the long-term burden of enteric pathogens as part of the *full value of enteric vaccines value assessment.*

The rationale for long-term morbidity evaluation, the analysis approach utilizing the MAL-ED[14] study to investigate the impact of pathogens on long-term morbidity and the systematic review methodology to identify evidence of long-term morbidity from ETEC, norovirus and *Campylobacter* were presented. IVIR-AC was asked for feedback on the proposed framework, analysis plan and systematic review.

Summary of IVIR-AC feedback and recommendations

- IVIR-AC acknowledged the unique suitability of the MAL-ED data set (a longitudinal cohort) to contribute long-term morbidity estimates but recommended an analysis plan a priori due to the complexity of such an assessment.
- IVIR-AC recommended a minimum agreement threshold[15] be pre-specified for the data extraction phase of the systematic review which, if not met, would trigger extraction of data from all articles by the second reviewer and a third reviewer, if necessary, to reach consensus.
- IVIR-AC noted several technical aspects to consider, namely:
  - individual-level episodes of infection and shedding could be probabilistic estimates in a Markov model, rather than pre-defined assumptions which could be artificial cut-off values for the duration of incubation and post diarrhoeal shedding;
  - the impact of co-infections in enhancing exposure effects could be estimated within the model framework;
  - self-controlled case series design could be an alternative to assessing short-term impacts of infection on growth, while accounting for individual-level confounders (e.g., comparing rate of growth prior to the enteric disease episode with growth after the episode).
- IVIR-AC suggested:
  - consideration of qualitative, person-centered methods to prepare for future work on disease burden (educational, cost, social etc.), such as a small sample which could examine the

[13] Hasso-Agopsowicz M et al. WHO Expert Working Group: Recommendations for assessing morbidity associated with enteric pathogens. Vaccine. 2021;39(52):7521–5. doi:10.1016/j.vaccine.2021.11.033.

[14] MAL-ED Network Investigators. 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. Clin Infect Dis. 2014;59(Suppl 4):S193–206. doi:10.1093/cid/ciu653.

[15] A Minimum agreement threshold is the lowest percent agreement allowed between 2 reviewers to still conclude consensus when evaluating studies as part of a systematic review.

leur impact général à long terme (par exemple le retard de croissance, l'altération de l'état mental, etc.). L'OMS et le Groupe de travail sur la charge de la morbidité liée aux maladies entériques[13] cherchent à évaluer la charge à long terme des agents pathogènes entériques dans le cadre de *l'évaluation de la pleine valeur des vaccins contre les maladies entériques.*

La justification de l'évaluation de la morbidité à long terme, la méthode d'analyse utilisant l'étude MAL-ED[14] pour étudier l'impact des agents pathogènes sur la morbidité à long terme et la méthode utilisée pour la revue systématique visant à identifier les données probantes sur la morbidité à long terme due à ETEC, au norovirus et à *Campylobacter* ont été présentées. Il a été demandé à l'IVIR-AC d'émettre des commentaires sur le cadre, le plan d'analyse et la revue systématique proposés.

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

- L'IVIR-AC a reconnu la pertinence unique de l'ensemble de données de l'étude MAL-ED (cohorte longitudinale) pour fournir des estimations de morbidité à long terme, mais a recommandé un plan d'analyse a priori en raison de la complexité d'une telle évaluation.
- L'IVIR-AC a recommandé de définir préalablement un seuil d'accord minimum[15] pour la phase d'extraction des données de la revue systématique qui, s'il n'est pas atteint, déclencherait l'extraction des données de tous les articles par le deuxième examinateur, et un troisième examinateur si nécessaire, pour parvenir à un consensus.
- L'IVIR-AC a relevé plusieurs aspects techniques à prendre en compte, à savoir:
  - les épisodes d'infection et d'excrétion au niveau individuel pourraient être des estimations probabilistes dans un modèle de Markov, plutôt que des hypothèses prédéfinies qui pourraient être des valeurs limites artificielles pour la durée de l'incubation et de l'excrétion post-diarrhéique;
  - l'impact des co-infections sur l'augmentation des effets de l'exposition pourrait être estimé dans le cadre du modèle;
  - la conception de séries de cas autocontrôlées pourrait être une alternative pour évaluer les effets à court terme de l'infection sur la croissance, tout en tenant compte des facteurs de confusion au niveau individuel (par exemple en comparant le taux de croissance avant et après la maladie entérique).
- L'IVIR-AC a suggéré:
  - d'envisager des méthodes qualitatives, centrées sur la personne, pour préparer les travaux futurs sur la charge des maladies (éducation, coût, social, etc.), par exemple en sélectionnant un petit échantillon pour

[13] Hasso-Agopsowicz M et al. WHO Expert Working Group: Recommendations for assessing morbidity associated with enteric pathogens. Vaccine. 2021;39(52):7521–5. doi:10.1016/j.vaccine.2021.11.033.

[14] MAL-ED Network Investigators. 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. Clin Infect Dis. 2014;59(Suppl 4):S193–206. doi:10.1093/cid/ciu653.

[15] Le seuil d'accord minimum est le pourcentage d'accord le plus bas autorisé entre 2 examinateurs pour conclure à un consensus lors de l'évaluation d'études dans le cadre d'une revue systématique.

in-depth lived experience of the impact of enteric pathogens on children and families; noting that these could enhance future measures of quality-of-life impact by ensuring that the full scope of the impact is identified;

- consideration of site-specific analyses to understand the optimal age of vaccination for the MAL-ED analysis.

Vaccine Impact Modelling Consortium (VIMC)

The VIMC[16] 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 for 12 vaccine-preventable diseases (VPDs). Data generated by the Consortium can support evaluation of immunization programmes and inform potential future investments and/or vaccine scale-up. 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 2021 model runs and complementary workstreams that examine the effect of subnational heterogeneity on vaccination coverage, the role of demographic uncertainty and investigations on vaccine equity as part of a systematic literature review. IVIR-AC members provided their perspective on the work presented.

Summary of IVIR-AC feedback and recommendations

- IVIR-AC stressed the importance of VIMC's 2021 modelling efforts, especially with respect to understanding the impact of COVID-19. To that end, IVIR-AC recommended:
  - clarification and justification of the basis for quantifying the impact of external factors (such as the COVID-19 pandemic or global and economic unrest) on vaccination coverage;
  - proposals for modelling scenarios with different levels of impact of these external factors.
- IVIR-AC thanked VIMC for its ongoing support and collaboration with WHO and suggested the inclusion of an illustration/figure to delineate the different coverage scenarios considered, making them easier to understand.
- IVIR-AC acknowledged VIMC's ongoing workstreams and suggested:
  - exploring geographical heterogeneity of vaccination for more vaccines to understand whether heterogeneity is vaccine-specific – i.e., results which may inform policy;
  - clearly describing the definition of "effectively protected", "clustering of coverage" and the methodology assessing the effect of clustering in coverage and indirect benefits; and

[16] See www.vaccineimpact.org (accessed March 2022).

étudier l'expérience vécue en profondeur en termes d'impact des agents pathogènes entériques sur les enfants et les familles; en veillant à saisir toute l'ampleur de l'impact de ces maladies, cela pourrait améliorer les mesures futures de l'impact sur la qualité de vie;

- d'envisager des analyses spécifiques à chaque site pour comprendre l'âge optimal pour recevoir la vaccination aux fins de l'étude MAL-ED.

Consortium de modélisation de l'impact des vaccins

Le Consortium de modélisation de l'impact des vaccins (VIMC, Vaccine Impact Modelling Consortium)[16] 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 pour 12 maladies à prévention vaccinale. Les données générées par le Consortium peuvent aider à l'évaluation des programmes de vaccination et guider les investissements futurs potentiels et/ou la mise à l'échelle 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 ses dernières séries de modèles 2021 et ses axes de travail complémentaires qui examinent l'effet de l'hétérogénéité infranationale sur la couverture vaccinale, le rôle de l'incertitude démographique et les enquêtes sur l'équité vaccinale dans le cadre d'une revue systématique de la littérature. L'IVIR-AC a fait part de ses observations sur les travaux présentés.

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

- L'IVIR-AC a souligné l'importance des travaux de modélisation effectués par le VIMC en 2021, en particulier en ce qui concerne la compréhension de l'impact de la COVID-19. À cet effet, l'IVIR-AC a recommandé:
  - de clarifier et de justifier la base sur laquelle repose la quantification de l'impact de facteurs externes (tels que la pandémie de COVID-19 ou les troubles mondiaux et économiques) sur la couverture vaccinale;
  - de proposer des scénarios de modélisation avec différents niveaux d'impact de ces facteurs externes.
- L'IVIR-AC a remercié le VIMC pour son soutien et sa collaboration continus avec l'OMS et a suggéré l'inclusion d'une illustration/figure pour présenter les différents scénarios de couverture envisagés afin d'en faciliter la compréhension.
- L'IVIR-AC a pris acte des axes de travail actuels du VIMC et a suggéré:
  - d'étudier l'hétérogénéité géographique de la vaccination pour un plus grand nombre de vaccins afin de déterminer si elle dépend du vaccin utilisé et d'orienter les politiques en conséquence;
  - de définir clairement les termes «efficacement protégé» et «regroupement de la couverture» ainsi que la méthode utilisée pour évaluer l'effet du regroupement de la couverture et ses avantages indirects; et

[16] Voir www.vaccineimpact.org (consulté en mars 2022).

– gaining a wider understanding, evaluating vaccine equity and access with other possible contributing factors such as vaccine acceptance.

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

IVIR-AC previously reviewed[17, 2, 18] several iterations of the modelling methodology for estimating vaccine impact as part of the *WHO Immunization Agenda 2030(IA 2030): A global strategy to leave no one behind.*[19] Recent recommendations from IVIR-AC19[19] focused on uncertainty analysis and model validation, with the inclusion of high-income countries (HICs). This session served to update IVIR-AC on modifications which addressed the detailed technical recommendations provided by IVIR-AC in September 2021[19] and to present the refined uncertainty analysis and status of the validation work of the first iteration of estimates of deaths averted for HICs.

IVIR-AC validated plans to include propagation of uncertainty through the entire modelling process and applauded the team for consistently and swiftly addressing guidance from IVIR-AC. Further guidance was sought on integrating data from high-income systematic reviews into the estimation process.

Summary of IVIR-AC feedback and recommendations

IVIR-AC recommended ways to simplify yet strengthen the proposed methodology, namely:

- Support the uncertainty analysis by liaising with VIMC[16] and the Institute for Health Metrics Evaluation (IHME)[20] to access and utilize their estimates of deaths averted and to avoid recreating such estimates using arbitrary assumptions about parameter distribution and independence.
- Decouple HIC and LMIC vaccine impact assessments in order not to delay the progress of LMICs (in which the burden of VPD is higher) by methodological challenges related to the former.
- Publish (or post a pre-print version of) the literature review and synthesize the review with summary metrics (e.g., countries covered; size of VPD burden addressed; time period).

IVIR-AC is uniquely positioned to provide highly technical modelling feedback to the IA 2030 initiative in order to shape, validate and reinforce the initiative's proposed modelling framework. To that end, IVIR-AC recommended the importance of:

[17] See No. 49, 2020, pp. 609–623.

[18] See No. 47, 2021, pp. 569–578.

[19] Immunization Agenda 2030: A Global Strategy to Leave No One Behind (https://www.who.int/teams/immunization-vaccines-and-biologicals/strategies/ia2030 (accessed September 2022).

[20] See https://www.healthdata.org (accessed March 2022).

– d'acquérir une compréhension plus large, en évaluant l'équité vaccinale et l'accès aux vaccins avec d'autres facteurs contributifs possibles tels que l'acceptation des vaccins.

Estimations de l'impact des vaccins pour le Programme pour la vaccination à l'horizon 2030 (IA 2030) – mise à jour

L'IVIR-AC a précédemment examiné,[17, 2, 18] plusieurs itérations de la méthode de modélisation pour estimer l'impact des vaccins dans le cadre du *Programme de vaccination de l'OMS à l'horizon 2030: Une stratégie mondiale pour ne laisser personne de côté.*[19] Les recommandations récentes de l'IVIR-AC[19] ont porté sur l'analyse des incertitudes et la validation des modèles, avec l'inclusion des pays à revenu élevé. Cette séance a permis d'informer l'IVIR-AC sur les modifications apportées en réponse aux recommandations techniques détaillées fournies par l'IVIR-AC en septembre 2021[19] et de présenter l'analyse affinée de l'incertitude et l'état d'avancement des travaux de validation de la première itération des estimations des décès évités pour les pays à revenu élevé.

L'IVIR-AC a validé les plans visant à inclure la propagation de l'incertitude à travers le processus de modélisation et a vivement félicité l'équipe pour avoir répercuté de manière cohérente et rapide les conseils de l'IVIR-AC. D'autres conseils ont été sollicités sur l'intégration des données des revues systématiques pour les pays à revenu élevé dans le processus de production des estimations.

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

L'IVIR-AC a recommandé des moyens de simplifier la méthode proposée tout en la renforçant, à savoir:

- étayer l'analyse de l'incertitude en établissant une liaison avec le VIMC[16] et l'Institute for Health Metrics Evaluation[20] pour accéder à leurs estimations des décès évités et les utiliser, et pour éviter de recréer ces estimations en utilisant des hypothèses arbitraires sur la distribution et l'indépendance des paramètres;
- découpler les évaluations de l'impact des vaccins dans les pays à revenu élevé et dans les PRFI afin de ne pas retarder les progrès des PRFI (dans lesquels la charge des maladies à prévention vaccinale est plus élevée) en raison des difficultés méthodologiques liées aux pays à revenu élevé.
- publier (ou diffuser en préimpression) la revue de la littérature et en faire une synthèse avec des mesures sommaires (par exemple les pays couverts, l'ampleur de la charge des maladies à prévention vaccinale examinée, la période de temps).

L'IVIR-AC est particulièrement bien placé pour fournir des observations très techniques sur la modélisation à l'initiative IA2030 afin de façonner, valider et renforcer le cadre de modélisation proposé par l'initiative. À cet effet, l'IVIR-AC a souligné l'importance:

[17] Voir N° 49, 2020, pp. 609-623.

[18] Voir N° 47, 2021, pp. 569-578.

[19] 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 2022).

[20] Voir https://www.healthdata.org (consulté en mars 2022).

- elaborating on and clarifying the intended meaning of "location-specific Latin hypercube sampling";
- generating predictions by sampling multiple draws from the regression model and producing the full distribution, mean, median and 95% uncertainty intervals (UIs) (to consider whether multivariate normal distribution is the most appropriate distribution to use);
- providing more details on how Approach 3 ("Incidence reduction in a certain period directly provided by the studies"), Approach 5 ("QALY") and Approach 6 ("DALY") are implemented;
- considering fixing the mean of the beta distribution rather than giving extra weight to the mean difference in the objective function;
- gaining an understanding of the magnitude of scaling multipliers in the VIMC calibration;
- providing prediction intervals in background documents;
- leaving out 1 uncertainty type at a time when producing uncertainty intervals (UI; and,
- considering the herd effect of vaccination in Approach 4 ("Only the prevalence of the disease is known"). ■

- d'élaborer et de clarifier le sens de l'expression «échantillonnage par hypercube latin spécifique d'un lieu»;
- de générer des prédictions en échantillonnant plusieurs tirages du modèle de régression et en établissant la distribution complète, la moyenne, la médiane et les intervalles d'incertitude à 95% (pour déterminer si la distribution normale multivariée est la distribution la plus appropriée);
- de fournir davantage de détails sur la façon dont l'approche 3 («Réduction de l'incidence au cours d'une période donnée directement fournie par les études»), l'approche 5 («QALY») et l'approche 6 («DALY») sont mises en œuvre;
- d'envisager de fixer la moyenne de la distribution bêta plutôt que de donner un poids supplémentaire à la différence moyenne dans la fonction objective;
- d'acquérir une compréhension de l'ampleur des multiplicateurs d'échelle dans le calibrage du VIMC;
- de fournir des intervalles de prédiction dans les documents d'information;
- d'écarter un type d'incertitude à la fois lors de la détermination des intervalles d'incertitude; et
- de tenir compte de l'effet de groupe de la vaccination dans l'approche 4 («Seule la prévalence de la maladie est connue»). ■

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

World Health Organization

Background information to the sessions

World Health Organization

Session 1
COVID 19 vaccine impact modelling

COVID-19 vaccine impact modelling

Stefan Flasche (LSHTM),
co-chair of the WHO SAGE COVID-19 WG modelling SG

SAGE recommendations for COVID-19

Modelling SG → COVID-19 WG → SAGE

Latest interim statements

11 August 2022 | Statement

Interim statement on COVID-19 vaccination for children

17 June 2022 | Statement

Interim statement on decision-making considerations for the use of variant updated COVID-1...

Recommendations

- Interim recommendations for use of the Pfizer–BioNTech BNT162b2 vaccine against COVID-19
- Interim recommendations for use of the Moderna mRNA-1273 vaccine against COVID-19
- Interim recommendations for use of the Valneva VLA2001 vaccine against COVID-19
- Good practice statement on the use of second booster doses for COVID-19 vaccines

IVIR-AC March 2022

IVIR-AC highlighted future COVID-19 immunity modelling considerations:

- Modelling variant scenarios should focus on deter-mining thresholds (for immune escape–against infection versus severe disease, transmissibility and/or severity) that would necessitate a change in current health policy approaches (with a focus on vaccine policy) and the data needed to rapidly characterize the properties of new variants.
- The SG COVID-19 should continue to identify, support and advise modelling groups from different countries, to ensure a variety of modelling approaches and perspectives are included.
- Models should differentiate between infection- and vaccine-derived immunity against infection versus severe disease. Future modelling efforts should focus on prevention of severe disease as the primary outcome of interest.
- Future strategies for repeat “booster” vaccination should consider whether the frequency of vaccination be timed to waning of immunity or the re-emergence of new variants.

Priority questions to the SG (5 May 2022)

Shifting vaccination priorities with high infection derived immunity

Cost effectiveness of COVID-19 vaccines (compared to other vaccines)

Impact of VoC on vaccination priorities

Priority questions to the SG (5 May 2022)

Shifting vaccination priorities with high infection derived immunity

- What is the incremental benefit of a first, second, booster or second booster vaccine *dose* (J&J + others) in a population with high prevalence of past infection?
- If focus is to protect against severe disease and death what *use groups* need to be vaccinated in high seroprevalence settings (and what use group derive little benefit from vaccination)?
- What is the *vaccine preventable* disease burden in different priority-use groups and how does it compare to other vaccine preventable diseases?
- What serological data is needed to formulate serology informed national policy on vaccination?

Priority questions to the SG (5 May 2022)

Cost effectiveness of COVID-19 vaccines (compared to other vaccines), e.g.:

- For yet (largely) unvaccinated LMICs, in what use groups would vaccination be cost-effective?
- For yet (largely) unvaccinated LMICs, in what use groups would vaccination be affordable (possible wider benefits for co-administration or co-delivery with other health intervention included, e.g. influenza vaccine)?
- For well vaccinated countries, in what use groups would a fourth/fifth dose in Autumn 2022 (or annually) be cost-effective?
- In what circumstances is vaccination of children and adolescents cost effective?

Priority questions to the SG (5 May 2022)

Impact of VoC on vaccination priorities, e.g.:

- With Omicron prevailing at what point would (re-) vaccination be needed?
- What profile would a VoC have to warrant (re-) vaccination with current vaccines as an “insurance policy” and what use groups should be prioritized for this?
- What profile would a VoC have to warrant reactive (re-) vaccination with current vaccines in response to a surge in cases?
- What profile would a VoC have to warrant (re-)vaccination with vaccines including new variants or a more broadly protective vaccine?

Open call to generate evidence

- US$25,000 per distinct objective/deliverable to support modelling work of key importance to the SAGE WG
- To support the extension of ongoing work but insufficient to support new workstreams
- Phase I: funded 2 groups (presentations today)
- Phase II: shortlisting completed

Good Practice Statement on the use of second booster doses for COVID-19 vaccines

Annelies Wilder-Smith MD PhD

WHO Focal Point SAGE Working Group COVID-19 vaccines

On behalf of the SAGE Working Group

[11 August 2022]

World Health Organization | IVB

Background: Omicron-dominant era

- Omicron (including its various sub-lineages BA.1, BA.2, BA. 4, BA. 5) is associated with less severe disease compared to pre-Omicron variants. However, it is also more transmissible and circulated faster than the pre-Omicron variants and thus is still causing many hospitalisations and deaths due to the high incidence.
- Of the different viral variants that have caused infection waves, Omicron is antigenically the most distant from the ancestral strain, and is associated with more immune evasion and lower vaccine effectiveness (VE).
- Whilst VE is still relatively well maintained against severe disease, protection against mild disease and infection declines rapidly with time since last vaccination:
- *The decline in VE in the period following the booster vaccination is small for severe disease (5 % (95% CI 2 to 9) from 1 month to 4 months after booster vaccination and 8% (95% CI 4 to 14%) projected out to 6 months after booster vaccination.*
- *The decline in VE against symptomatic disease 1 month to 4 months after booster vaccination is 24% decrease over time (95% CI 20 to 29%), and a 29% (95% CI 18 to 41%) when projected out to 6 months after booster vaccination*
- Older adults and those with comorbidities continue to be at greatest morbidity and mortality risk due to the Omicron variant of SARS-CoV-2 as vaccine effectiveness declines. Even a minor decrease in VE in such vulnerable persons will translate into a rise in severe disease and deaths

General underpinning principle

- Vaccinating those at highest risk, as outlined in the WHO SAGE Roadmap, with a primary series and a booster dose prior to embarking on further vaccination with additional booster doses is a public health priority.

To reduce the risk of severe disease, deaths and disruptions of health services, WHO recommends countries should consider a second booster dose for:

- all older persons (age specific cut-off should be defined by countries based on local COVID-19 epidemiology)
- all persons with moderate and severe immunocompromising conditions, regardless of age
- adults with comorbidities that put them at higher risk of severe disease
- pregnant women
- health workers

Timing of second booster

- As VE wanes over a period of 4-6 months, a second booster dose should be offered 4-6 months after the last dose, or - if this time period is missed- as soon as possible thereafter.
- Individuals at high risk for severe death should receive a second booster dose in this time interval.
- Once authorized for use, variant updated vaccines can be considered but high risk individuals should not delay boosting in anticipation of variant-updated vaccines.

What about using 2nd boosters to prevent symptomatic illness?

- The high incidence of mild to moderate symptomatic COVID illness continues to cause significant disruptions to society. SARS-CoV-2 infections, even if not severe and not requiring hospitalization, may have an impact on economies and resilience of the work force due to the need for isolation, loss of productivity and the ability to travel.
- The impact of currently available vaccines on reducing symptomatic illness and transmission in the context of omicron is modest. The impact of a second booster dose on restoring VE against symptomatic illness will be transient and likely not last longer than a few months.
- Countries considering methods to reduce the socio-economic impact due to mild and moderate SARS-CoV-2 infections need to take into account cost-benefit, affordability, opportunity costs to other vaccination programmes, and community acceptance of a second booster dose before offering second boosters to persons who do not fall into the high risk categories as listed above.

Seroprevalence

- On a population level, basing national vaccination policies on seroprevalence rates or individual pre-vaccination screening is currently not recommended.
- Seroprevalence rates observed in population-based studies may not be representative of the entire population or certain high-risk subpopulations and age groups.
- Seroprevalence is likely to be lower in older age groups in most settings.

Expectations to IVIR-AC:

- To provide feedback on each group’s conducted work and their plans
- To provide feedback on key messages to SAGE groups with regards to the priority questions

Using seroprevalence data to guide future COVID-19 vaccination

WHO IVIR-AC
September 12-14,2022

Carol Y Liu, MSc

Benjamin A Lopman, MSc, PhD

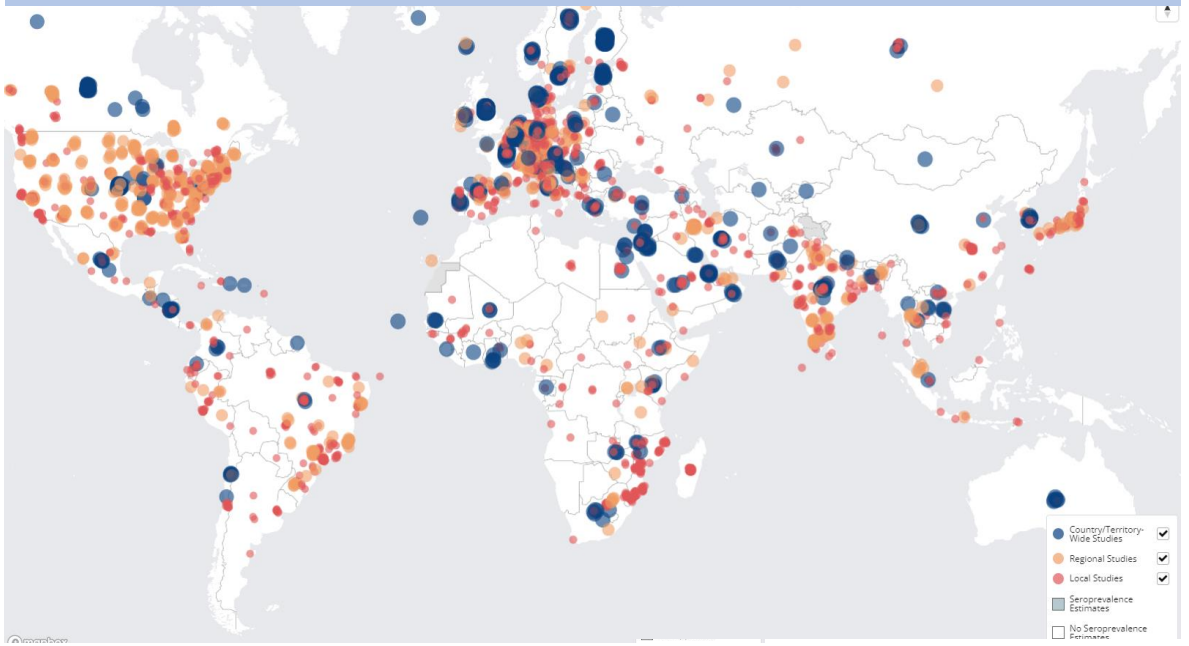
Department of Epidemiology
Rollins School of Public Health

EMORY
UNIVERSITY

SARS-CoV-2 serological survey data

- **Antibody tests**
  - Detect SARS-CoV-2 serological status
  - Imperfect correlate of protection
    - Wane over time and become undetectable
      - Time to seroreversion range: 200 days – up to 2 years
    - New variants
- **Serosurveys**
  - Measure prevalence of antibodies as population-level marker for immunity
  - Many conducted around the world to estimate past exposure
    - 3668 studies in 139 countries

Map of COVID-19 serosurveys conducted to date



Source: SeroTracker (https://serotracker.com/en/Explore)

Objectives

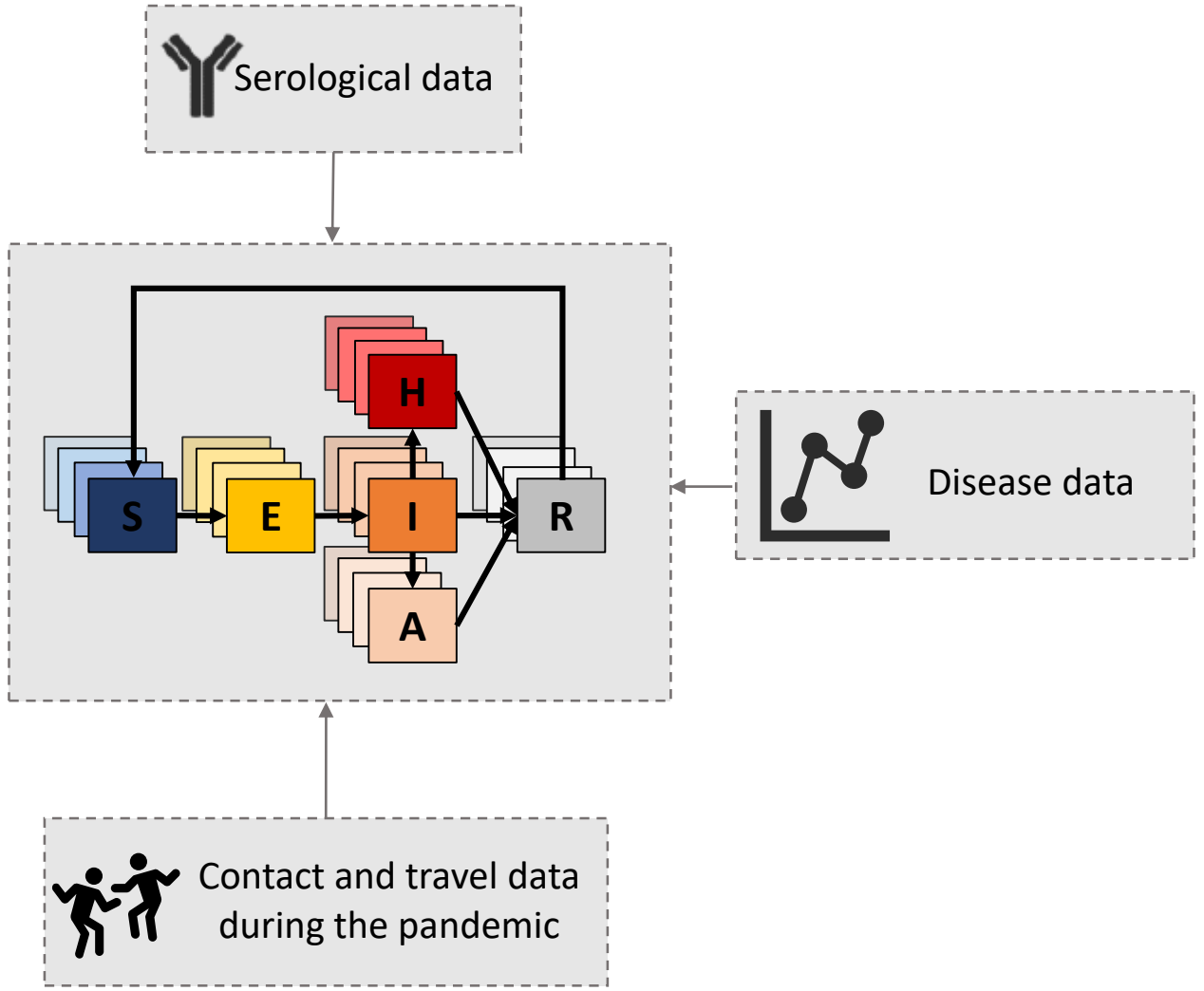
To assess the impact on epidemic dynamics and mortality of using seroprevalence thresholds to trigger an additional round of vaccination*…

a. considering a **seroprevalence threshold range** of 60-90%
b. with thresholds **for the overall population or age-specific** (0–17 and 50+ year age groups)
c. given different **timing of new variant emergence**

**assuming perfect knowledge of seroprevalence*

Model structure and integrating data streams

- Demographic strata
  - Age group
    - <18 years, 18-49 years, >50 years
  - Urban/rural
- Immunity tiers, combinations of:
  - Four tiers of vaccination
    - Unvaccinated, 1-3 doses
  - Three tiers of exposure
    - Unexposed, 1-2 prior exposures)



Approach

Track seroprevalence

- Seroconversion after infection or vaccination
- Waning antibodies independent from waning immunity

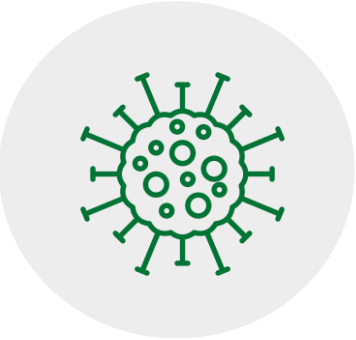
Model calibration

- historical age-specific seroprevalence at several time points
- time-series of reported cases adjusted for underreporting

Vaccination scenarios

- Simulate forward for 2 years with modest new wave
  - R_0=4.9 with immune escape
- Additional dose (1% per day) if/when seroprevalence falls below thresholds

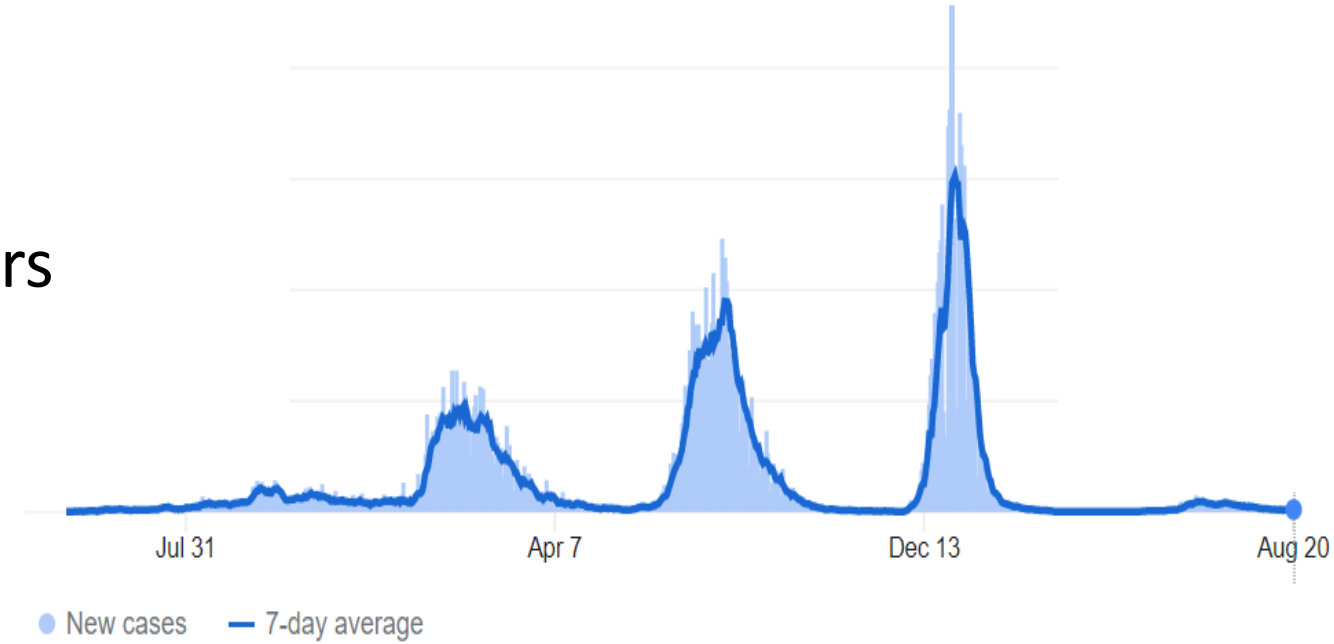
Assess outcomes



- Timing of vaccination
- Seroprevalence
- Deaths

Background: Mozambique

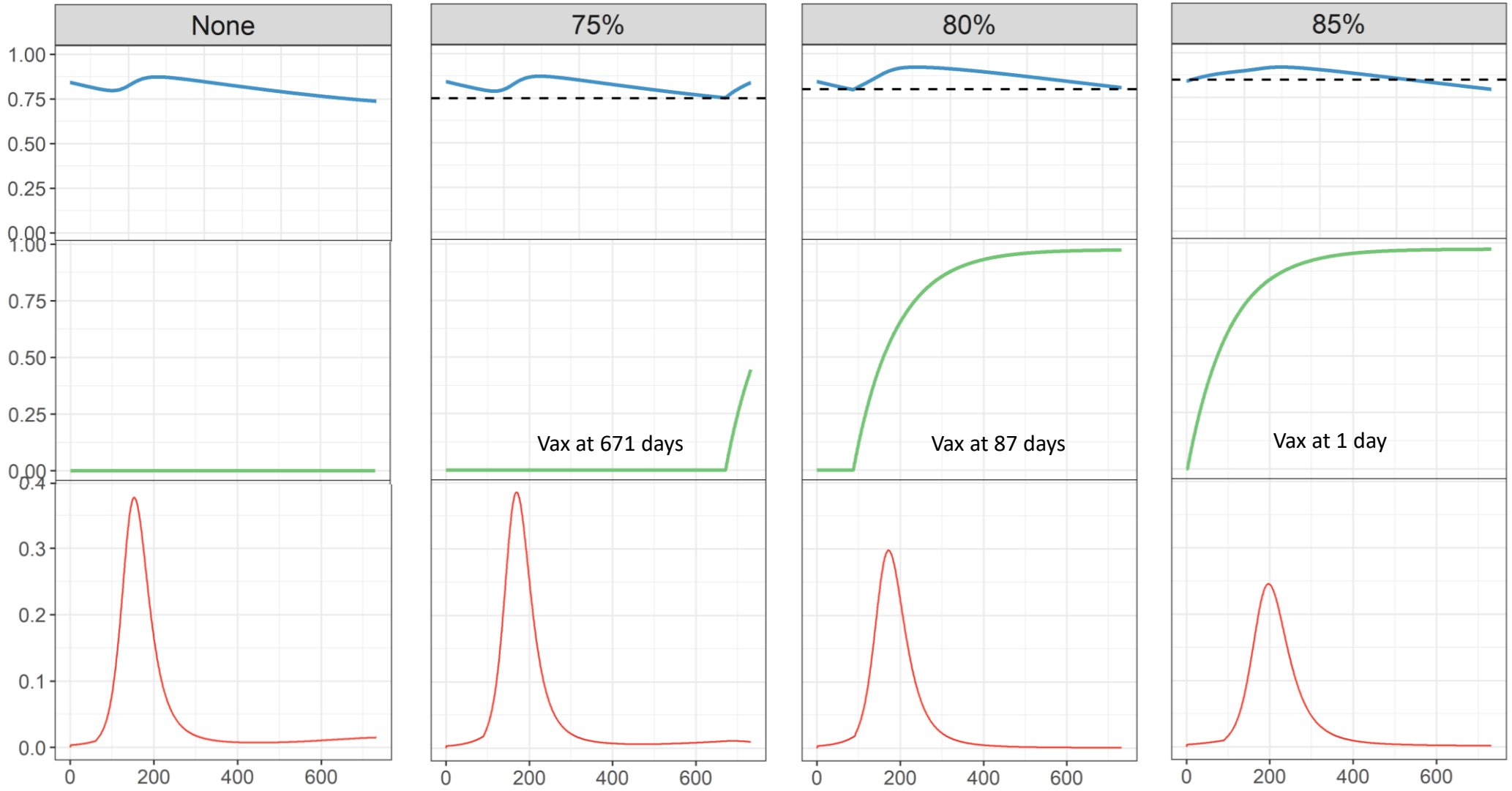
- Population 31.2 million
  - 52% under 17 years
- Four COVID waves
  - Omicron largest
- Vaccination coverage to date
  - High coverage in adults (>90%)
  - No/little vaccination in <18 years
- Seroprevalence
  - High in adults and children



What is the effect of using a seroprevalence threshold for the overall population to trigger vaccination?

EMORY
UNIVERSITY

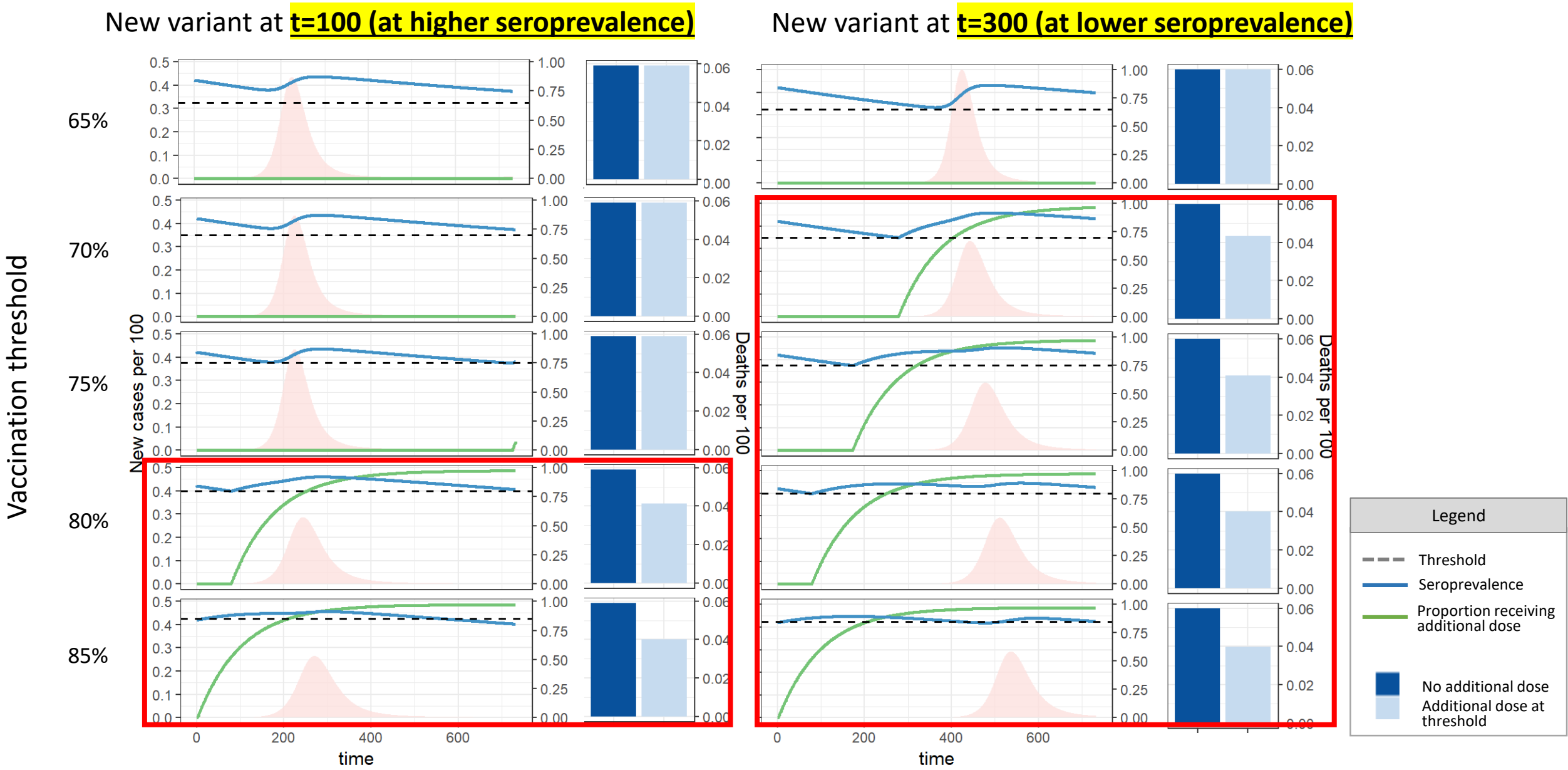
Narrow range of thresholds balancing trade-offs



How does the timing of a new variant emergence affect the utility of seroprevalence triggers for vaccination?

EMORY
UNIVERSITY

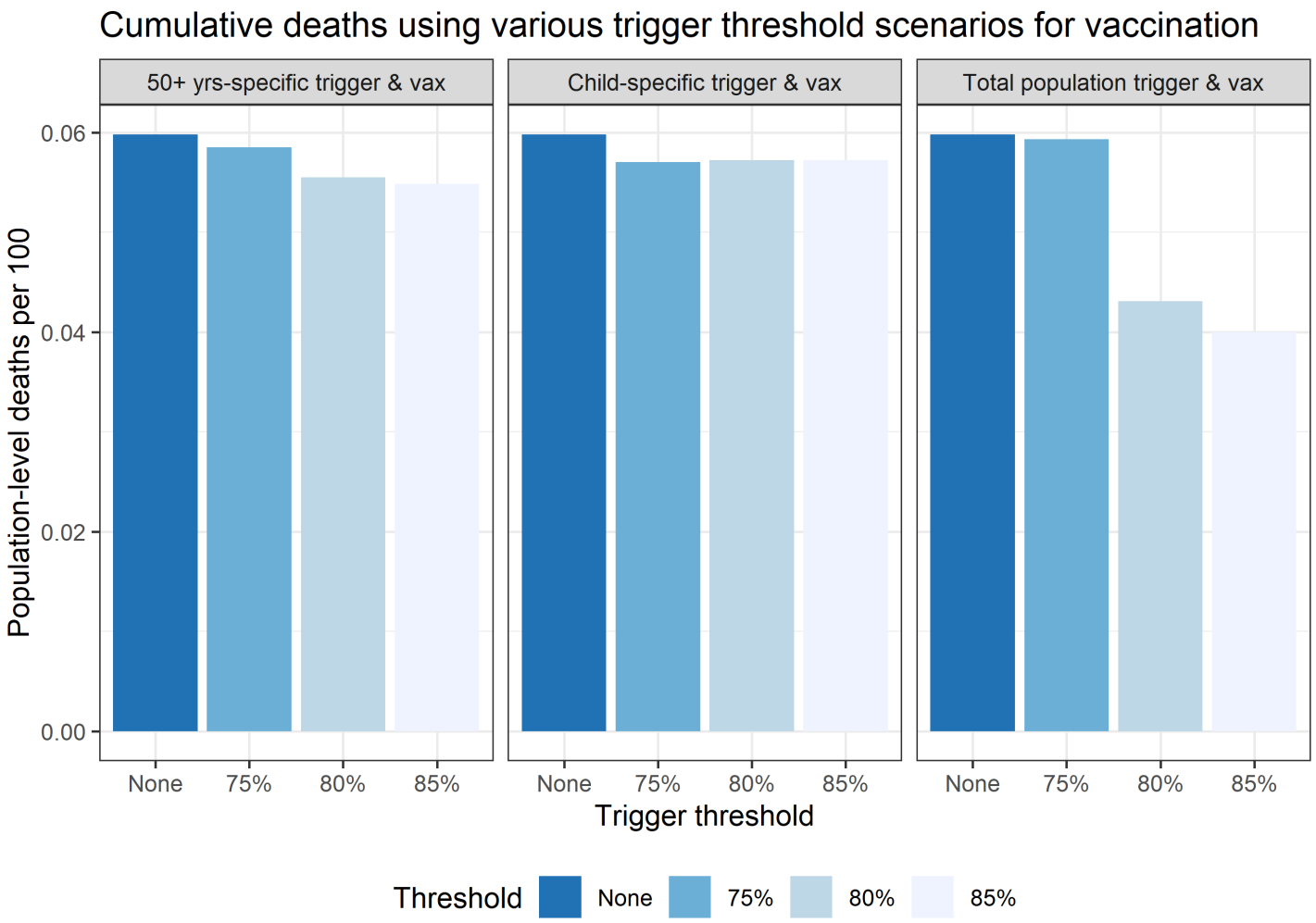
New variant timing changes “best case” threshold



What is the effect of using age-specific seroprevalence thresholds to trigger vaccination?

EMORY
UNIVERSITY

Summary of impact of age-specific trigger scenarios



- Age-specific thresholds trigger vaccinations earlier than triggers for the entire population

Limitations and next steps

- Limitations
  - Data for calibration
    - Accuracy and timing of serological data
    - Underreporting of cases and deaths
  - Results may not apply to low seroprevalence settings
  - We assumed new variant emergence drives subsequent waves rather than endemic or seasonal dynamics

- Planned analyses
  - Simulate more realistic serological surveillance
    - Sampling serology at fixed intervals
  - Sensitivity analysis
    - Varying waning immunity

Conclusions

- MAIN FINDING:

In high seroprevalence settings, population serosurveys may have limited value in determining the timing of vaccination over the next few years

- There is a trade-off whereby
  - high threshold results in early (immediate) vaccination
  - low threshold results in delayed vaccination so ability to impact the next wave is missed
  - even with perfect knowledge of seroprevalence, only a narrow range of thresholds can balance trade-offs
- Timing of new variant can change the range of effective thresholds

Acknowledgements

Emory University

- Dr. Ben Lopman
- Dr. Kristin Nelson
- Dr. Sam Jenness
- Dr. Kayoko Shioda
- Dr. Alicia Kraay (former)
- Dr. Moses Kiti

Lopman Lab Group

Global Mix Study Team

Yale University

- Dr. Saad Omer

CISM

- Dr. Sergio Massora
- Dr. Inacio Mandomando
- Dr. Charfudin Sacoor

CISPOC

- Dr. Celso Monjane

INS

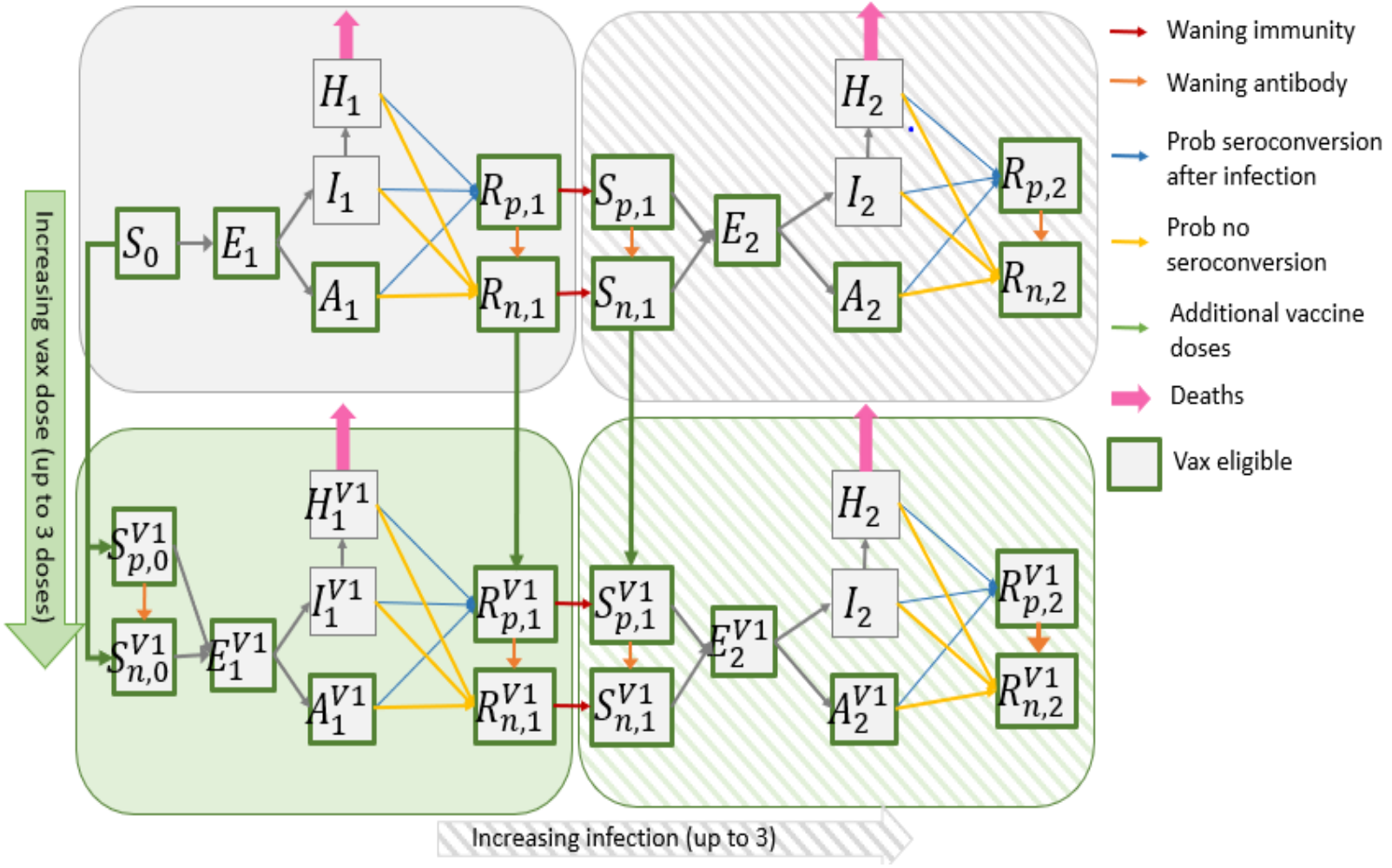
- Dr. Ivalda Macicame

WHO SAGE COVID-19 Vaccine Modeling Working Group

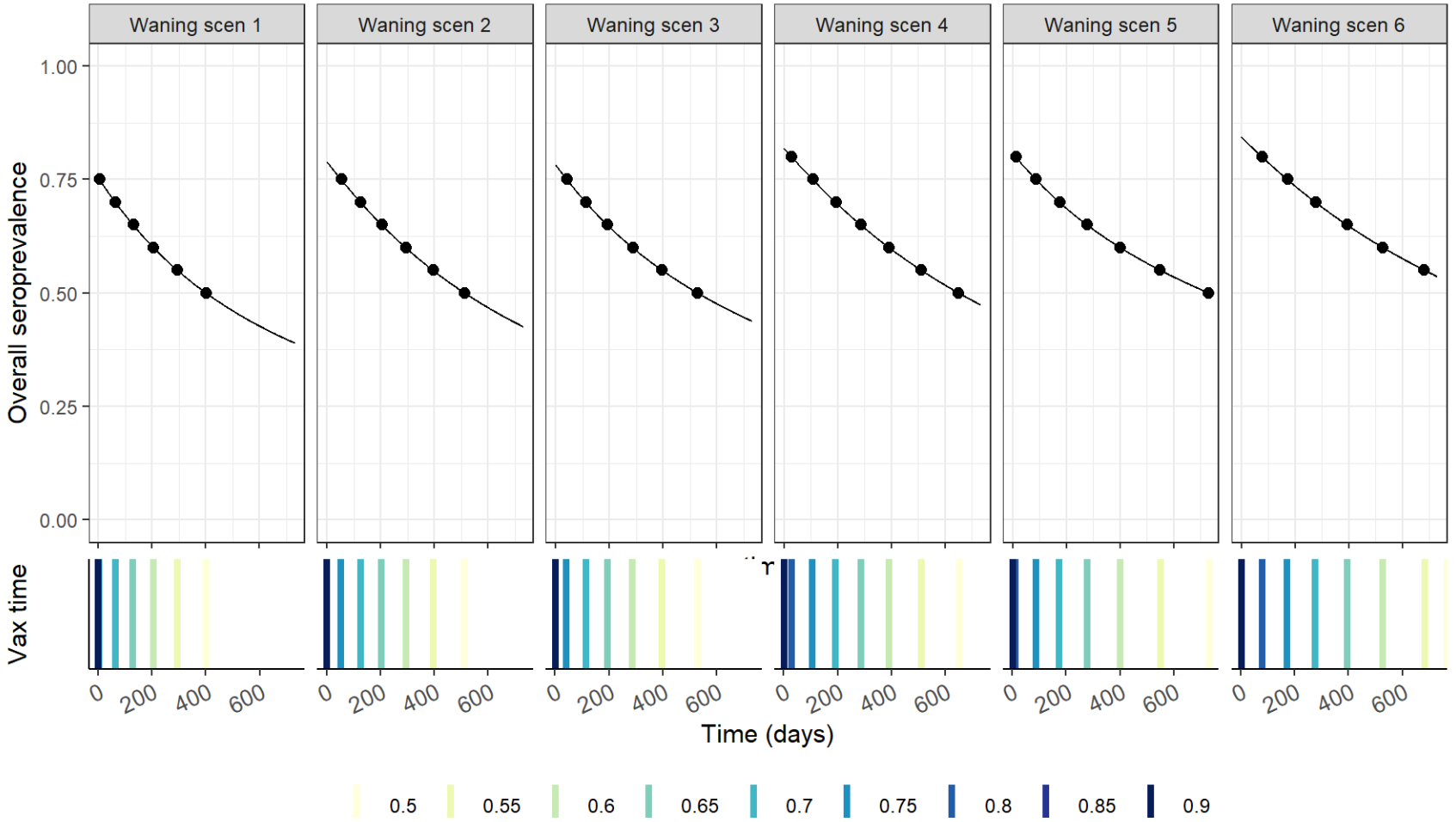
Thank you

Extra slide: Model schematic diagram

Schematic of an S-E-I-R-like compartment for a single demographic strata (out of six total: three age groups in each of urban and rural) with four tiers of immunity shown (two tiers of vaccination: unvaccinated and one dose of vaccine, with the superscript V1 the vaccine dose and two tiers of exposure: no prior exposure and one exposure, with the subscript representing the number of exposures). Individuals who recover from infection are immune for a period. The majority seroconvert after infection (Rp) while others do not (Rn). Immunity for both seropositive (Rp) and seronegative (Rn) can wane over time, returning individuals to Sp and Sn, respectively, allowing for subsequent infection. Individuals in classes outlined in green are eligible for vaccination. The majority of individuals also seroconvert after vaccination. Individuals in vaccinated and previously exposed strata have a reduced probability of infection and disease.

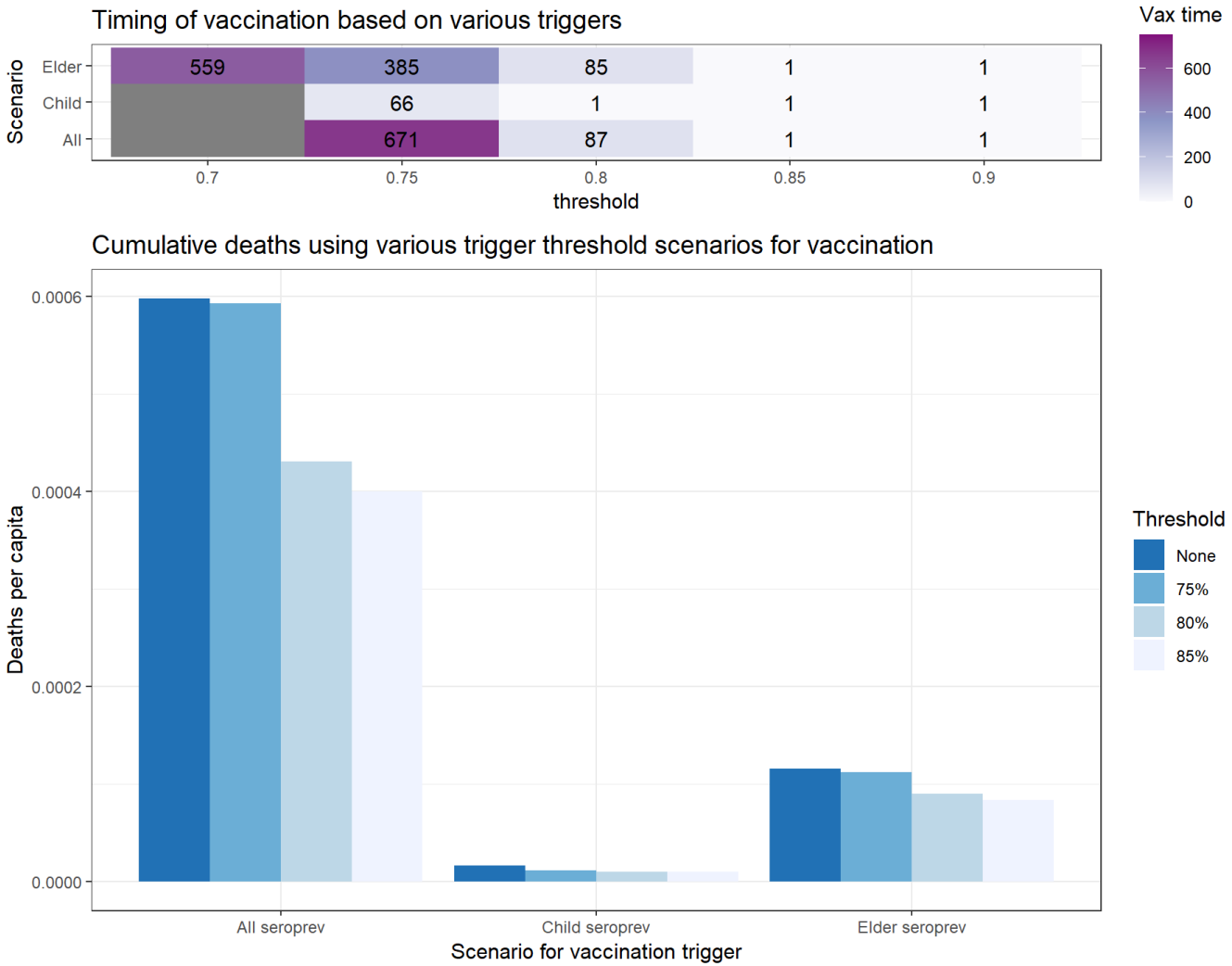


Extra slide: Waning rate sensitivity analysis

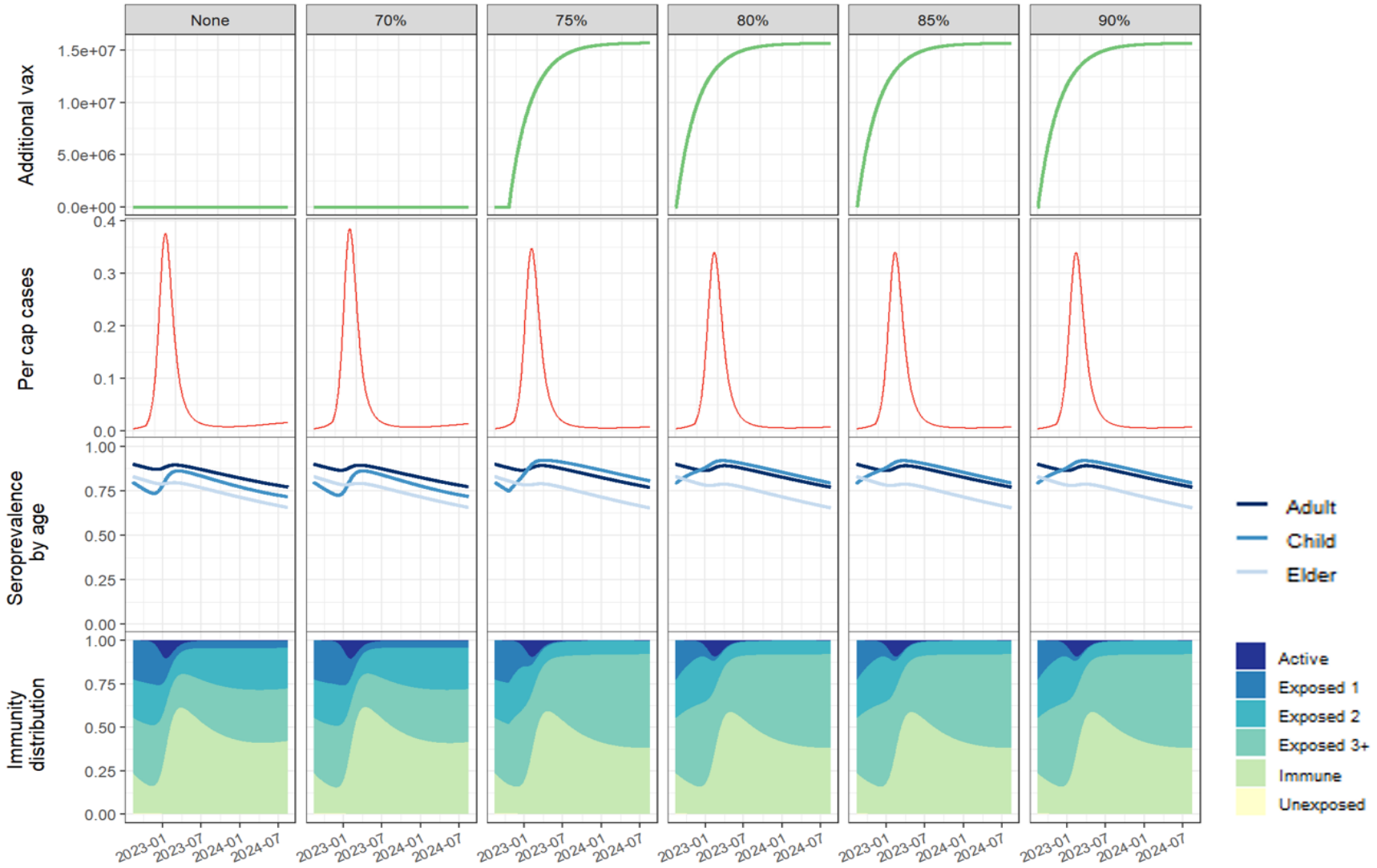


Overall seroprevalence (top) and timing of vaccination triggers (bottom) using thresholds between 50% -90% over the following waning scenarios (slower waning from left to right): 1) first exposure 1/400, second exposure 1/600; 2) first exposure 1/600, second exposure 1/600; 3) first exposure 1/400, second exposure 1/1000; 4) first exposure 1/600, second exposure 1/1000; 5) first exposure 1/400, second exposure 1/2000; 6) first exposure 1/600, second exposure 1/2000. Colored lines on bottom panel denotes the time when seroprevalence falls below a specific threshold which would trigger vaccination. No new variant was introduced during the two-year simulation period.

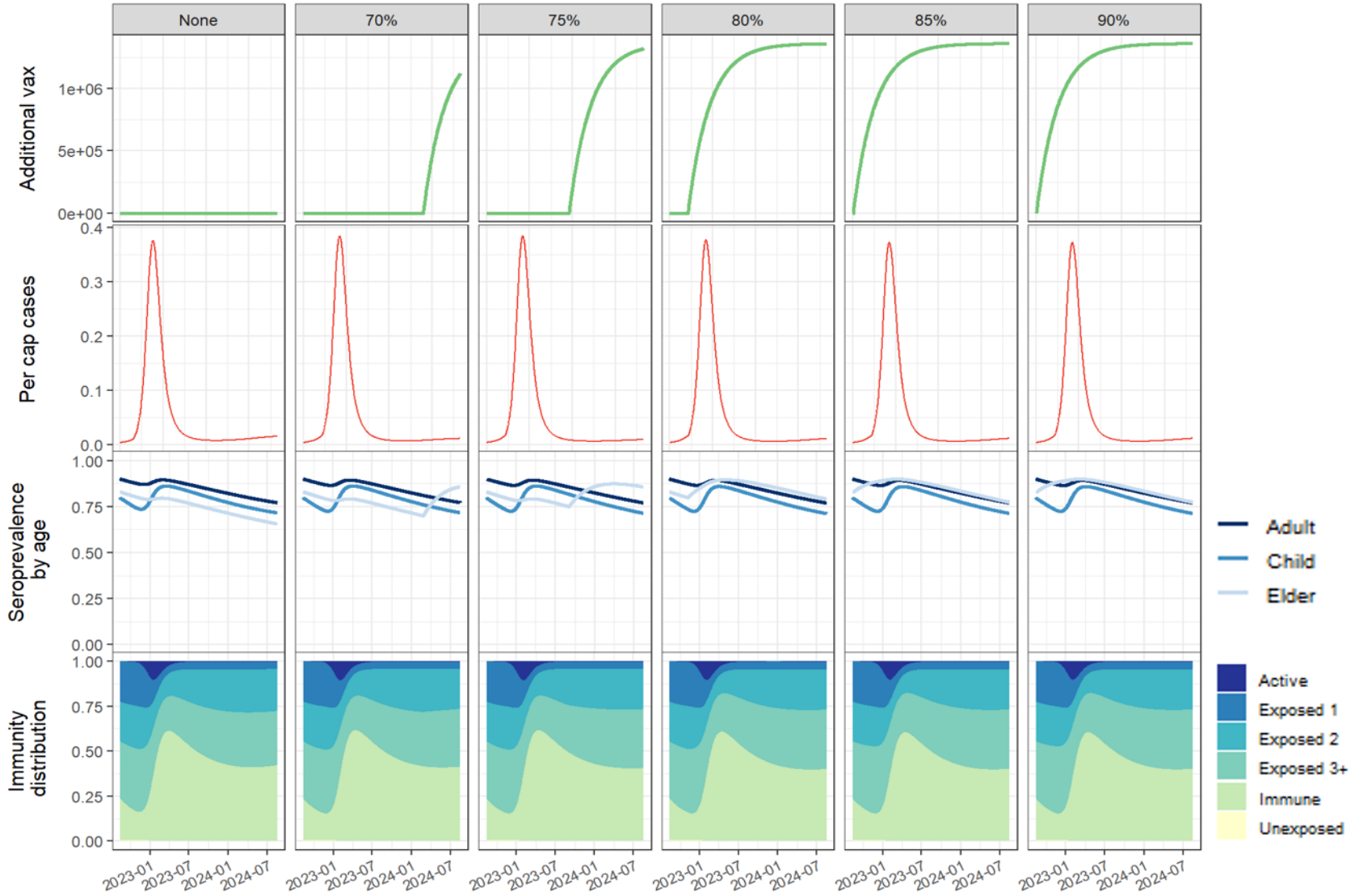
Timing of vaccination based on various triggers



Impact of older-adult specific seroprevlance trigger



Impact of child-specific seroprevalence trigger



Using seroprevalence data to guide future COVID-19 vaccination

Carol Y Liu[1], Benjamin A Lopman[1]

Contributors

Alicia NM Kraay[2], Kayoko Shioda[1], Kristin Nelson[1], Inacio Mandomando[3], Sergio Massora[3], Celso Monjane[4]

August 23, 2022

[1]Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA, USA
[2]College of Applied Health Sciences, University of Illinois Urbana-Champaign, IL, USA
[3] Centro de Investigação em Saúde de Manhiça (CISM), Maputo CP1929, Mozambique
[4] Instituto Nacional de Saúde, Maputo, Mozambique

Abstract

We explore the utility of seroprevalence thresholds in triggering additional doses of vaccinations using an S-E-I-R-like model parameterized to Mozambique, a country with high levels of primary series vaccine coverage among adults and high levels of seroprevalence. Given high seroprevalence, population-wide serosurveys may have limited value in determining the timing of vaccination efforts in the medium term. Further, the timings of vaccination based on seroprevalence triggers is sensitive to assumptions on the rate of antibody waning and the impact of such strategies are dependent on the magnitude and timing of future waves.

Background

SARS-CoV-2 antibodies are a correlate of protection conferred from prior infection or vaccination. In the past, population-level immunity markers have been used to direct measles, rubella, and polio vaccination campaigns[1] to areas and age groups with the highest immunity gaps. Monitoring changing immunity for SARS-CoV-2 to trigger subsequent rounds of booster vaccines has been proposed for COVID-19 control[2], yet its potential utility is unknown. We use Mozambique as a case study to explore the utility of seroprevalence thresholds in guiding the timing of additional doses of vaccination. In Mozambique, adults have high two-dose vaccination coverage (>90%) while children have not been vaccinated. Estimates representative of a rural area from June 2022 show high seroprevalence in adults and children alike (>85%), in line with the latest estimates of SARS-CoV-2 seroprevalence in multiple low and middle-income countries (LMICs)[3].

Objectives

In this preliminary analysis, we aim to achieve the following objective:

- Assess the impact of using different overall seroprevalence thresholds to trigger an additional round of vaccination in Mozambique
- Assess the impact of using different seroprevalence thresholds specific to children (0-17 year olds) and older adults (50 years and above)

Model structure

We extended on a previously developed SEIR-like model that was used to address questions about vaccine distribution. After being exposed, individuals enter a latent, non-infectious period (E), after which they progress to either infectious and asymptomatic (A) or infectious and symptomatic (I). Some symptomatic individuals progress to more severe disease and are hospitalized (H). A subset of those who are hospitalized ultimately die from SARS-CoV-2 (entering the D class). All individuals who are not hospitalized are assumed to recover (entering the R class) and can either be seropositive (Rp) or seronegative (Rn). The R class is temporarily immune to subsequent infections; however, immunity wanes over time and individuals return to a partially susceptible class (S1p for seropositive and S1n for seronegative). The current model is stratified by age group (<=18 years, 19-49 years and > 50 years) and urban/rural strata and includes twelve tiers of immunity status: combinations of four tiers of vaccine status (unvaccinated, vaccinated with one dose, two doses and three doses) and three tiers of exposure status (unexposed, one prior exposure and two prior exposures). The multiple tiers of immunity allow differential susceptibility based on prior exposure from either infection or vaccination. The model diagram is described in Figure 1, equations and parameters are in Supplementary Information.

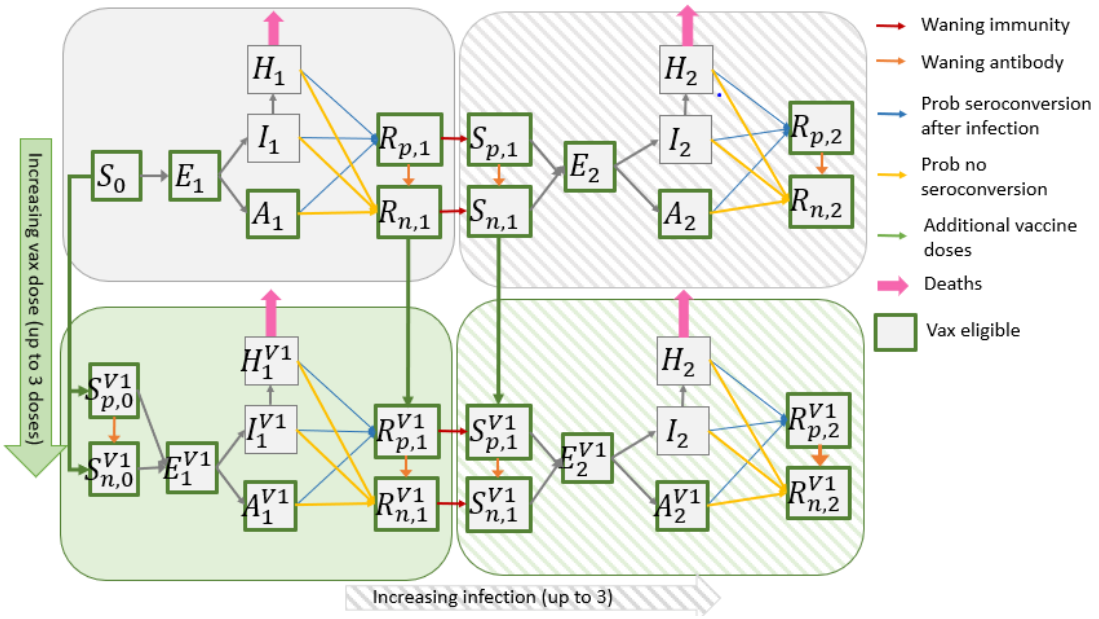


Figure 1. Schematic of an S-E-I-R-like compartment for a single demographic strata (out of six total: three age groups in each of urban and rural) with four tiers of immunity shown (two tiers of vaccination: unvaccinated and one dose of vaccine, with the superscript V1 the vaccine dose and two tiers of exposure: no prior exposure and one exposure, with the subscript representing the number of exposures). Individuals who recover from infection are immune for a period. The majority seroconvert after infection (Rp) while others do not (Rn). Immunity for both seropositive (Rp) and seronegative (Rn) can wane over time, returning individuals to SP and Sn, respectively, allowing for subsequent infection. Individuals in classes outlined in green are eligible for vaccination. The majority of individuals also seroconvert after vaccination. Individuals in vaccinated and previously exposed strata have a reduced probability of infection and disease.

Seroprevalence

We explicitly track population-level seropositivity for detectable (total) antibodies. Upon exposure through either infection or vaccination, individuals can seroconvert and become seropositive. We assume that 95%[4,5] of infected individuals seroconvert after recovering and 85% of vaccinated individuals seroconvert upon moving to the vaccinated class following first dose. Further, we assume 85% of seronegative individuals receiving an additional vaccine dose will seroconvert. Over time, antibodies can wane and seropositive individuals serorevert to seronegative. Immune and seropositive individuals (Rp) will serorevert to immune and seronegative (Sp) while partially susceptible and seropositive individuals (Sp) will serorevert to partially susceptible and seronegative (Sn). The rate of seroreversion is fastest following the first exposure (range of 1/200-1/600)[6–9] and declines after multiple exposures (range of 1/600-1/2000 after second exposure and 1/3000 after third exposure), in line with recent evidence that antibody titers are higher after multiple exposures[10,11].

Vaccination

Individuals in S, E, A, R compartments are eligible for vaccination. Vaccinated individuals move to a higher vaccination class with reduced rates of infection and probability of hospitalized if infected. We parameterize vaccine effectiveness based on performance of Astra Zeneca, the main vaccine used in

Mozambique (and many LMICs) and assume that one dose of vaccine reduces rate of infection by 65%, two doses by 70% and three doses by 75%. Further, one and two dose of vaccine reduces the probability of progression to severe disease by 49% and by 77% respectively. Overall vaccine effectiveness against hospitalization is 83% and 93% for first and second dose, respectively. Historical vaccinations were implemented based on documented first and second dose vaccination administered in Mozambique over time with an early preference towards the age group of 50 years and above.

Calibration

We calibrate the model to age-specific seroprevalence data available at several time points and time-series of reported cases[12] adjusted for an underreporting factor. We implement historical vaccination based on first and second doses administered in country over time[13]. The two-dose vaccination coverage among adults is >90%. While children in Mozambique have not yet been vaccinated, children and adults alike have high seroprevalence (>85%).

Forward simulation

We simulate the epidemic forward for two years from August 15th, 2022, with the arrival of a new variant 100 days from the start of simulation. The hypothetical new variant was less infectious than omicron with a level of immune escape that resulted in 1.7 times increase in the force of infection (FOI) for individuals with prior exposure from start of simulation. To test the utility of seroprevalence data in guiding vaccination policy, we assess the impact of triggering vaccination based on various seroprevalence thresholds targeting 1) overall population followed by providing an additional dose of vaccination to the overall population at 1% per day (first dose for children and third dose for adults) and 2) children (0-17 years) only followed by vaccinating children at 1% per day and 3) older adults (50 years and above only) followed by vaccinating older adults at 1% per day.

Preliminary results

With vaccination triggers of 70%, we would never reach that threshold. Vaccination would be triggered at 671 days (75% threshold), 87 days (80% threshold) and immediately after the start of the simulation for the 85% and 90% thresholds (Figure 2). In our simulations, the new wave is partially averted when using trigger levels of 80% or above, with larger burdens averted at higher thresholds. Selecting a high trigger threshold results in the need to vaccinate earlier but provides an earlier increase in population immunity that could reduce the impact of a subsequent wave. For example, using high vaccination trigger thresholds of 85% and 90%, we trigger and finish vaccination prior to the new wave and would avert 33% of deaths for the entire population during the two-year simulation period (Figure 6 and SI 5). In contrast, selecting a lower threshold would conserve vaccines and resources but would leave the population with higher susceptibility and a lower possibility of averting future waves. For example, when we use a lower trigger threshold of 80%, we are still vaccinating during the new wave and thus avert a lower percentage of deaths. When using even lower trigger thresholds of 70% and 75%, we would not vaccinate before the new wave. In fact, seroprevalence increases after the new wave when a proportion of newly infected seronegative individuals seroconvert, further delaying the time until we reach lower thresholds.

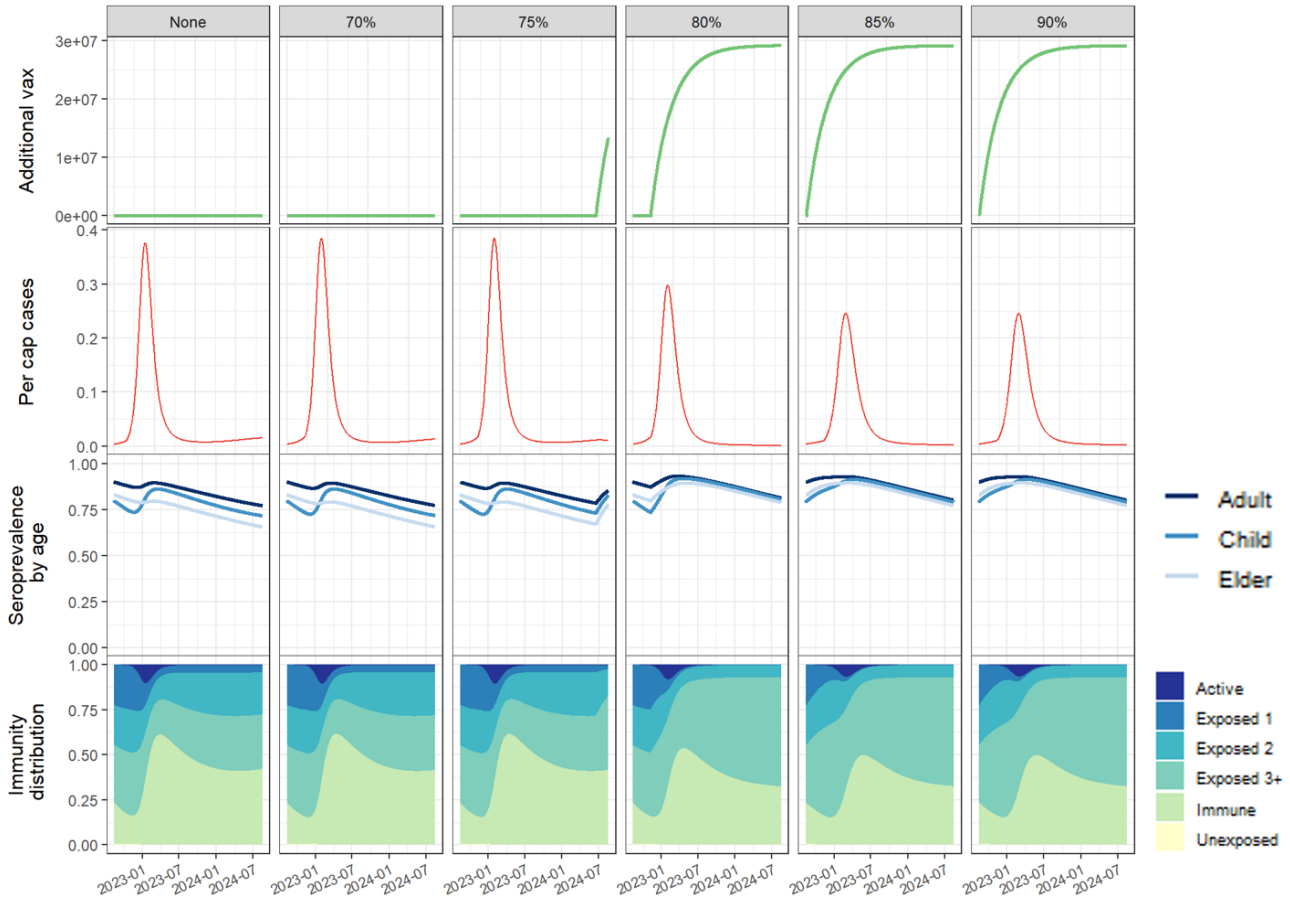


Figure 2. Impact of triggering an additional vaccination dose using total population seroprevalence triggers (70%, 75%, 80%, 85% and 90%). From top to bottom, the rows show 1) cumulative new vaccinations over time triggered by the seroprevalence threshold; 2) symptomatic cases per capita; 3) seroprevalence stratified by children 0-17 years, adult 18-49 years and elderly 50 years and above and 4) immunity distribution within the population of actively infected, immune, susceptible with various levels of prior exposure.

Using triggers for child vaccination

When using the same thresholds for children, we would trigger vaccination at an earlier time for the 75% and 80% thresholds (Figure 3). The impact on population-level cases is less noticeable due to the focus of triggering and responding based on children alone. While the seroprevalence among children increases noticeably following vaccination, the seroprevalence among adults continues to decline.

Using triggers for elderly vaccination

Seroprevalence among those aged 50 years and above declines slightly faster than among other age groups partially due to earlier seroconversion from being prioritized for vaccination. When we use the same trigger thresholds for older adults, we would always trigger vaccination at some point over the two-year simulation period (Figure 4). The impact on population-level cases is less noticeable due to the focus of triggering and responding based on older adults alone.

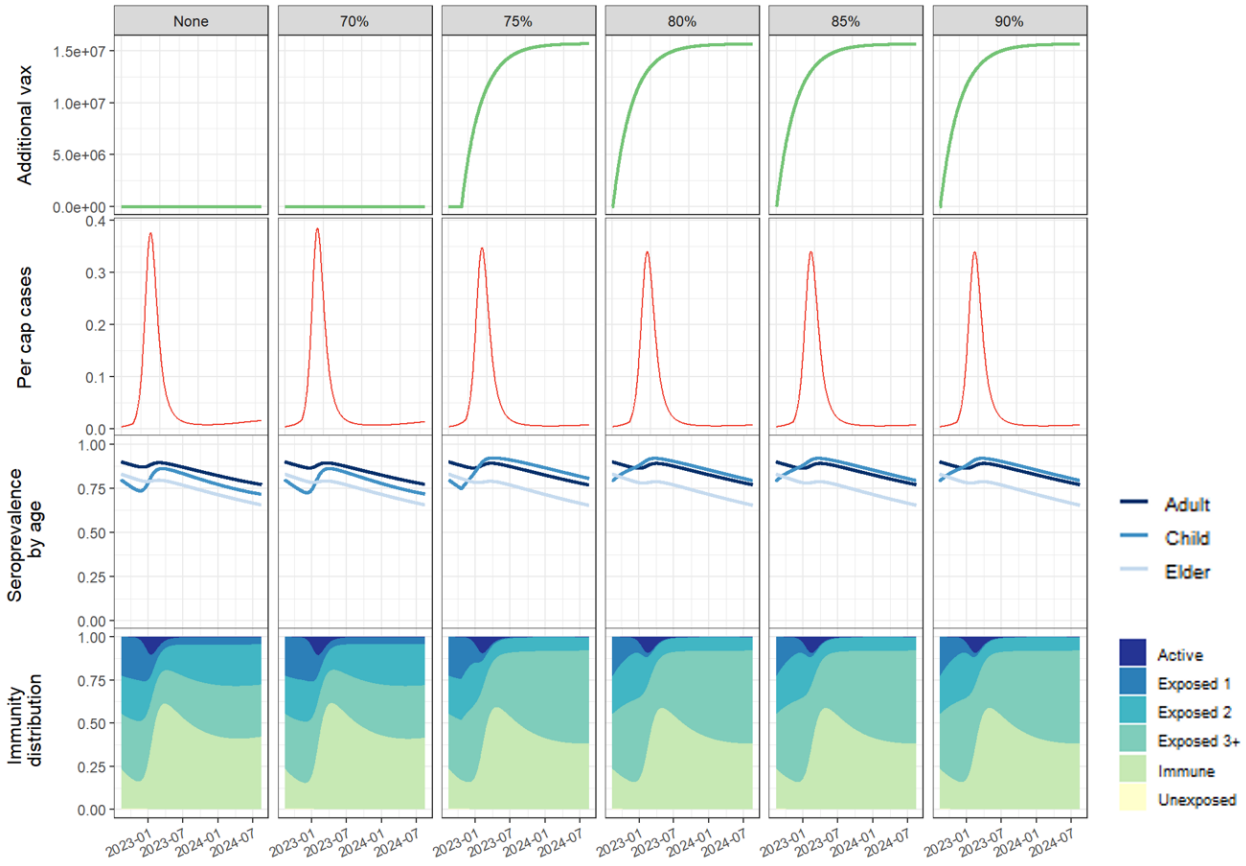


Figure 3. Impact of triggering an additional vaccination dose using child seroprevalence triggers (70%, 75%, 80%, 85% and 90%). From top to bottom, the rows show 1) cumulative new vaccinations over time triggered by the seroprevalence threshold; 2) symptomatic cases per capita; 3) seroprevalence stratified by children 0-17 years, adult 18-49 years, and elderly 50 years and above and 4) immunity distribution within the population of actively infected, immune, susceptible with various levels of prior exposure.

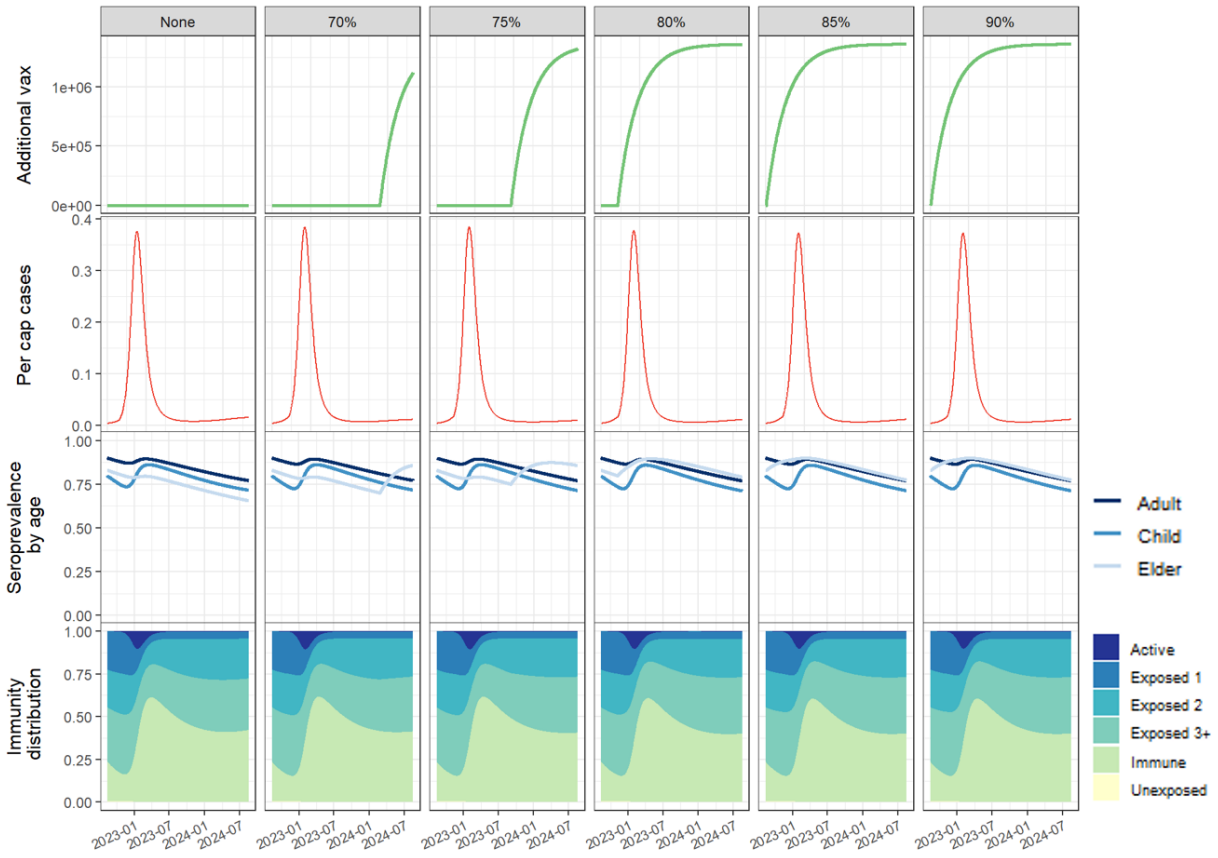


Figure 4. Impact of triggering an additional vaccination dose using seroprevalence triggers for older adults only (70%, 75%, 80%, 85% and 90%). From top to bottom, the rows show 1) cumulative new vaccinations over time triggered by the seroprevalence threshold; 2) symptomatic cases per capita; 3) seroprevalence stratified by children 0-17 years, adult 18-49 years and elderly 50 years and above and 4) immunity distribution within the population of actively infected, immune, susceptible with various levels of prior exposure

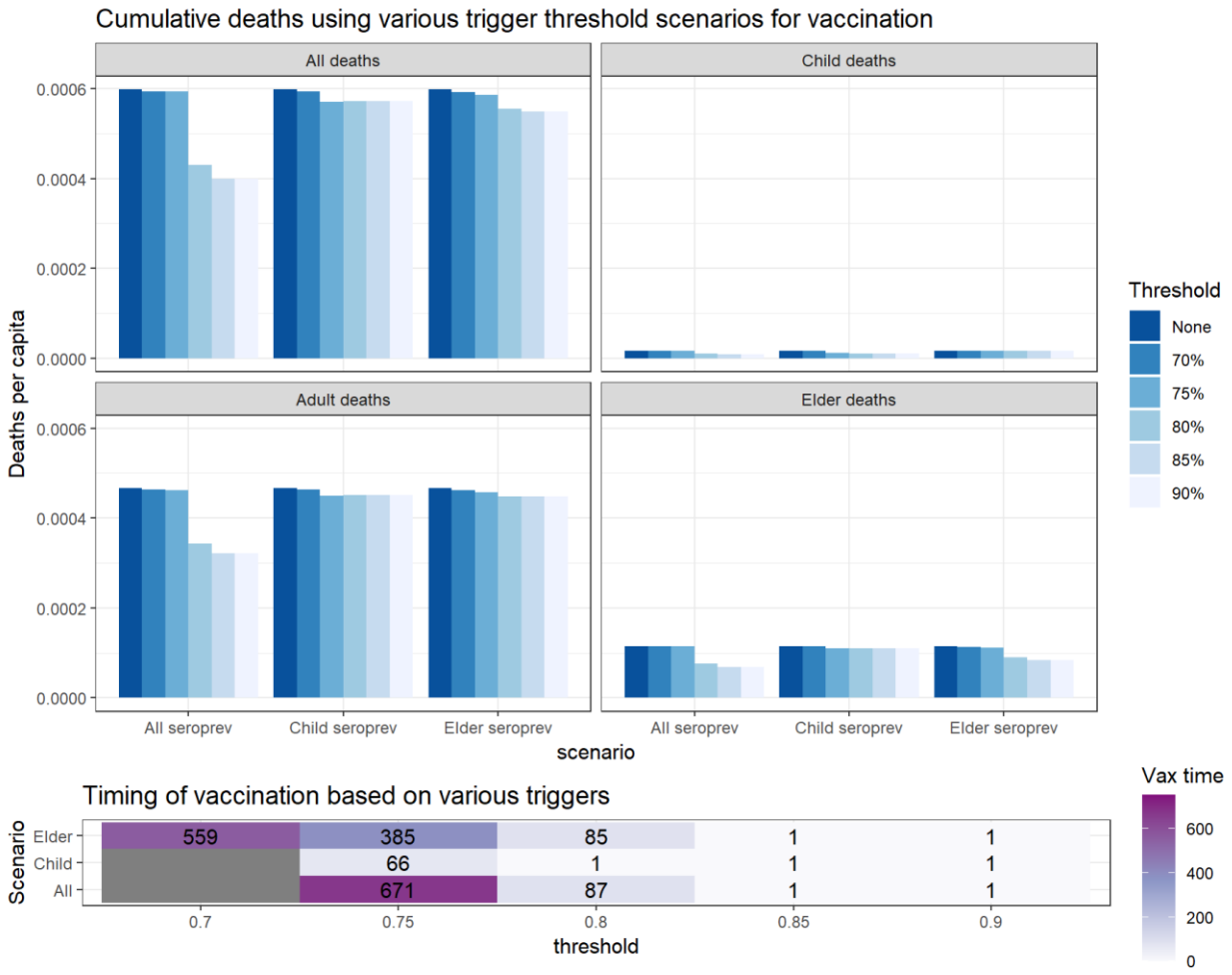


Figure 5. Comparison of the timing of vaccination based on various scenarios (total seroprevalence, child seroprevalence and elder seroprevalence) and trigger thresholds and the subsequent relative impact on deaths.

Waning rate sensitivity analysis

Our results are sensitive to the assumed rate of waning antibodies. Estimates from the literature vary, especially over longer durations and in the context of new variants and constant exposure. We find a range of waning rates are compatible with the seroprevalence data and the historical epidemic curve from Mozambique. Under a base case scenario where no new variants are introduced, we assess the times when the seroprevalence would fall below specific thresholds under various waning assumptions. We find that for lower seroprevalence trigger thresholds, the rate of waning can substantially affect the timing of an additional vaccination dose.

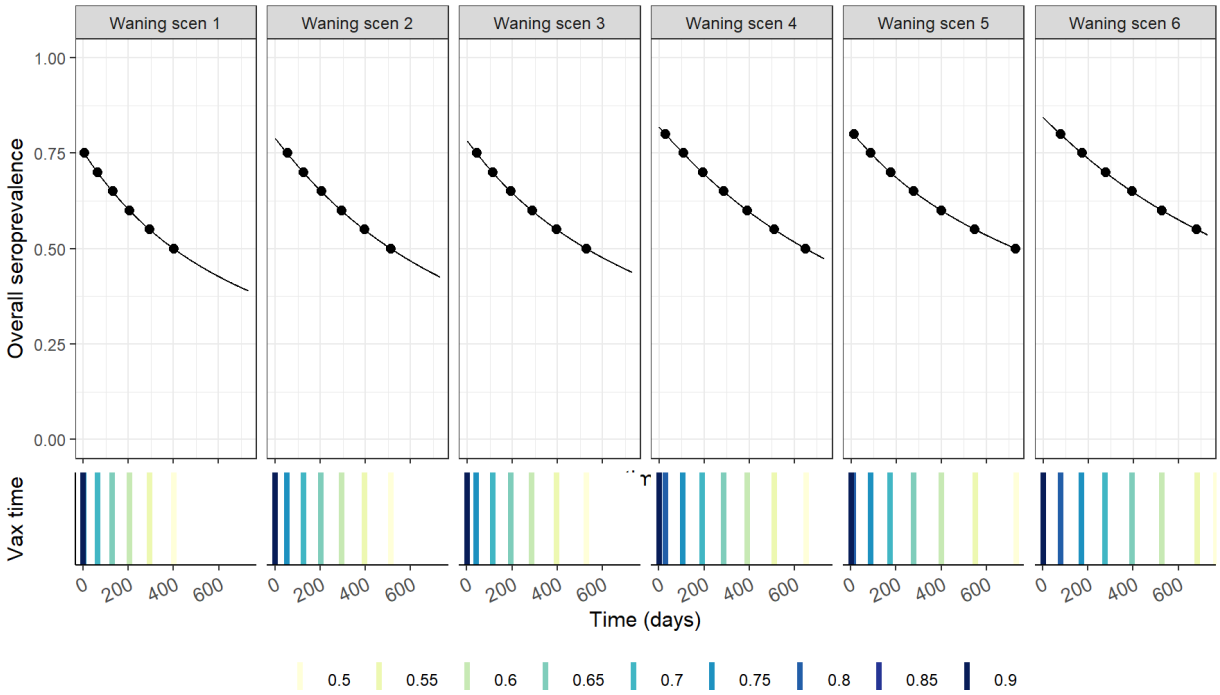


Figure 3. Overall seroprevalence (top) and timing of vaccination triggers (bottom) using thresholds between 50% -90% over the following waning scenarios (slower waning from left to right): 1) first exposure 1/400, second exposure 1/600; 2) first exposure 1/600, second exposure 1/600; 3) first exposure 1/400, second exposure 1/1000; 4) first exposure 1/600, second exposure 1/1000; 5) first exposure 1/400, second exposure 1/2000; 6) first exposure 1/600, second exposure 1/2000. Colored lines on bottom panel denotes the time when seroprevalence falls below a specific threshold which would trigger vaccination. No new variant was introduced during the two-year simulation period.

Limitations

- This model was parameterized for the Mozambique population using local data on demographics, contact rates, mortality time series, and, most importantly, serosurveys. Seroprevalence was high, which limits generalizing our findings to setting of lower seroprevalence
- Because of the model structure, we assumed that immunity waned after infection but not vaccination. However, we expect this had little effect on results since most people had infection-acquired or hybrid immunity.
- We assumed that subsequent waves are a result of new variant emergence rather than endemic or seasonal dynamics.

Summary of results

- With high seroprevalence, as observed currently in Mozambique (and likely many settings), population-wide serosurveys may have limited value in determining the timing of vaccination efforts over the medium term

- Age-stratified serosurveys may be more useful in determining age-specific vaccination strategies, given that different ages were infected and vaccinated at different times in the pandemic.

Supplementary Information

SI.1 Model equations

$$\frac{dS_{i,k,v}}{dt} = -\lambda_{i,k,v}(t)S_{i,k,v} - \delta_{i,k,v}S_{i,k,v} + \omega_{i,v}R_{i,k,v}$$

$$\frac{dE_{i,k,v}}{dt} = \lambda_{i,k,v}(t)S_{i,k,v} - \sigma E_{i,k,v} - \delta_{i,k,v}E_{i,k,v}$$

$$\frac{dI_{i,k,v}}{dt} = (\nu_i)\sigma E_{i,k,v} - \gamma_I I_{i,k,v}$$

$$\frac{dA_{i,k,v}}{dt} = (1-\nu_i)\sigma E_{i,k,v} - \gamma_A A_{i,k,v} - \delta_{i,k,v}A_{i,k,v}$$

$$\frac{dH_{i,k,v}}{dt} = (1-VEP_v)\phi_i\gamma_I I_{i,k,v} - \gamma_H H_{i,k,v}$$

$$\frac{dR_{i,k,v}}{dt} = (1-(1-VEP_v)\phi_i)\gamma_I I_{i,k,v} + \gamma_A A_{i,k,v} + (1-\mu_i)\gamma_H H_{i,k,v} - \delta_{i,k,v}R_{i,k,v} - \omega_{i,v}R_{i,k,v}$$

$$\frac{dM_{i,k,v}}{dt} = \mu_i\gamma_H H_{i,k,v}$$

$$\lambda_{i,k,v}(t) = \beta_i(1-VEI_v)\left[\sum_{j=c,a,e}\sum_{m=r,u}\left(\frac{\chi_{j,i,m,k}\sum_{e=0}^{3}\sum_{v=0}^{3}I_{j,m,v,e}(t) + \alpha A_{j,m,v,e}(t)}{\sum_{e=0}^{2}\sum_{v=0}^{3}N_{j,m,v,e}(t)}\right)\right]$$

SI.2 Model parameters

Abbreviation	Description	Value	Source
Transmission			
R0	Basic reproduction number	2.58	[14,15]
$\beta_c, \beta_a, \beta_e$	Prob. of infection by exposed age group	0.02326, 0.02442, 0.0116	Calibrated
α	Relative infectiousness btwn asympt & sympt	0.6	[16,17]
γ_I	Infectious period, symptomatic (days)	7	[18]
γ_A	Infectious period, asymptomatic(days)	7	[18]
γ_H	Hospital LOS (days)	5	[19]
σ	Latent period	5.5	[20–23]
ν_c, ν_a, ν_e	Probability of symptomatic infection by age group	0.45, 0.55, 0.65	[16]
$\phi_c, \phi_a, \phi_e,$	Probability of hospitalization upon infection by age group	0.0075, 0.15, 0.35	[24]

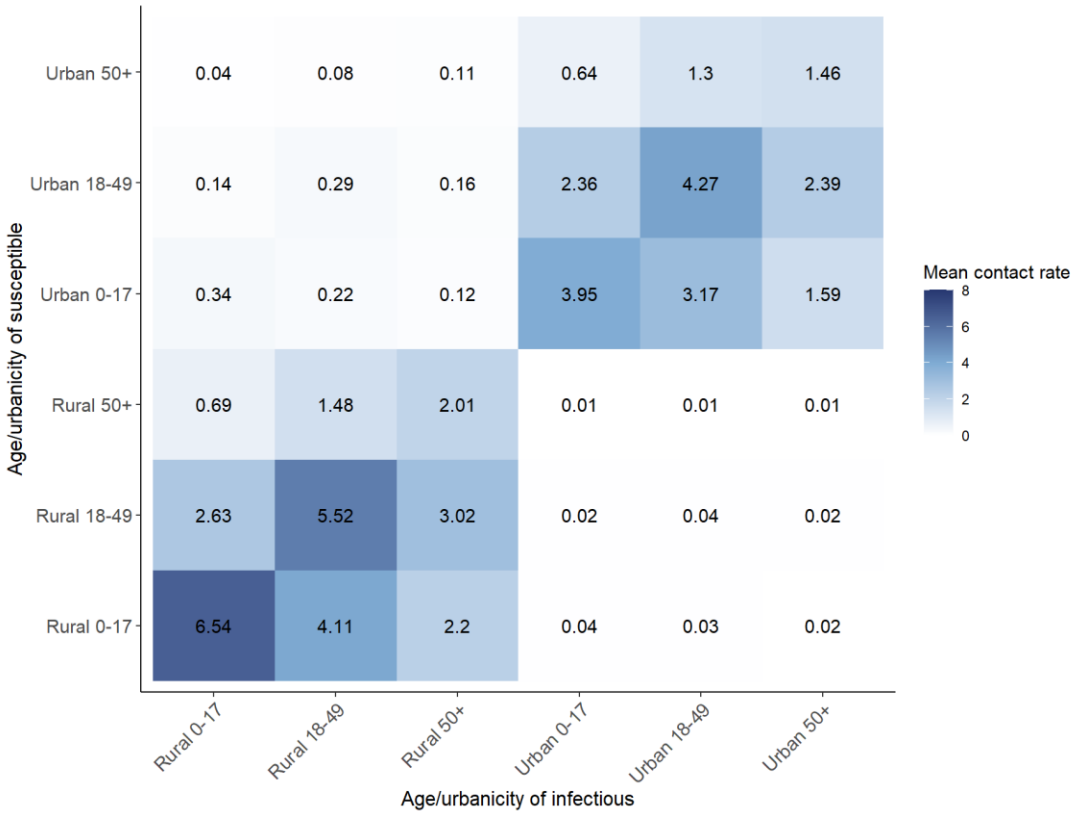
μ_c, μ_a, μ_e	Probability of death upon infection by age group	0.01, 0.0465, 0.1	[25]
$\omega_c, \omega_a, \omega_e$	Duration of full immunity by age group	1/150, 1/150, 1/150	[26]
Serology			
π	Probability of seroconversion after infection	0.95	[27]
$\rho_{v1}, \rho_{v2}, \rho_{v3}$	Probability of seroconversion among seronegative individuals after vaccination (dose 1-3)	0.85,0.9,0.9	Assumption
κ_1	Seroreversion rate for first exposure (either vaccine or infection)	1/200-1/600	[28,29]
κ_2	Seroreversion rate for second exposure	1/600-1/2000	[28,29]
κ_3	Seroreversion rate for three or more exposures	1/3000	[28,29]
Vaccination			
$\delta_{i,k,v}$	Per capita vaccination rate by age group, urban/rural and dose	Time-varying based on data (0.01%-4%)	[13]
$VEI_{v1}, VEI_{v2}, VEI_{v3}$	Vaccine effectiveness against infections by number of vaccine doses (assuming Astra Zeneca)	0.5, 0.6, 0.7	[30]
$VEP_{v1}, VEP_{v2}, VEP_{v3}$	Vaccine effectiveness against progression from infection to severe disease/hospitalization by number of vaccine dose (assuming Astra Zeneca)	0.4, 0.67, 0.7	[30]
Prior exposure protection			
red_inf_1	Protection from first infection	0.65	[31]
red_inf_2	Protection from second infection	0.75	Assumption
Variants			
R0 (delta)	R0 during delta wave	3.1	[32]
R0 (omicron)	R0 during omicron	6.4	[33]
R0 (new variant)	R0 for forward simulation new wave	4.9	Assumption
Immune escape (delta)	Increased transmission among those with prior exposure during delta wave	1.2	[34,35]

Immune escape (omicron)	Increased transmission among those with prior exposure during omicron wave	1.6	[34,35]
Immune escape (new variant)	Increased transmission among those with prior exposure for new variant	1.7	Assumption

SI3. Data sources from Mozambique

Parameter	Source	Notes
Age-specific social contact	GlobalMix Study (Comprehensively profiled social contact patterns in an urban and rural area in Mozambique)	Unpublished
Age-specific vaccination rates	Instituto Nacional de Saude, Mozambique/ Our World in data	[13]
Age-specific reported cases	Instituto Nacional de Saude, Mozambique/ Our world in data	[13]
Probability of travel between urban and rural	Travel survey as part of MP3	Assumption
Seroprevalence data	Instituto Nacional de Saude, Mozambique	[36]

SI4. Contact matrix



SI.5 Table of % reduction in deaths and symptomatic cases during the two-year simulation period across varying vaccination trigger scenarios and thresholds

Trigger threshold	Vaccination timing	% reduction in deaths				% reduction in symptomatic cases			
		All	Children	Adults	Elderly	All	Children	Adults	Elderly
Using total population seroprevalence to trigger additional vaccination for all									
70%	Never	-	-	-	-	-	-	-	-
75%	671	0.8	0.8	0.8	0.8	0.9	0.8	1	1
80%	87	28	33.6	26.4	33.4	18.9	15	24.1	31.6
85%	1	33.1	43.5	31	40.4	20.6	15.4	27.5	37.9
90%	1	33.1	43.5	31	40.4	20.6	15.4	27.5	37.9
Using child seroprevalence to trigger additional vaccination for children									
70%	Never	-	-	-	-	-	-	-	-
75%	66	4.6	32	3.7	4.4	6.6	8.5	4	4.6
80%	1	4.3	38.9	3.2	4	6.8	9.2	3.5	4.3
85%	1	4.3	38.9	3.2	4	6.8	9.2	3.5	4.3
90%	1	4.3	38.9	3.2	4	6.8	9.2	3.5	4.3
Using older adult (>50 years) to trigger additional vaccination for older adults									
70%	559	1	0.8	0.9	1.5	1	0.9	1.1	1.6
75%	385	2.2	1.7	1.9	3.1	2	1.9	2.1	3.2
80%	85	7.2	2.6	3.7	21.9	3.5	2.7	3.9	19.5
85%	1	8.3	2.4	3.8	27.5	3.5	2.5	3.9	24.3
90%	1	8.3	2.4	3.8	27.5	3.5	2.5	3.9	24.3

References

1. Cutts, F. T. & Hanson, M. Seroepidemiology: an underused tool for designing and monitoring vaccination programmes in low- and middle-income countries. *Trop. Med. Int. Health* **21**, 1086–1098 (2016).
2. dos Santos Ferreira, C. E. *et al.* The Role of Serology Testing in the Context of Immunization Policies for COVID-19 in Latin American Countries. *Viruses* **13**, 2391 (2021).
3. SeroTracker. SeroTracker Newsletter. https://serotracker.substack.com/embed.
4. Oved, K. Multi-center nationwide comparison of seven serology assays reveals a SARS-CoV-2 non-responding seronegative subpopulation. 10 (2020).
5. Lou, B. *et al.* Serology characteristics of SARS-CoV-2 infection after exposure and post-symptom onset. *Eur. Respir. J.* **56**, 2000763 (2020).

6. He, Z. *et al.* Seroprevalence and humoral immune durability of anti-SARS-CoV-2 antibodies in Wuhan, China: a longitudinal, population-level, cross-sectional study. *The Lancet* **397**, 1075–1084 (2021).
7. Swartz, M. D. *et al.* Antibody duration after infection from SARS-CoV-2 in the Texas Coronavirus Antibody Response Survey. *J. Infect. Dis.* jiac167 (2022) doi:10.1093/infdis/jiac167.
8. Wei, J. *et al.* Antibody responses to SARS-CoV-2 vaccines in 45,965 adults from the general population of the United Kingdom. *Nat. Microbiol.* **6**, 1140–1149 (2021).
9. Wang, H. *et al.* Dynamics of the SARS-CoV-2 antibody response up to 10 months after infection. *Cell. Mol. Immunol.* **18**, 1832–1834 (2021).
10. Ward, H. Population antibody responses following COVID-19 vaccination in 212,102 individuals. *Nat. Commun.* **13**, 6 (2022).
11. Ali, H. *et al.* Previous COVID-19 Infection and Antibody Levels After Vaccination. *Front. Public Health* **9**, 778243 (2021).
12. Ritchie, H. *et al.* Coronavirus Pandemic (COVID-19). *Our World Data* (2020).
13. Total COVID-19 vaccine doses administered per 100 people. *Our World in Data* https://ourworldindata.org/grapher/covid-vaccination-doses-per-capita.
14. Li, Q. *et al.* Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. *N. Engl. J. Med.* NEJMoa2001316 (2020) doi:10.1056/NEJMoa2001316.
15. Liu, Y., Gayle, A. A., Wilder-Smith, A. & Rocklöv, J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J. Travel Med.* **27**, taaa021 (2020).
16. Poletti, P. *et al.* Association of Age With Likelihood of Developing Symptoms and Critical Disease Among Close Contacts Exposed to Patients With Confirmed SARS-CoV-2 Infection in Italy. *JAMA Netw. Open* **4**, e211085 (2021).

17. Mizumoto, K., Kagaya, K., Zarebski, A. & Chowell, G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. *Eurosurveillance* **25**, (2020).

18. Kissler, S. M., Tedijanto, C., Goldstein, E., Grad, Y. H. & Lipsitch, M. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. 10 (2020).

19. Rees, E. M. *et al.* COVID-19 length of hospital stay: a systematic review and data synthesis. *BMC Med.* **18**, 270 (2020).

20. Lauer, S. A. *et al.* The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. *Ann. Intern. Med.* (2020) doi:10.7326/M20-0504.

21. Backer, J. A., Klinkenberg, D. & Wallinga, J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20–28 January 2020. *Eurosurveillance* **25**, (2020).

22. McAloon, C. *et al.* Incubation period of COVID-19: a rapid systematic review and meta-analysis of observational research. *BMJ Open* **10**, e039652 (2020).

23. Qin, J. *et al.* Estimation of incubation period distribution of COVID-19 using disease onset forward time: A novel cross-sectional and forward follow-up study. *Sci. Adv.* **6**, (2020).

24. Lemaitre, J. C. *et al.* A scenario modeling pipeline for COVID-19 emergency planning. *Sci. Rep.* **11**, 7534 (2021).

25. Brazeau, N. F. *et al.* Estimating the COVID-19 infection fatality ratio accounting for seroreversion using statistical modelling. *Commun. Med.* **2**, 54 (2022).

26. Leidi, A. *et al.* Risk of reinfection after seroconversion to SARS-CoV-2: A population-based propensity-score matched cohort study. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* ciab495 (2021) doi:10.1093/cid/ciab495.

27. Sonabend, R. *et al.* Non-pharmaceutical interventions, vaccination, and the SARS-CoV-2 delta variant in England: a mathematical modelling study. *The Lancet* **398**, 1825–1835 (2021).

28. Harris, J. E. Data from the COVID-19 epidemic in Florida suggest that younger cohorts have been transmitting their infections to less socially mobile older adults. *Rev. Econ. Househ.* **18**, 1019–1037 (2020).

29. Chen, S., Flegg, J. A., White, L. J. & Aguas, R. Levels of SARS-CoV-2 population exposure are considerably higher than suggested by seroprevalence surveys. *PLOS Comput. Biol.* **17**, e1009436 (2021).

30. Higdon, M. *et al.* A systematic review of COVID-19 vaccine efficacy and effectiveness against SARS-CoV-2 infection and disease. *Open Forum Infect. Dis.* **ofac138**, (2022).

31. Lacy, J. *et al.* Protective effect of a first SARS-CoV-2 infection from reinfection: a matched retrospective cohort study using PCR testing data in England. *Epidemiol. Infect.* **150**, e109 (2022).

32. Public Health England. SARS-CoV-2 variants of concern and variants under investigation. 66 (2021).

33. Baker, J. M. *et al.* SARS-CoV-2 B.1.1.529 (Omicron) Variant Transmission Within Households — Four U.S. Jurisdictions, November 2021–February 2022. *MMWR Morb. Mortal. Wkly. Rep.* **71**, 341–346 (2022).

34. Hansen, C. H. *et al. Vaccine effectiveness against SARS-CoV-2 infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: A Danish cohort study*. http://medrxiv.org/lookup/doi/10.1101/2021.12.20.21267966 (2021) doi:10.1101/2021.12.20.21267966.

35. Harder, T. *et al.* Effectiveness of COVID-19 vaccines against SARS-CoV-2 infection with the Delta (B.1.617.2) variant: second interim results of a living systematic review and meta-analysis, 1 January to 25 August 2021. *Eurosurveillance* **26**, (2021).

36. Arnaldo, P. *et al.* Prevalence of SARS-CoV-2 antibodies in the Mozambican population: a cross-sectional Serologic study in three cities, July-August 2020. *Clin. Infect. Dis.* ciac516 (2022) doi:10.1093/cid/ciac516.

Cost-Effectiveness Analysis of a second COVID-19 booster vaccination in the United States

Lei Zhang

Central Clinical School
Faculty of Medicine, Nursing and Health Sciences
Monash University, Australia

Content

Part 1: Cost-Effectiveness analysis of second booster vaccination for adults aged 50 years and older

Part 2: Cost-Effectiveness analysis of second booster vaccination for those younger age group (5-11, 12-17, 18-49)-**ongoing**

Background

❖ 29th March 2022, the U.S. FDA authorised a second booster dose.

Recommended
1 Booster

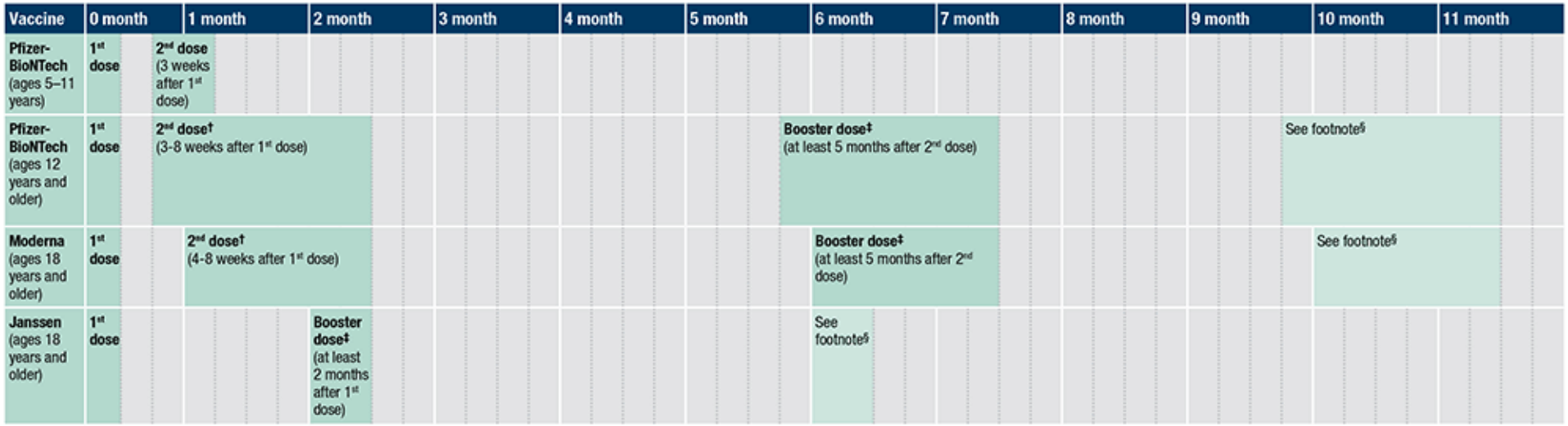
- Everyone ages 5 years and older should get 1 booster after completing their COVID-19 vaccine primary series, if eligible.

Learn when you should get your 1st booster below.

Recommended
2 Boosters

- Adults ages 50 years and older
- Some people ages 12 years and older who are moderately or severely immunocompromised

Learn when you should get your 2nd booster below.



Background

COVID-19 vaccination in the US

As of 29th March 2022, for people ≥ 50 years in US (refs)

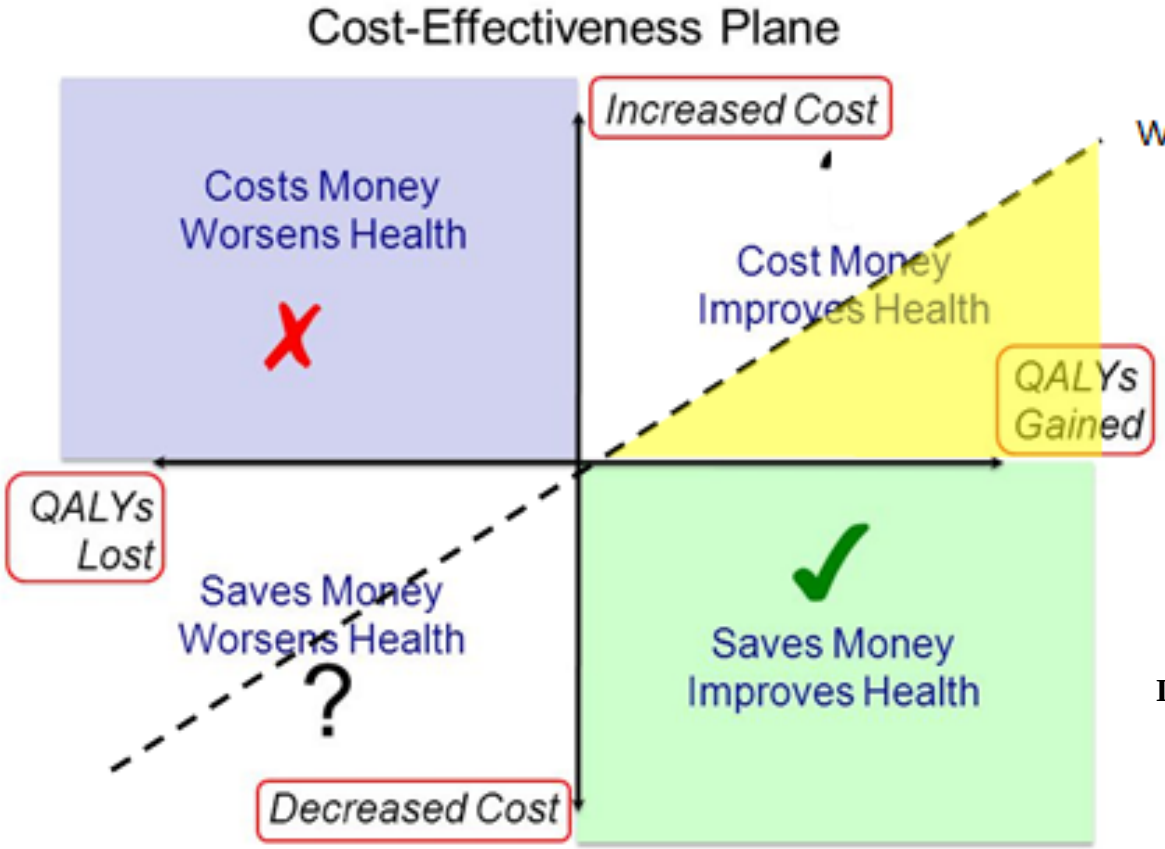
- ❑ 2.9% never vaccinated;
- ❑ 97.1% vaccinated with at least one dose
- ❑ 84.7% vaccinated with at least two doses
- ❑ 50.3% vaccinated with at least two doses and one booster
- ❑ 0.8% vaccinated with at least two doses and two boosters
- ❑ 57.7% US population has been previously infected, ##% is among aged ≥ 50 years

Aim:

1. To evaluate the cost-effectiveness of a second COVID-19 booster vaccination for those aged ≥50yrs in the United States.

2. To explore the key factors that may affect its cost-effectiveness.

Methods



Willingness-to-pay

QALYs = Quality-adjusted life years

Incremental cost-effectiveness ratios (ICERs)

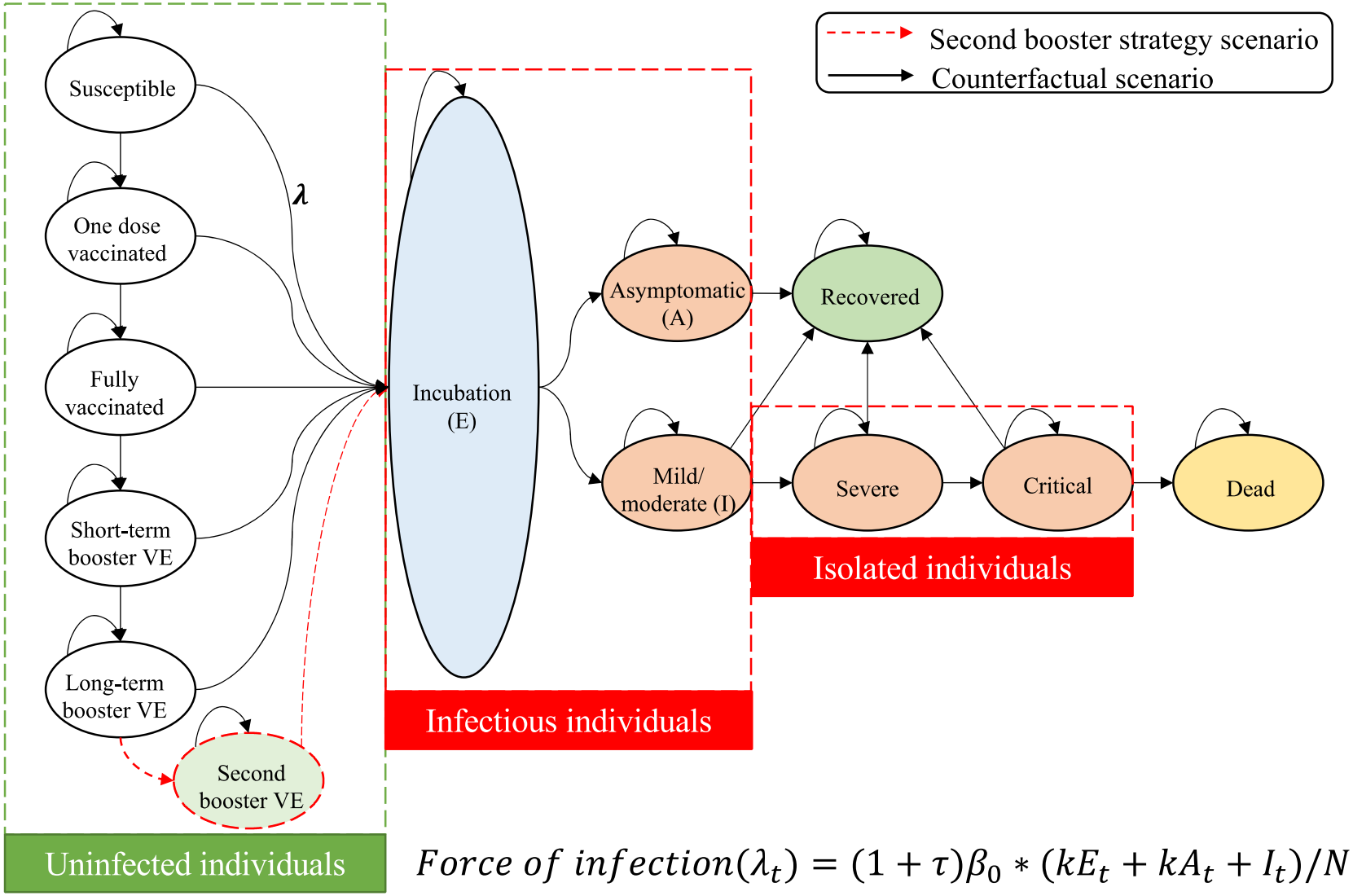
$$\mathrm{ICER} = \frac{C_{\text{intervention}} - C_{\text{status quo}}}{E_{\text{intervention}} - E_{\text{status quo}}}$$

The potential results of one intervention, compared to status quo:

- **Cost-saving:** in fourth quadrant (Green color)
- **Cost-effective:** in first quadrant (Yellow color)
- **Not cost-effective:** in first quadrant (White color).

Methods

We developed a **decision-analytic SEIR-Markov model** to simulate the disease transmission and progression of the Omicron in those aged ≥50 years **over a period of 180 days** in the US.



$$Force\ of\ infection(\lambda_t) = (1+\tau)\beta_0 * (kE_t + kA_t + I_t)/N$$

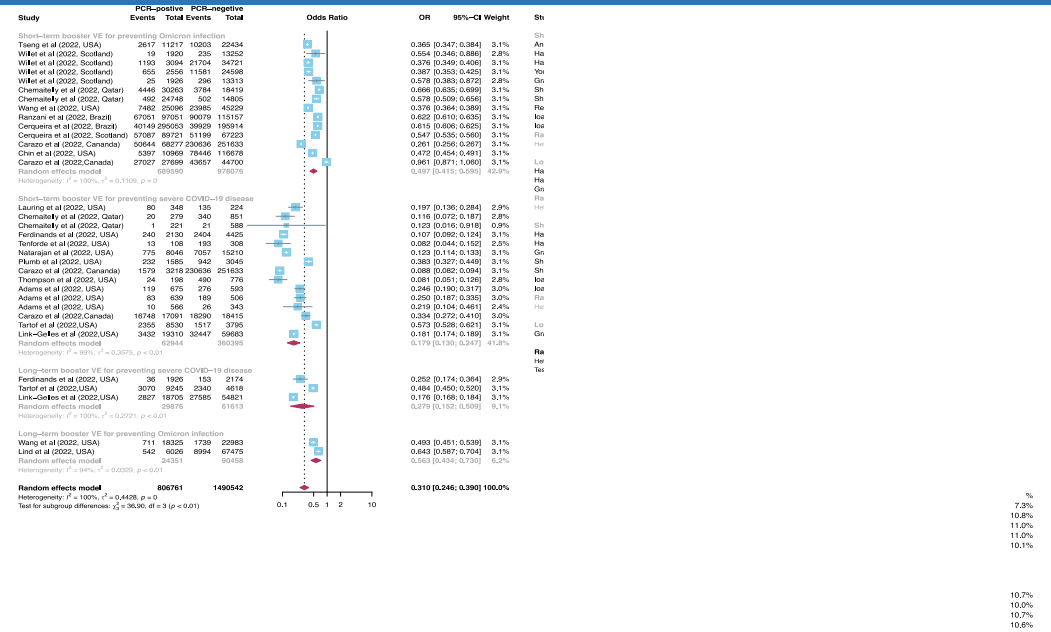
Methods

Model parameters

1. **Booster vaccine efficacy against Omicron**
2. **Epidemiological parameters**: transition probability from one status to another
    - Force of infection (affected by vaccine efficacy)
    - Disease progression (affected by vaccine efficacy)
3. **Costing parameters:** cost in each status or its transition
4. **Life quality parameters:** health outcomes in each status or its transition

Model parameters collection

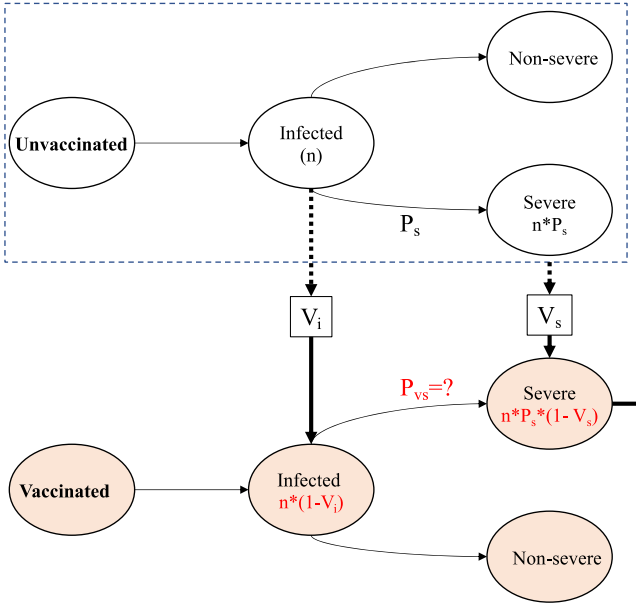
We conducted a **Meta-analysis** to summary the first and second booster vaccine efficacy against Omicron.



Variables	Case-control designs	Retrospective cohort designs	Average VE
Short-term booster VE for preventing Omicron infection (%)	50.3 (40.6, 58.5)	52.2 (44.7, 58.7)	**51.2 (40.6, 58.7)**
Short-term booster VE for preventing severe COVID-19 disease (%)	82.1 (75.3, 87.0)	79.2 (67.3, 86.8)	**80.6 (67.3, 87.0)**
Long-term booster VE for preventing Omicron infection (%)	43.7 (27.0, 56.6)	38.4 (25.4, 49.1)	**41.0 (25.4, 56.6)**
Loge-term booster VE for preventing severe COVID-19 disease (%)	72.1 (49.1, 84.8)	48.9 (38.5, 57.6)	**60.5 (38.5, 84.8)**
2nd booster VE for preventing Omicron infection, compared with long-term booster vaccination	46.8 (27.1, 61.2)	42.8 (23.5, 57.2)	**44.8 (23.5, 61.2)**
2nd booster VE for preventing severe COVID-19 disease, compared with long-term booster vaccination	46.3 (0.0, 80.6)	66.9 (64.4, 69.2)	**56.6 (0.0, 80.6)**
2nd booster VE for preventing Omicron infection, compared with no vaccination			**67.4 (42.9, 83.2)**
2nd booster VE for preventing severe COVID-19 disease, compared with no vaccination			**82.9 (38.5, 97.0)**

Methods

2. Distribution of clinical disease stages of various vaccination status



V_i :Vaccine efficacy for preventing a SARS-CoV-2 infection

V_s :Vaccine efficacy for preventing a severe COVID-19 case

P_s :Proportion of severe cases in all unvaccinated COVID-19 infections

P_{vs} :Proportion of severe cases in all vaccinated COVID-19 infections

$$P_{vs} = \frac{n \times P_s \times (1 - V_s)}{n \times (1 - V_i)}$$

Different combination of vaccine effcacy for preventing Omicron infection and for severe COVID-19 disease creates different distribution of clinical outcomes after Omicron infection.

Clinical outcomes	**The distribution of unvaccinated group**	**The distribution of short-term booster VE group**	**The distribution of long-term booster VE group**	**The distribution of 2nd booster VE group**
Asymptomatic infection	31.00%	31.37%	31.20%	31.29%
Mild/Moderate illness	67.07%	67.86%	67.50%	67.69%
Severe illness	1.05%	0.42%	0.70%	0.55%
Critical illness	0.88%	0.35%	0.59%	0.46%
Critical (recover) illness	0.35%	0.14%	0.24%	0.19%
Critical (die) illness	0.53%	0.21%	0.35%	0.28%

Methods

3. Direct medical cost

We collected the direct medical costs of COVID-19 disease in the US from published literature and Medicare Administrative Contractor report[14-16]. The cost of PCR tests and rapid antigen self-test for COVID-19 infection was estimated to be $51 and $11 per person, respectively. In addition, we collected cost per outpatient visit, general hospitalisation and ICU admission and the duration of each disease stage[17]. The cost of medical services varied across clinical disease stages, and we calculated the total direct medical cost of COVID-19 cases with varied severity by multiplying the unit cost of the medical services by the duration of each disease stage

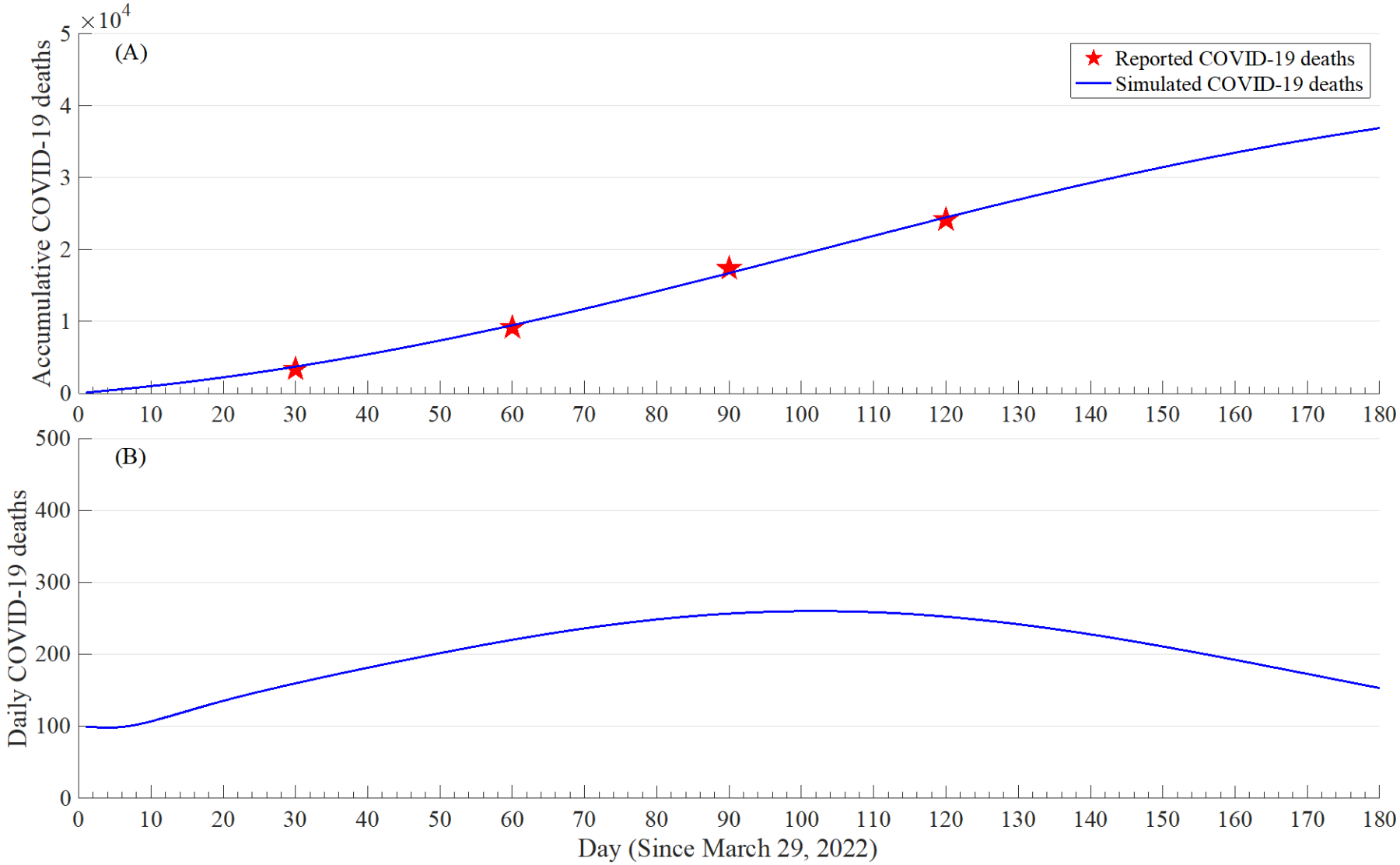
Clinical outcomes	Self-tests cost (per person, $)	PCR test cost (per person, $)	Outpatient cost (per visit, $)	Hospitalization cost (per person, $)			ICU cost (per person, $)			Total direct medical cost (per person, $)
				length of stay	per day cost	total cost	length of stay	per day cost	total cost	
Asymptomatic infection	11	0	0	0	2364	0	0	3111	0	11
Mild/Moderate illness	11	51	164	0	2364	0	0	3111	0	226
Severe illness	11	51	164	9.2	2364	21752	0	3111	0	21978
Critical (die) illness	11	51	164	4.2	2364	9930	7.1	3111	22085	32241
Critical (recover) illness	11	51	164	10 (4.2+5.8)	2364	23643	7.1	3111	22085	45954

4. Health state utilities

Health states	Disability weight 1	Disability weight 2	**Average utility**
In asymptomatic state	—	—	**1**
In mild/moderate state	—	—	**1**
In severe state	0.13 (0.09, 0.19)	0.30	**0.785 (0.700, 0.910)**
In critical state	0.41 (0.27, 0.56)	0.50-0.60	**0.520 (0.400, 0.730)**
In recuperable state	—	0.19	**0.905 (0.810, 1.000)**
In dead state	0	0	**0**

Model calibration and validation

We varied COVID-19 transmission coefficient and speed of vaccination (%/day) automatically with **TreeAge Pro's calibration tool** to calibrate model outputs to observed COVID-19 related mortality and vaccination distribution in the US.



Model calibration and validation

We varied COVID-19 transmission coefficient and speed of vaccination (%/day) automatically with **TreeAge Pro's calibration tool** to calibrate model outputs to observed COVID-19 related mortality and vaccination distribution in the US.

Calibration results of the uninfected proportion in individuals with various vaccination status (day 90)								
	Unvaccinated	One dose vaccinated	Fully vaccinated	Short-term booster	Long-term booster	Second booster		
Observed	0.43%	3.44%	9.18%	2.22%	20.53%	11.22%		
Modelled	0.43%	3.44%	9.40%	4.43%	18.13%	11.19%		
Calibration results of accumulative COVID-19 mortality and deaths								
	Accumulative COVID-19 mortality				Accumulative COVID-19 and deaths			
	Day 30	Day 60	Day 90	Day 120	Day 30	Day 60	Day 90	Day 120
Observed	2.86E-05	7.75E-05	1.47E-04	2.04E-04	3390	9178	17366	24143
Modelled	2.81E-05	7.49E-05	1.40E-04	2.18E-04	3329	8867	16576	25859

Results

Table 1. The results of the cost-effectiveness analysis of second COVID-19 booster vaccination in older adults aged ≥50 years in the United States over an evaluation period of 180 days.

	Counterfactual scenario with **no second booster strategy**	Current **second booster strategy**	Incremental benefits of second booster strategy*
QALY	57,926,476	57,929,037	2,561
Costs ($, million)	8,506.1	6,776.3	-1,729.8
Second booster vaccination cost	0	791.8	791.8
Other vaccination cost	365.0	373.8	8.8
Direct medical cost	8,141.0	5,610.6	-2,530.4
Death cases	52,778	36,882	15,896
ICER	--	--	**cost-saving**
Benefit-cost ratio	--	--	3.16
Cost/death prevented, $	--	--	50,365
Net monetary benefit, ($, million)	--	--	1,857.8

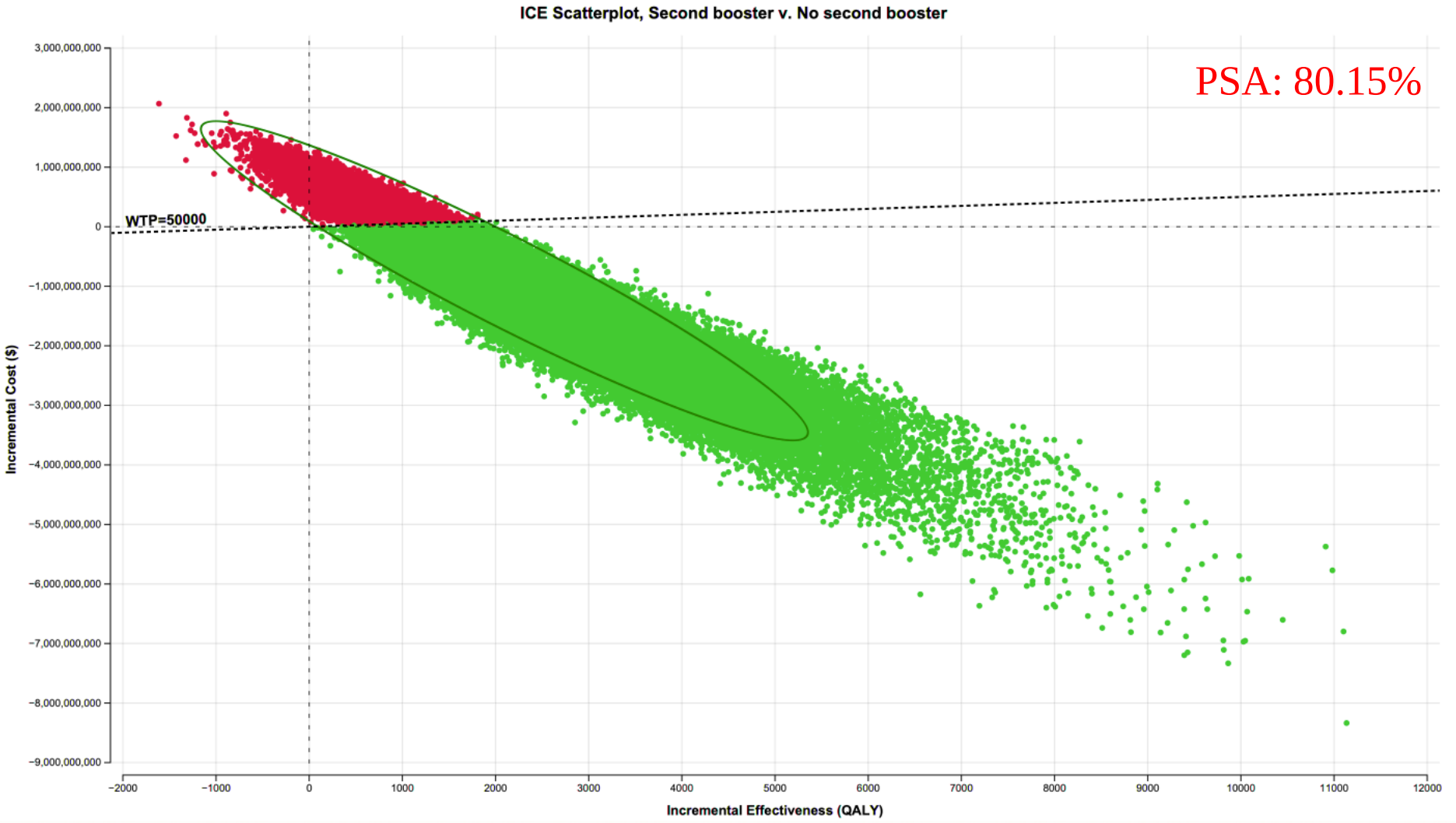
* Incremental benefits = difference in QALY while comparing to the no second booster strategy.

Benefit-cost ratio: the ratio between the reduction in the direct medical cost for COVID-19 and the investment in booster vaccination for individuals aged ≥50 in the United States.

Net monetary benefit (NMB) is calculated as (incremental benefit × willingness-to-pay threshold) – incremental cost.

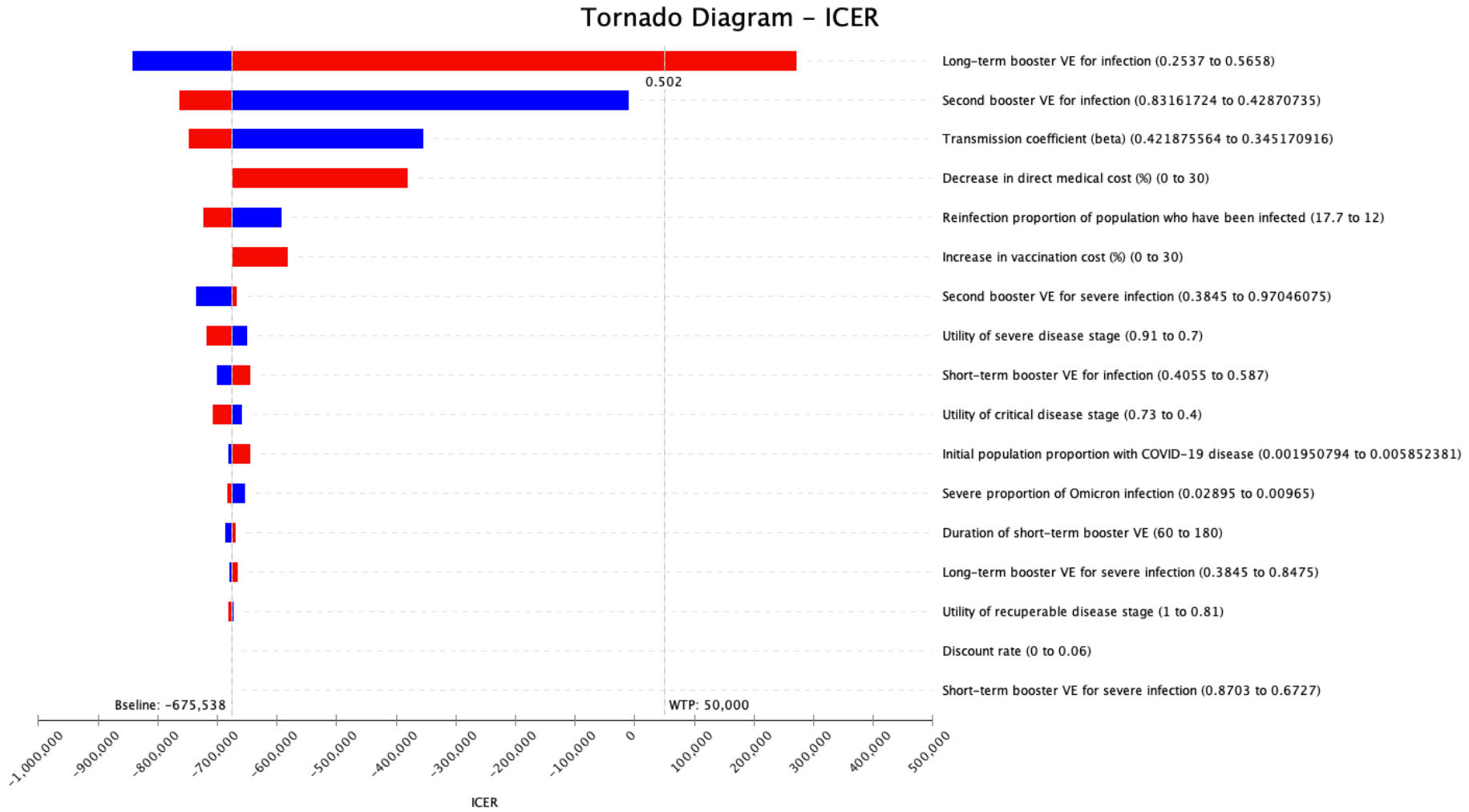
Current second COVID-19 booster strategy in the US is likely to be cost-effective for curbing this Omicron epidemic.

Results



Probabilistic sensitivity analysis (PSA) based on 10,000 simulations confirmed that current second booster strategy had a high chance (**80.15%**) to be cost-effective.

Results



Univariable sensitivity analysis demonstrated that the top three of most sensitive parameters on ICER were long-term and second booster VE for Omicron infection, transmission coefficient (beta) of Omicron variant.

Summary

Second COVID-19 booster vaccination strategy in the US

- COVID-19 still causes huge disease burden in the US. Despite with rollout of a second booster shot, there would be 9.2 million cumulative infections, 136,743 cumulative hospitalization, 62,267 cumulative ICU-admission, and 36,882 cumulative death over an evaluation period of 180 days.

- Compared to no second booster strategy, the second booster strategy would reduce 4.5 million cumulative infections, 68,777 cumulative hospitalization, 31,318 cumulative ICU-admission, and 15,896 cumulative death.

- Second booster strategy would reduce direct medical cost by $2530.4 million and but only incur an additional vaccination cost of $800.2 million, corresponding to a benefit-cost ratio of 3.16.

- Second booster strategy would gain 2,561 QALYs during the 180 days. This suggested the current second booster strategy is cost-saving.

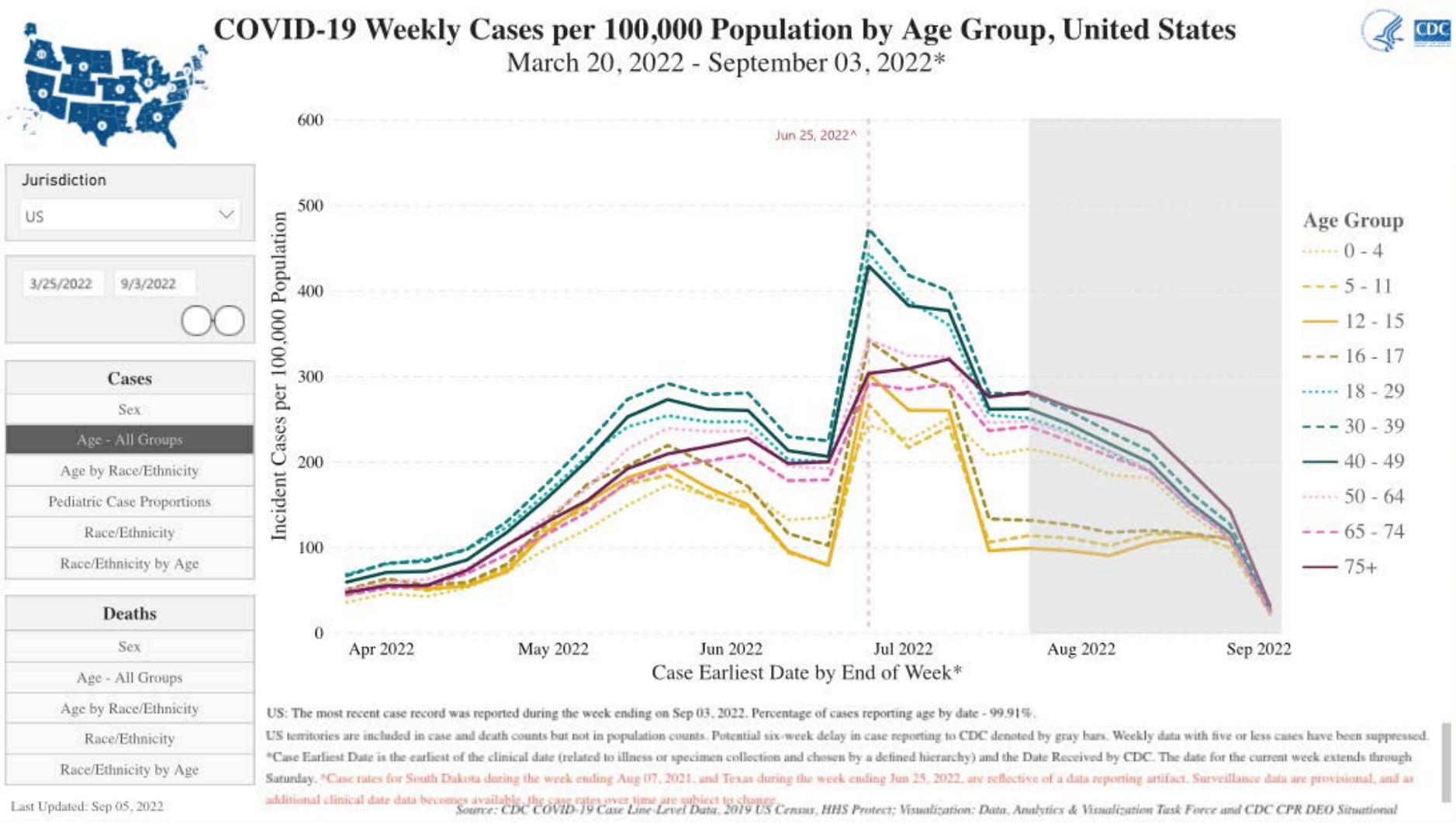
Content

Part 1: Cost-Effectiveness analysis of second booster vaccination for adults aged 50 years and older

Part 2: Cost-Effectiveness analysis of second booster vaccination for those younger age group (5-11, 12-17, 18-49)-**ongoing**

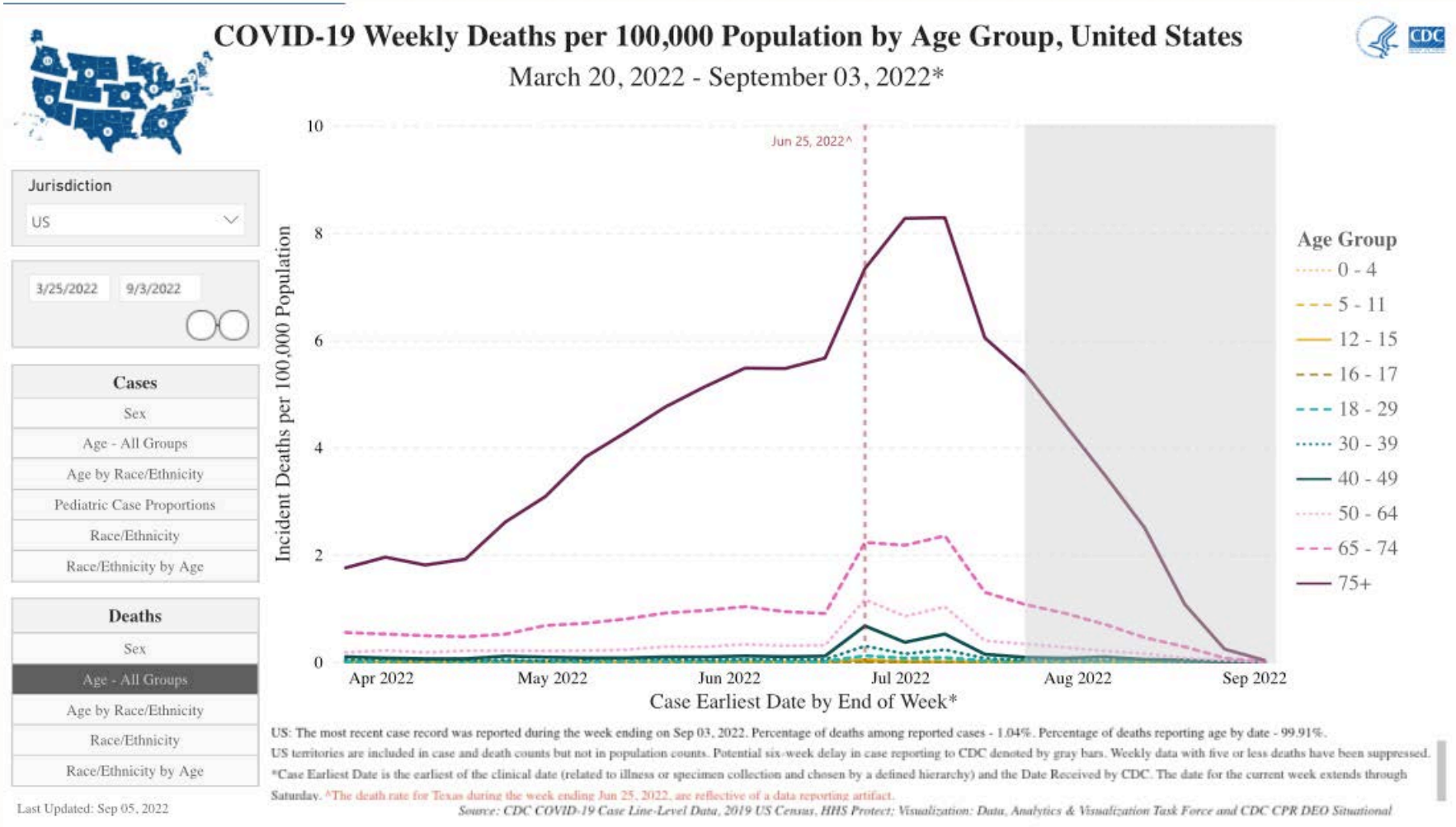
Methods

- The people aged 18-49 has higher population incidence than those aged ≥50yrs.
- The people aged 5-11 and 12-18 have lower population incidence than those aged ≥50yrs.



Methods

- The people aged 18-49 has lower population mortality than those aged ≥50yrs.
- The people aged 5-11 and 12-18 have lower population mortality than those aged ≥50yrs.

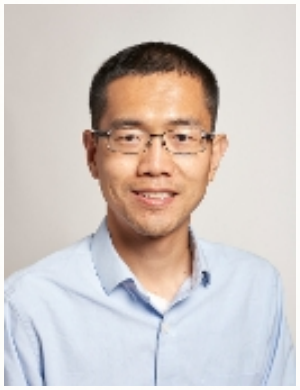


Thus, it's cost-effectiveness of second booster strategy for younger popualtion remains uncertain.

Next steps (4-6 weeks):

- Identify the vaccine efficacy in preventing infection and severe diseases in various age groups (5-11, 12-17, 18-49 years, assume to be identical to ≥50 years?)
- Identify the number of complications and mortality cases in 5-11, 12-17, 18-49 age groups, but these numbers are very small in younger age groups (barriers for model calibration?).
- Use re-calibrated model to evaluate the cost-effectiveness of 2nd booster in these age groups.
- Sensitivity on the reinfection rate and its impact on cost-effectiveness

Research team



Yan LI PhD

ASSOCIATE PROFESSOR
Population Health Science and Policy
Icahn School of Medicine at Mount Sinai, the US

Mingwang SHEN PhD

ASSOCIATE PROFESSOR
School of Public Health,
Xi’an Jiaotong University, China

Rui LI

PhD Candidate
School of Public Health,
Xi’an Jiaotong University, China

Thank you for attention

World Health Organization

Session 2

Full Value of improved Influenza Vaccine Assessment

World Health Organization

Full value of improved influenza vaccines assessment (FVIVA)

Philipp Lambach

IVIR-AC meeting, Sep 12, 2022

Influenza disease

- **Seasonal influenza:** each year, across the globe, there are an estimated 1 billion cases
  - 3–5 million severe cases
  - 290 000–650 000 influenza-related respiratory deaths
  - In low-income countries in sub-Saharan Africa and Southeast Asia (particularly in elderly and children under 5 years) rates of illness and death from influenza are estimated to be even higher
- **Pandemic influenza:**
  - Influenza A viruses from animal reservoirs can spill over to human populations, posing a continuous threat of pandemic influenza
  - Vaccination is considered a key public health intervention to reduce both
    - burden of seasonal influenza
    - enhance preparedness for emergence of severe pandemic influenza

https://apps.who.int/iris/bitstream/handle/10665/311184/9789241515320-eng.pdf?ua=1

Global efforts to strengthen pandemic influenza preparedness

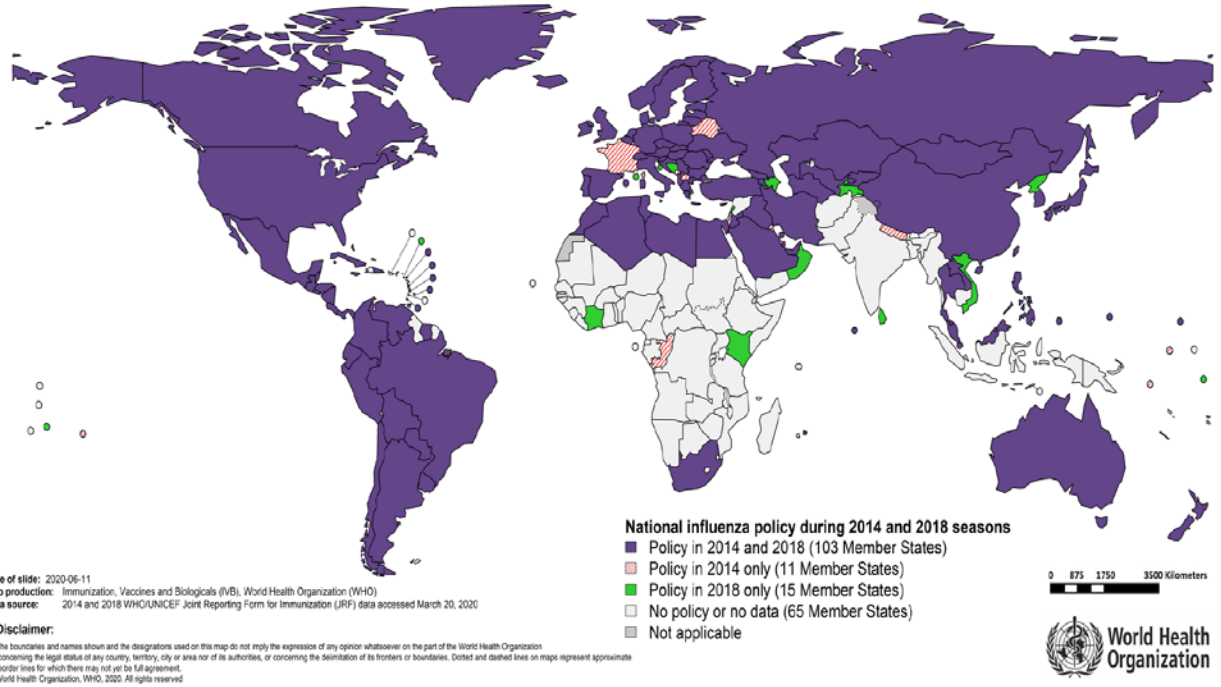
- **1999:** WHO released its 1st Influenza Pandemic Plan outlining responsibilities of WHO and national authorities to prepare and plan for pandemic outbreaks
- **2005:** WHA – new set of *International Health Regulations* (WHA58.3) and *Influenza preparedness resolution* (WHO58.5)
- **2006:** *Global Action Plan* for Influenza developed to expand influenza vaccine access: increase in seasonal and pandemic influenza manufacturing capacity:
  - 500 million and 1.5 billion doses in 2006 → 1.5 billion and 6.2 billion in 2013

Lack of demand for influenza vaccine

Introduction/sustainability of seasonal influenza programs in LMICs challenged among others by profile of current vaccines:

- moderate efficacy against ambulatory influenza illness
- need to be tailored each year to match circulating strains
- limited duration of protection

Existing seasonal influenza vaccines may not provide plausible and justifiable long-term solutions for LMICs as they challenge already strained vaccination programmes

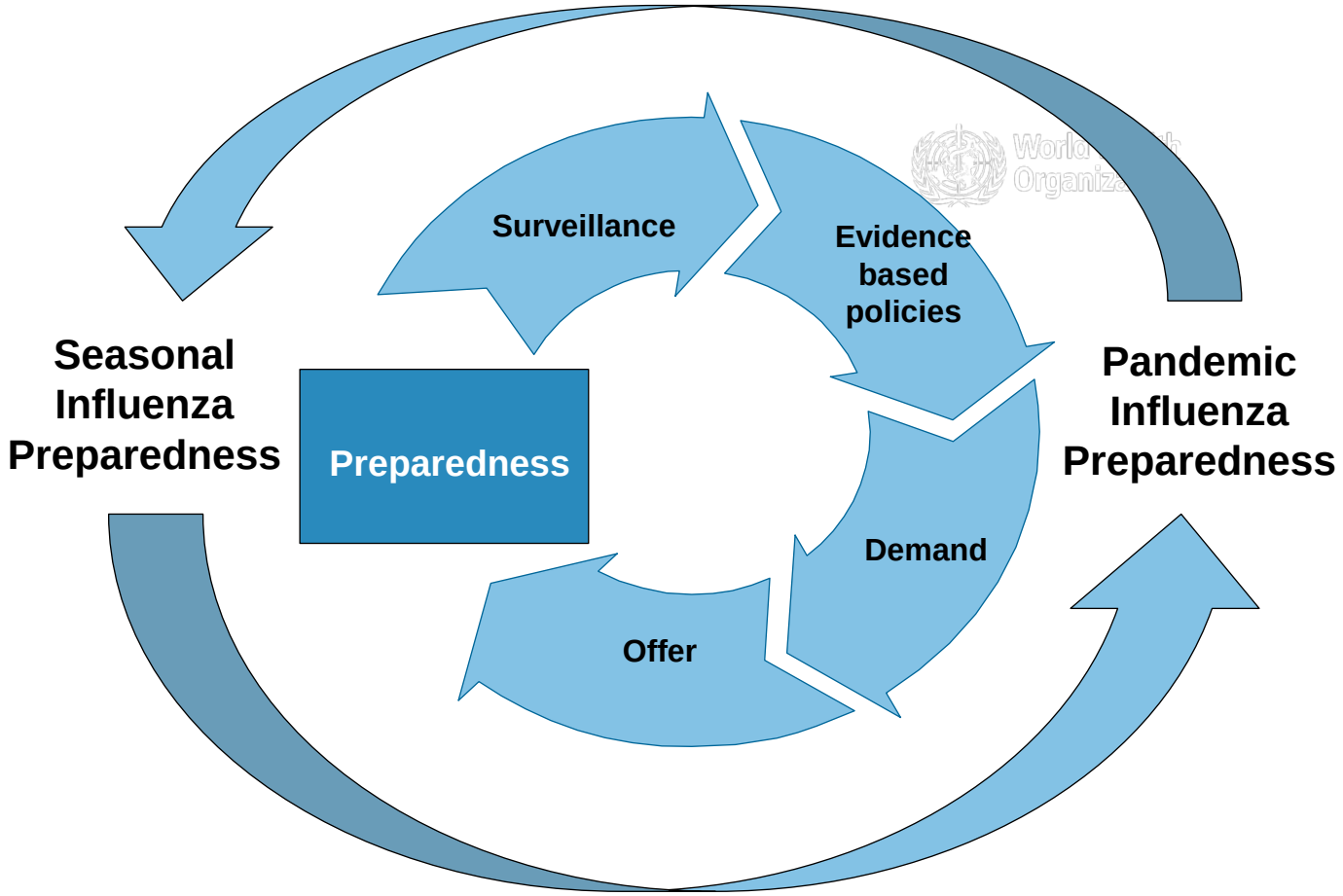


Supply Challenges: Unreliable demand prevents sustained pandemic production capacities

- Country decision makers hesitate to introduce vaccines due to financial constraints, competing priorities, and lack of evidence

- Pharmaceutical companies currently not tempted by market to continue to ramp up production of current vaccines to ensure pandemic preparedness

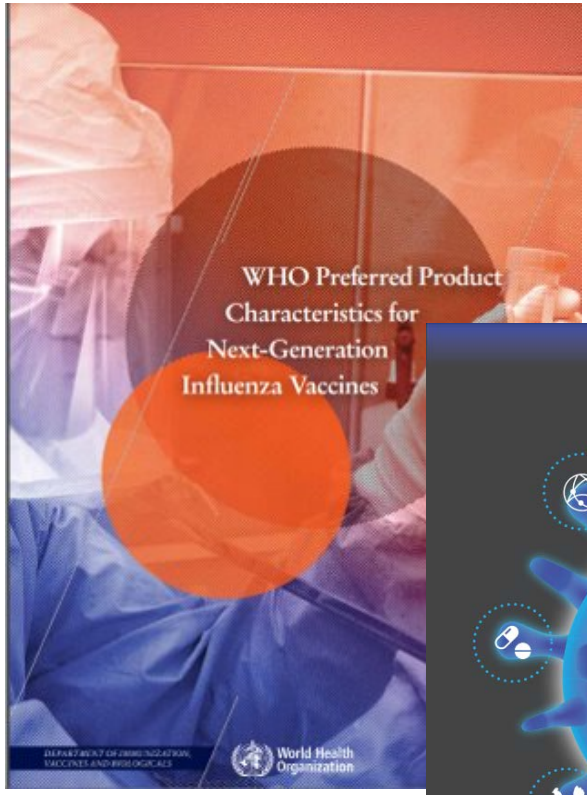
- **Vaccine development for next-generation seasonal influenza vaccines may help overcome challenges - but comes with uncertainties on how to best improve suitability of vaccines and increase uptake**

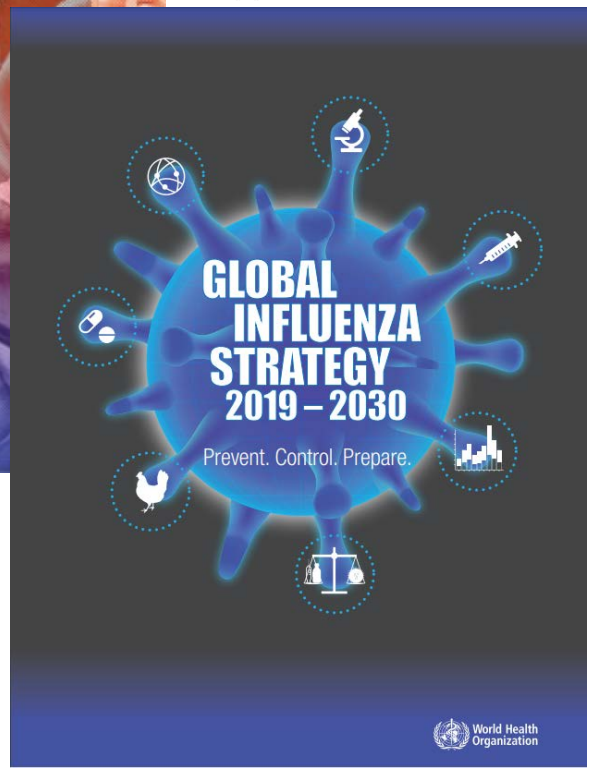


Courtesy for graphic to : Chadwick and Sparrow

Recent global policies/guidance supports next generation vaccine development

- **2017:** WHO Preferred Product Characteristics for Next – Generation Influenza Vaccines define preferences for parameters of vaccines shaped by “global unmet public health need in a WHO priority disease area”
- **2019:** WHO’s Global Influenza Strategy (GIS) 2019-30 stresses the need to develop new influenza vaccine technologies which improve the suitability of influenza vaccines for all countries
- **Funded by CDC,PIVI, and BMGF, WHO and LSHTM joined forces to complement the guidance available, with a *Full Value of Improved Influenza Vaccine Assesment***
  - To inform global efforts to expand seasonal influenza programs as part of a larger pandemic readiness effort
  - To drive innovative research for next generation influenza vaccines for LMICs





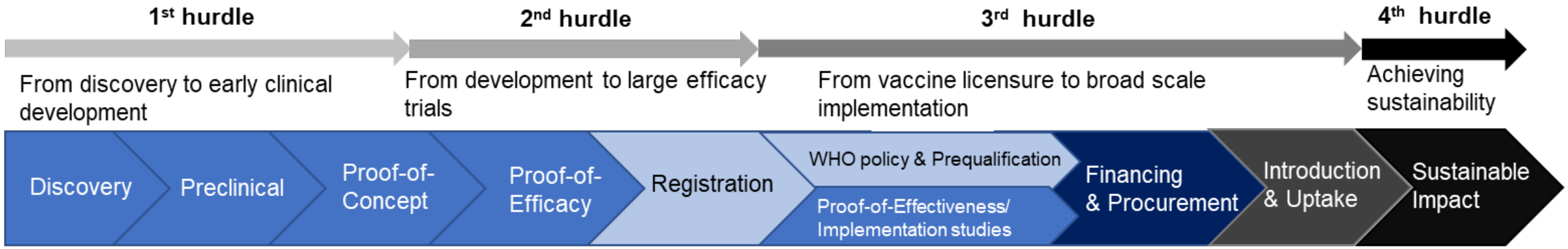
Impact of paediatric vaccination using next generation influenza vaccines in Kenya: a modelling study

- Study examined vaccinating children under 5 years of age with improved vaccines, evaluating:
  - vaccines with combinations of increased vaccine effectiveness, cross protection between strains (breadth) and duration of immunity.
  - CE using incremental cost-effectiveness ratios (ICERs) and incremental net monetary benefits (INMBs) for a range of values for the willingness-to-pay (WTP) per DALY averted.
  - threshold per-dose vaccine prices at which vaccination becomes cost-effective

Next generation vaccines may offer a cost-effective intervention to reduce influenza burden in low-income countries with year-round seasonality like Kenya.

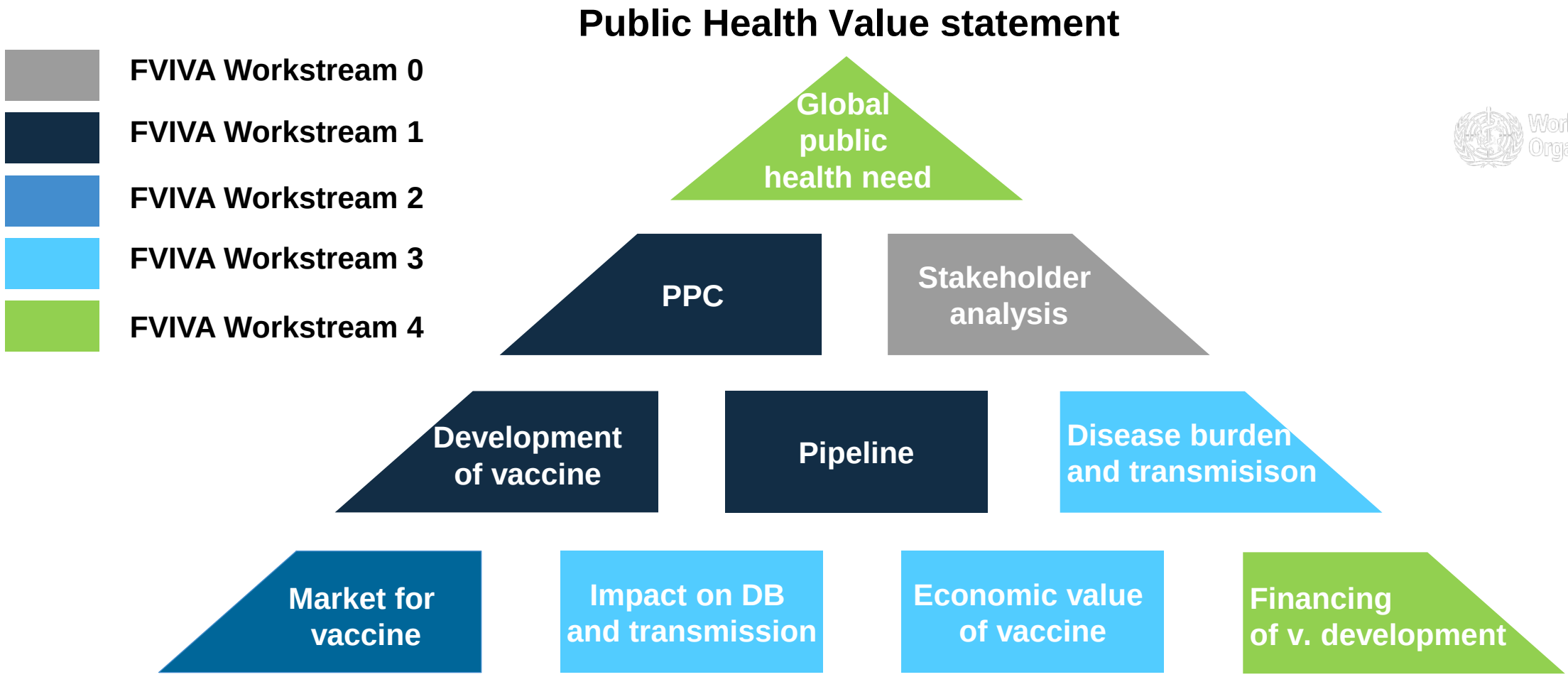
N N Waterlow, submitted to journal

Exepected benefits from value proposition



1. Funders, vaccine developers and implementers are provided with an improved understanding of influenza vaccine market conditions
2. Country policy decision making informed of optimal ways of implementing seasonal influenza vaccines
3. Vaccine manufacturers encouraged of the further development and production of vaccines tailored to refined Preferred Product Characteristics

Key components of the full value of improved influenza vaccines asessment (FVIVA)



Project structure

WS1 - Vaccine products and supply
(Lead: Chris Chadwick, WHO)

- **WSS1A - Products:** Collect, synthesize, document current seasonal and impr. influenza vacc. development, innovation, evidence:
  - vaccine development,
  - pipeline and
  - innovation assessments.
- **WSS1B – Supply (MI4A team)**: Collect, synthesize, & document current seasonal and improved influenza vaccine supply-related evidence: manufacturing and influenza vaccine supply drivers and barriers.

WS2 - Use cases and Vaccine market demand
(Leads: P. Lambach, WHO; J. Bresee, TFGH)

- **WSS2A – Use cases:** Assess country willingness to pay for current seasonal and improved influenza vaccines to inform refined use cases and country archetypes for influenza vaccine use.
- **WSS2B – Vaccine Demand (MI4A team):** Estimate potential market demand for current seasonal and improved influenza vaccines, including development of assumptions, scenarios and sensitivities.

Advisory Body reviewing methods and results: IVIR-AC

- Measure and quantify the incremental health and economic impact of improved seasonal influenza vaccines, based on their characteristics, compared to current seasonal influenza vaccines

WS3 – Vaccine Impact
(Lead: Mark Jit, LSHTM)

Work approach and expected outputs

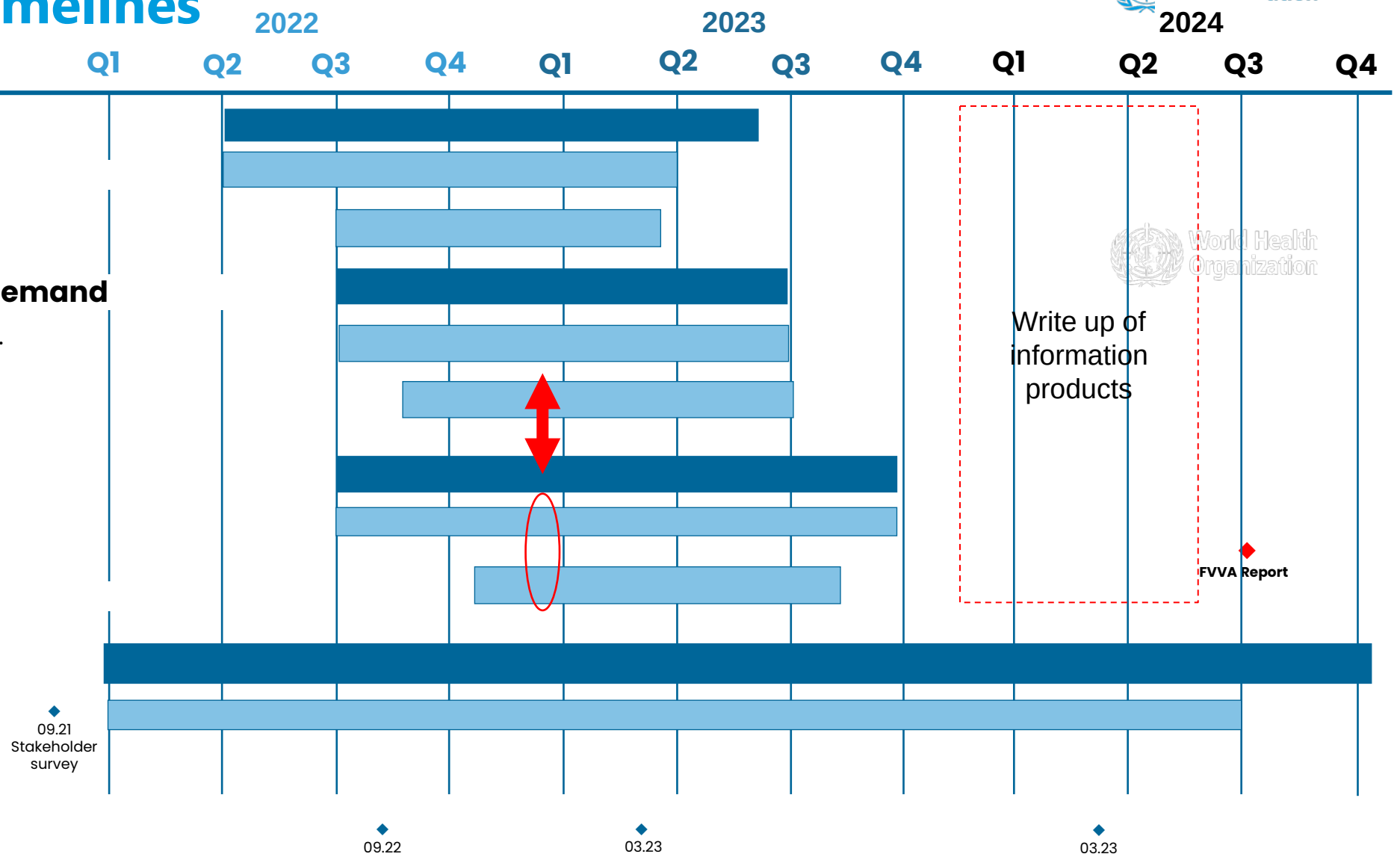
Outreach/Inclusiveness:

- A wide net was cast to identify relevant stakeholder through a survey developed with TFGH in 2021
- During the project, each workstream ensures identification of relevant stakeholders to contribute or advise on the FVIVA activities
- Where necessary stakeholder workshops will be organized, focusing on technical components of the FVIVA, to elicit and validate key insights, findings, and recommendations.

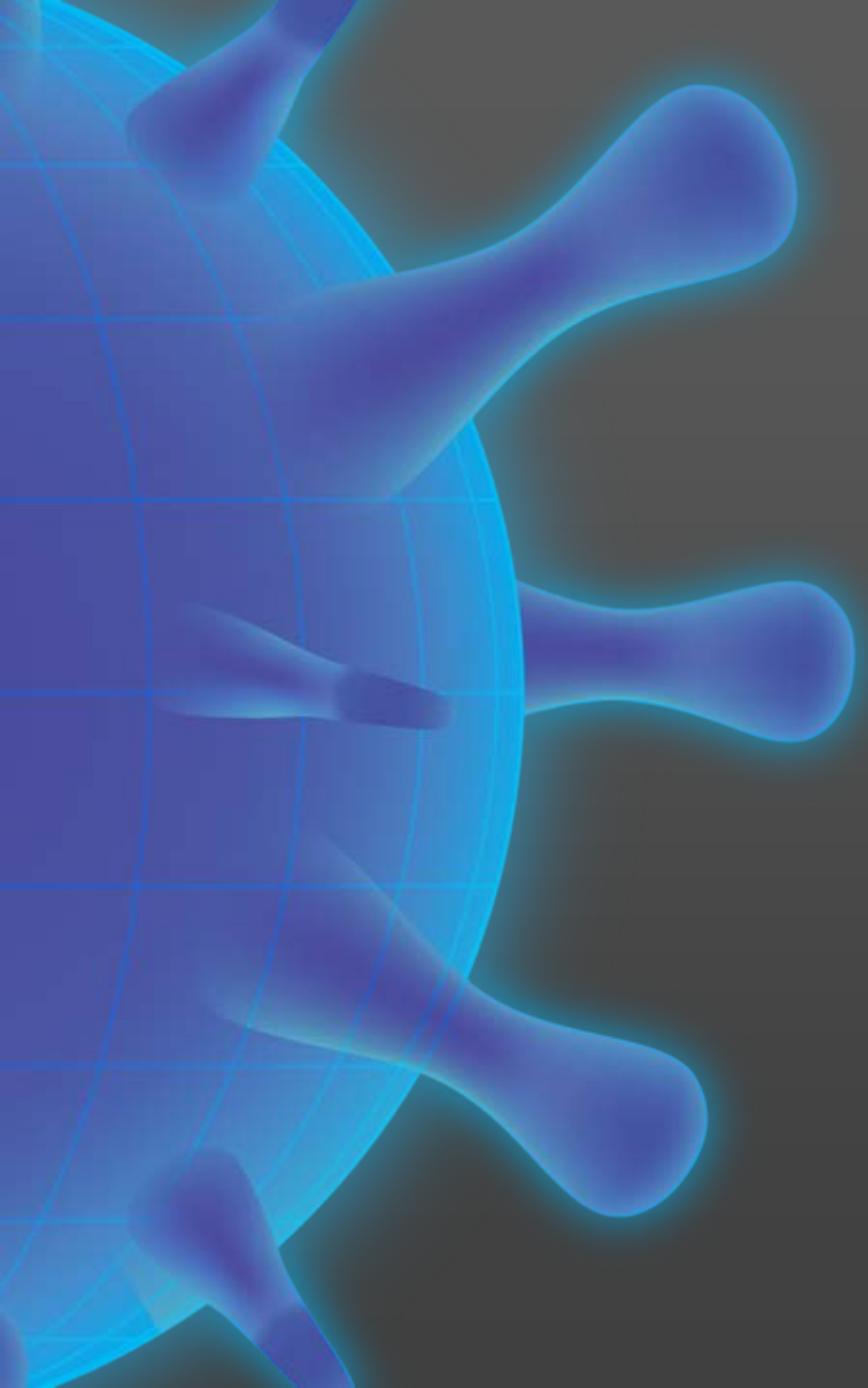
Output:

- WHO report describing the Full Value of improved Influenza Vaccine (FVVA)
- Peer review publications complementing the report with technical, underpinning information/evidence

Draft project timelines



*Subject to change pending funding decisions and additional partners' inputs



FVIVA: Analyzing the influenza vaccine product research, development, and production landscape

Christopher Chadwick
Influenza Preparedness and Response
World Health Organization

12 September 2022
IVIR-AC Meeting

Approved seasonal influenza vaccines

- **Traditional influenza vaccines:**
  - Inactivated
  - Live attenuated

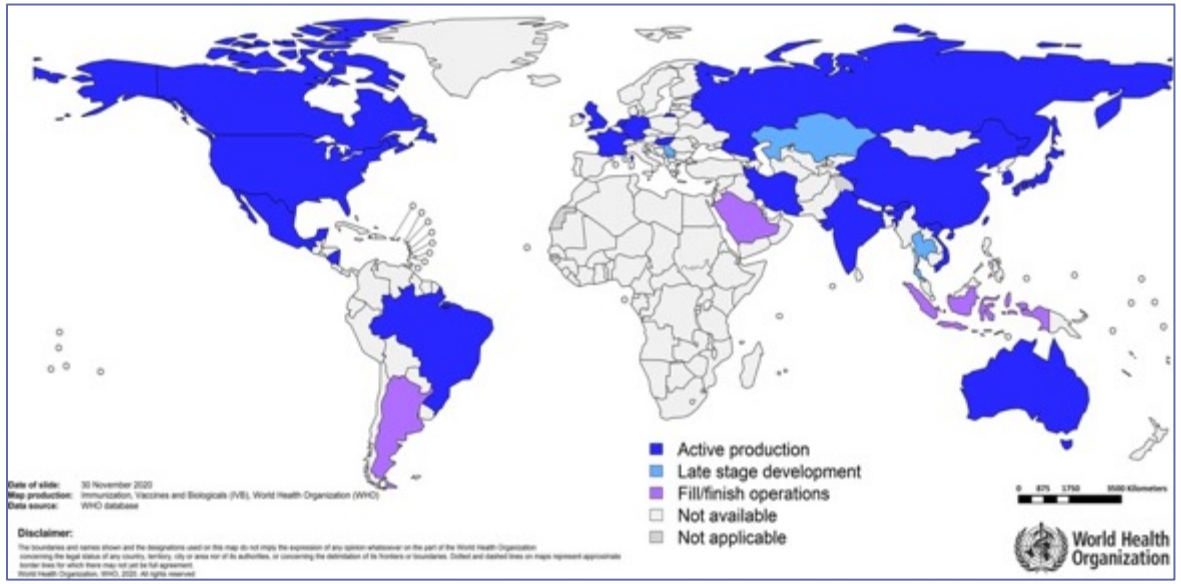
- **Enhanced/newer influenza vaccines*:**
  - Adjuvanted
  - Cell-based
  - High-dose
  - Recombinant

Trivalent and quadrivalent formulations based on GISRS-informed strain recommendations

As defined by the 2020 ECDC Systematic review of the efficacy, effectiveness and safety of newer and enhanced seasonal influenza vaccines: https://www.ecdc.europa.eu/en/publications-data/seasonal-influenza-systematic-review-efficacy-vaccines

Influenza vaccine supply

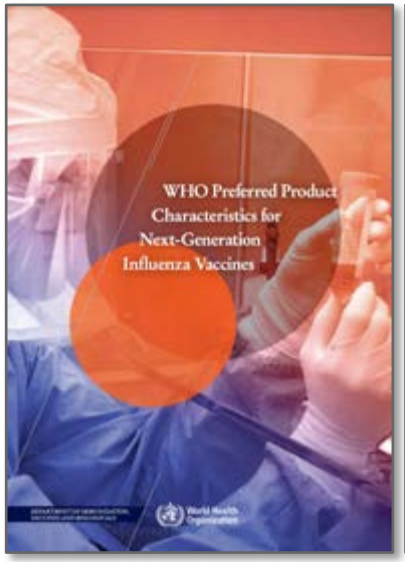
Breakdown of capacities	Seasonal	Pandemic
Total annual capacities		
Seasonal	1.48 billion doses	
Pandemic (moderate case)		4.15 billion doses
Pandemic (best case)		8.31 billion doses
By vaccine type		
IIV	89.6%	88.9%
LAIV	5.0%	3.4%
Recombinant	5.4%	7.7%
By substrate		
Embryonated eggs	84.5%	79%
Cell culture	15.5%	21%

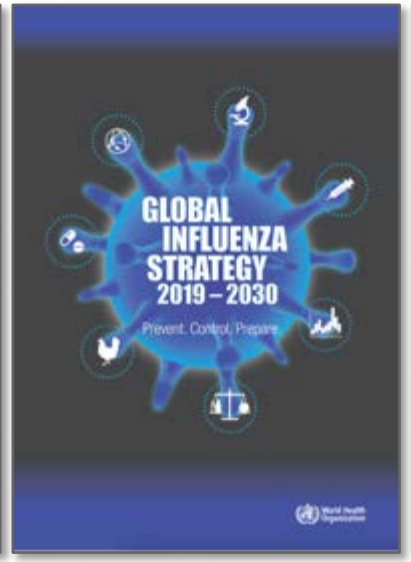


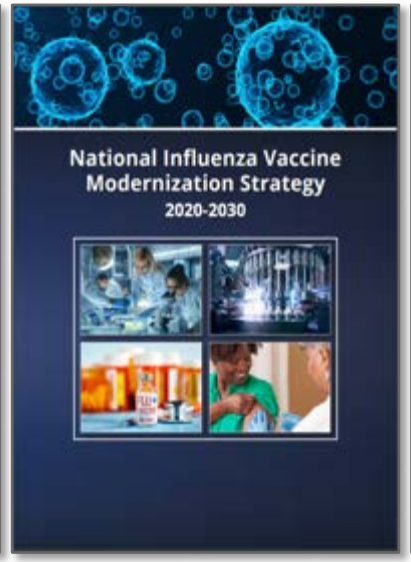
Income status	# of facilities	% capacity (seasonal)	% capacity (pandemic)	% of world population
LIC	0	0%	0%	9%
LMIC	5	2%	1%	38%
UMIC	15	29%	19%	37%
HIC	20	69%	80%	16%

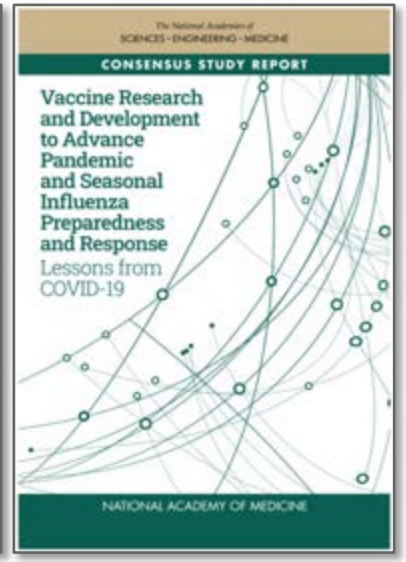
Sparrow E, Wood JG, Chadwick C, Newall AT, Torvaldsen S, Moen A, et al. Global production capacity of seasonal and pandemic influenza vaccines in 2019. Vaccine. 2021;39(3):512-20.

Global R&D priorities and objectives



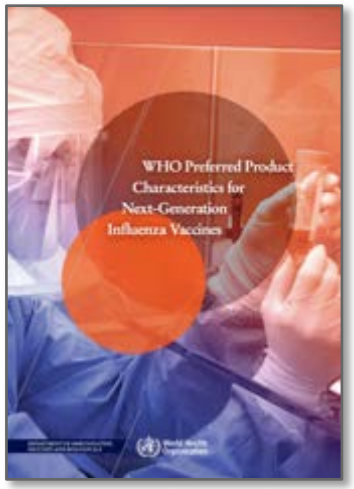


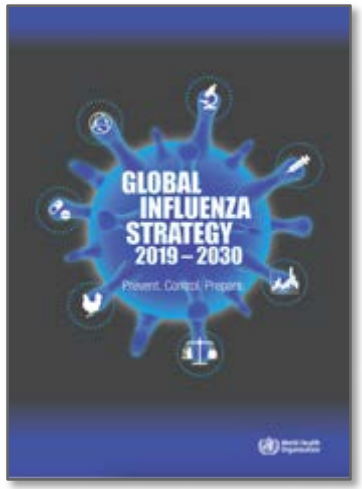


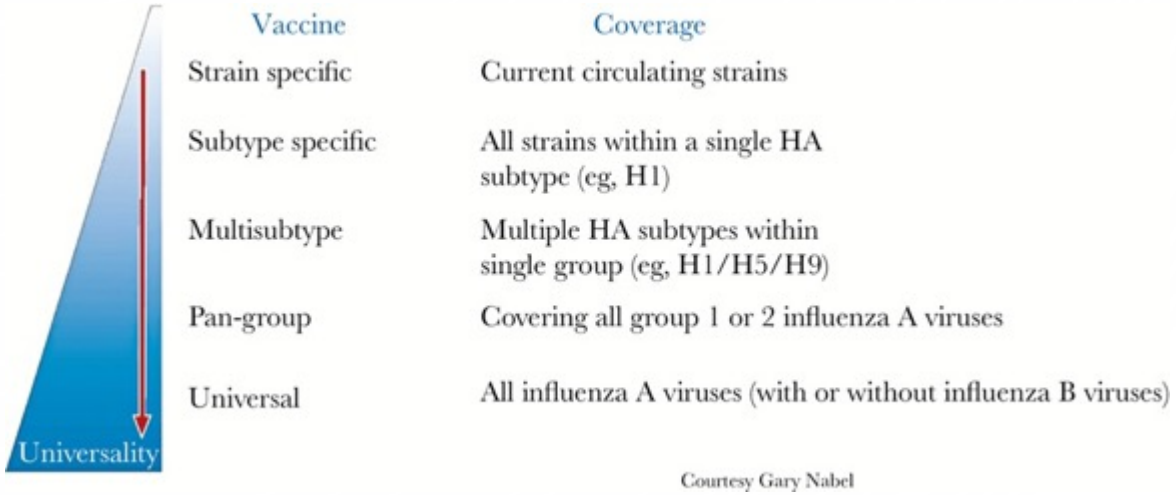


Improved/next-generation influenza vaccines

- **WHO PPCs (2017):**
  - Strategic goal 1: Greater protection than compared to currently PQ'd vaccines, protection against severe influenza for at least 1 year (2022)
  - Strategic goal 2: Protection against severe diseases for at least 5 years, suitable for LMICs (2027)
- **Global Influenza Strategy (2019):**
  - Increased breadth of protection, longer duration of protection, enhanced effectiveness against severe disease, decreased time for production
- **IVR Roadmap (2022): 10-year strategy to promote R&D for improved vaccines and broadly protective/universal vaccines**
  - Strategic priorities across virology; immunology and CoPs; vaccinology; animal models and CHIM; policy, financing, and regulation
- **NIAID strategy: stepwise approach to universal influenza vaccines**







Preferred product characteristics: Universal-type influenza A vaccines

Indication	• Prevention of severe lab-confirmed influenza illness caused by influenza A
Target population	• Persons aged 6 weeks and older belonging to a group at high risk for severe influenza illness
Safety	• Risk-benefit assessment should favor vaccine use to prevent severe influenza • Increase in mild reactogenicity may be acceptable • Severe reactogenicity should occur at a rate similar to or less than that of currently PQ'd seasonal influenza vaccines

Preferred product characteristics: Universal-type influenza A vaccines

Co-administration	• Absence of clinically important interference with concomitantly administered vaccines
Duration of protection	• Minimum of five years
Outcome measure & efficacy	• Severe lab-confirmed influenza illness is preferred outcome measure • Efficacy should be better than that of currently PQ'd seasonal influenza vaccines for vaccine-matched and antigenically drifted strains for preferred duration of protection

Preferred product characteristics: Universal-type influenza A vaccines

Immunogenicity	• If a CoP against severe lab-confirmed influenza illness is identified for a specific class of influenza vaccine, immunogenicity studies will be adequate to demonstrate vaccine efficacy
Registration & prequalification	• Product should be PQ'd according to standard procedures for assessing the acceptability for purchase by UN agencies
Value proposition	• Dosage, regimen, and cost of goods should be compatible with affordable supply • Should be cost-effective and price should not be a barrier to access

Universal Influenza Vaccine Landscape

- **Developed by CIDRAP to support IVR Roadmap**
- **Criteria for candidates that are monitored**
  - *Included* are technologies that target conserved epitopes or regions (e.g., the hemagglutinin stem domain) across multiple influenza A subtypes or influenza B lineages.
  - *Excluded* are technologies that are directed primarily at hypervariable regions of the virus (e.g., in the hemagglutinin head domain), are strain-specific, or use adjuvants as the primary mechanism for broader immunogenicity.
- **Tracks progress for the following platforms:**
  - Recombinant (proteins)
  - Recombinant (virus-based)
  - Virus-vectored
  - Virus-like particles (VLPs)
  - Non-VLP nanoparticles
  - Nucleic acid-based

https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape

Number of Universal Influenza Vaccine Candidates *by platform and phase*

	Preclinical	Phase 1	Phase 2	Phase 3	Approved
Recombinant proteins	32	3	1	1	0
Recombinant influenza virus-based	9	3	2	0	0
Virus-vectored	21	2	3	0	0
Virus-like particles (VLP)	22	1	0	1	0
Non-VLP nanoparticles	22	3	1	1	0
Nucleic acid-based	16	4	1	1	0

Visit the IVR initiative at ivr.cidrap.umn.edu

Courtesy of CIDRAP

Objectives of FVIVA Workstream 1

- **Collect, synthesize, and document current and improved influenza vaccine development, innovation, and supply-related evidence**
- **Split into two parallel sub-workstreams:**
  - WS1A: Vaccine products → research, development, and innovation assessments
  - WS1B: Vaccine supply → manufacturing, supply drivers and barriers

WS1 Activities for 2022-23

1A: Vaccine products

- Analyze current seasonal vaccines (by antigen, technology, delivery, etc.) and shortcomings
- Analyze improved seasonal vaccines (pipeline, progress, etc.) and ancillary products
- Review and update (if needed) WHO PPCs
- Conduct case studies on R&D drivers, barriers, successes, and failures
- Review clinical evaluation and regulatory considerations

1B: Vaccine supply

- Analyze influenza vaccine production aspects for current and improved vaccines (processes, access to technology, costs of production, sustainability, etc.)
- Assess production capacity (for preparedness purposes and available supply for commercialization)
- Describe uptake/utilization by regions
- Estimate future potential available supply for commercialization

Stakeholder inputs

Global Funders Consortium For Universal Influenza Vaccine Development

BILL & MELINDA GATES foundation

IFPMA

dcvmn
Developing Countries Vaccine Manufacturers Network

PATH

Bio

CIVICs
Collaborative Influenza Vaccine Innovation Centers

Questions for IVIR-AC

- **Does IVIR-AC agree with the approach for analyzing current and improved seasonal influenza vaccines?**

- **Does IVIR-AC have additional feedback on how to engage developers and manufacturers?**

Thank you

chadwickc@who.int

World Health Organization

GLOBAL HEALTH CONSULTING

Assessing the balance of global influenza vaccine supply and demand

MMGH Consulting
September 2022

01

Sizing of Influenza vaccine use cases

Refined high-level use cases for seasonal influenza vaccines

To whom: Target population

Where: Delivery location	Pregnant women	Health workers	Children (6-59mo)	Individuals w/comorbidities and underlying conditions	Older adults (>65yo)
Health facility (hospital, health center, health post)	**1. Vaccination in a health facility** Delivery strategy: Fixed site *Service provider: Doctor, Nurse, Midwife* Cold chain equipment: Yes – fixed equipment				
Pharmacy (public or private accredited)	**2. Vaccination in a pharmacy** Delivery strategy: Fixed site or outreach *Service provider: Pharmacist, Nurse* Cold chain equipment: Yes – fixed equipment				
Setting with limited or no health service (e.g., school, workplace, religious institution, nursing home, other locations)	**3. Vaccination in setting with limited/no health services** Delivery strategy: Outreach / mobile or fixed site *Service provider: Doctor, Nurse* Cold chain equipment: No – cold boxes				

Overview of the draft detailed seasonal influenza vaccine use cases to explore when sizing

	Pregnant women	Health workers	Children (6-59mo)	Individuals w/ underlying conditions	Older adults (>65yo)
Health facility (hospital, health center, health post) Delivery strategy: Fixed site with cold chain	Pregnant woman is vaccinated in a health facility with full cold chain by a HW	Health worker is vaccinated in a health facility with full cold chain by a HW	Child, accompanied by caregiver, is vaccinated in a health facility with full cold chain by a HW	Individual w/underlying conditions is vaccinated in a health facility with full cold chain by a HW	Older adult is vaccinated in a health facility with full cold chain by a HW
Pharmacy (public or private accredited) Fixed site or outreach with cold chain	Pregnant woman is vaccinated in a pharmacy with full cold chain by a HW or pharmacist	Health worker is vaccinated in a pharmacy with full cold chain by a HW or pharmacist	Child, accompanied by caregiver, is vaccinated in a pharmacy with full cold chain by a HW or pharmacist	Individual w/underlying conditions is vaccinated in a pharmacy with full cold chain by a HW or pharmacist	Older adult is vaccinated in a pharmacy with full cold chain by a HW or pharmacist
Setting with limited or no health service (e.g., school, workplace, religious institution, nursing home, other locations) Outreach/mobile or fixed site without cold chain	Pregnant woman is vaccinated in the community with no cold chain by a HW in a mobile session	Health worker is vaccinated in the community with no cold chain by a HW in a mobile session	Child, accompanied by caregiver, is in the community with no cold chain by a HW in a mobile session	Individual w/underlying conditions is vaccinated in the community with no cold chain by a HW in a mobile session	Older adult is vaccinated in the community with no cold chain by a HW in a mobile session

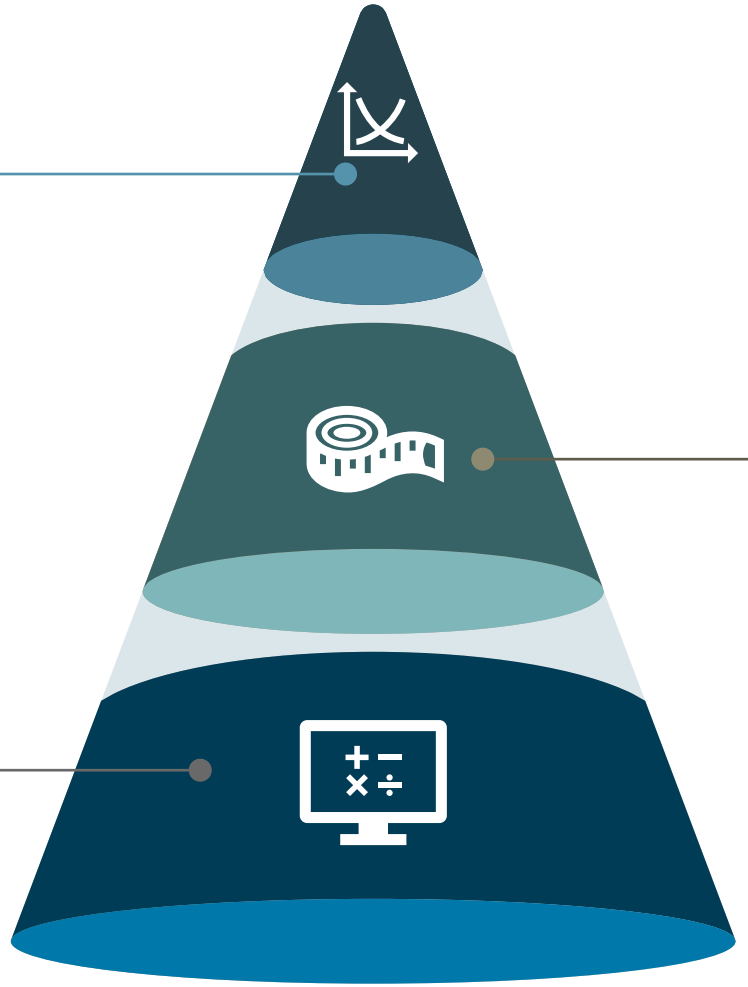
The use cases are the foundation for assessing how influenza vaccines are used, in what quantities, and potential changes over time

DEMAND FORECAST (SEASONAL & IMPROVED)

Use cases and sizing inform estimates current and future demand based on actual and projected influenza vaccination coverage, new influenza vaccine introductions, potential changes to policy recommendations

MAXIMUM SIZE OF USE CASES

Represents the theoretical maximum size of each use case (i.e., 100% coverage), assuming all countries delivered influenza vaccine to all 5 priority target populations, irrespective of existing policy recommendations



CURRENT SIZE OF USE CASES

Estimation of the actual size of each use case, based on existing influenza policies and populations recommended for vaccination (i.e., excludes countries without influenza vaccination policies)

Overview of use case sizing methodology

Total target population (pregnant women, health workers, children, individuals with comorbidities and underlying conditions, older adults)

✖

% of target population vaccinated at each delivery location

N of each target population from all countries

% of each target population potentially vaccinated at each delivery location

Key variables to estimate size of use cases

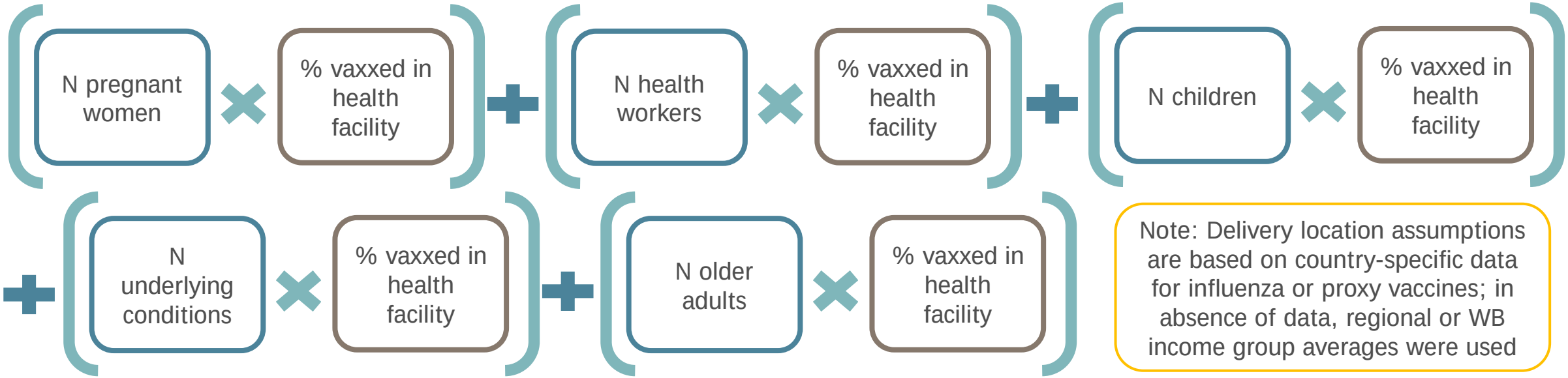
UC1	UC2	UC3
UC3	UC5	UC6

Global estimates for current and maximum size of each Use Case

(data disaggregated WB income groups, WHO regions)

Illustration of how the size of each use case will be calculated for each country

Formula



Note: Delivery location assumptions are based on country-specific data for influenza or proxy vaccines; in absence of data, regional or WB income group averages were used

Example

	Pregnant women	Health workers	Children	Underlying conditions	Older adults
N of target population	1,000,000	50,000	9,000,000	14,000,000	20,000,000
% vaxxed in health facility	90%	100%	70%	90%	80%

Estimated size for UC1:

(1,000,000 *90%)+(50,000 *100%)+(9,000,000 *70%)+(14,000,000 *90%)+(20,000,000 *80%)=

35,850,000

Estimated size of each target population

Target population	Estimated global size	Data source
Pregnant women	209.5M pregnant woman	UN WPP estimates
Health workers	59M health workers	WHO Global Observatory
Children	742M children 6-59mo	UN WPP estimates
Underlying conditions	1,270M people with underlying conditions	IHME
Older adults	769M older adults (>65yo)	UN WPP estimates

Desk review and consultations to develop delivery location assumptions per target population, per country

01

Desk review

Appraisal of published and grey literature to identify influenza vaccination delivery location data for each target population across countries/regions
-- 23 articles identified and reviewed with delivery location data

02

Survey with PIVI countries

Surveyed PIVI country stakeholders to solicit feedback about the locations used to deliver influenza vaccines to different populations in each country – responses received from 10 PIVI countries[1]

03

Interviews

Interviewed national and regional stakeholders as well as IFPMA and DCVMN industry associations to get direct inputs about the influenza vaccine delivery locations used in countries driving global volumes[2]

Country specific data identified through each activity was directly incorporated into delivery location assumptions used for UC sizing

1. Responding countries included: Albania, Armenia, Bhutan, Cote d'Ivoire, Kyrgyzstan, Lao PDR, Moldova, Mongolia, Ukraine, Viet Nam
2. Stakeholders interviewed included: Brazil, China, India, Japan, PAHO, Philippines, South Africa, IFPMA and DCVMN industry associations

Summary of assumptions for delivery locations used by each target population for influenza vaccination

Pregnant women

- Primary input is vaccine delivery location data from MIACSA[1]
- For HICs without MIACSA data, WB income group averages used; regional averages used for all other countries
- Expert consultations used for specific countries (e.g., China, India)

Health workers

- For all countries, health workers assumed to received seasonal influenza vaccine in health facility
- Assumption supported by expert consultations
- Several PIVI countries indicated small numbers of HWs receive vaccines outside health facilities

Children

- Assumptions based on data from EPI Reviews, cMYPs, Gavi joint appraisals used to inform UC sizing for MR-MAPs
- Routine delivery assumptions used for countries in EUR, WPR, North America
- Campaign delivery assumptions used for all other countries

Underlying conditions & older adults

- Assumed 100% health-facility where population not included in policy recommendations
- Country specific estimates where data available or experts consulted (e.g., Australia, Brazil)
- Assumed at least 10% in pharmacy where allowed (higher % where supported by literature or consultations)
- Filled remaining gaps by matching delivery location assumptions for children

[1] Maternal Immunization and Antenatal Care Situation Analysis

Sensitivity analyses to be performed to further explore the sizing results

Current size based on current policy recommendations

Estimate the current size of use cases based on populations prioritized in existing national influenza policy recommendations

Datasource: WHO JRF

01

Lower bound estimate for underlying condition pop.

Use lower bound estimate of the underlying conditions population to account for uncertainties in current estimates

Datasource: IHME

02

Increased pharmacy use & outreach for older adults

Increased use of pharmacies and outreach to vaccinate older adults to assess size of population that can be reached via UC2 and UC3

Datasource: Desk review

05

Increased utilization of pharmacy vaccination

Increase the proportion of vaccination (UC2) occurring in pharmacies in HICs and UMICs to understand potential impact of increased pharmacy utilization for influenza vaccination

Datasource: Desk review, expert inputs

03

Increased outreach to vaccinate pregnant women

Increased use of outreach to vaccinate pregnant women in LIC/LMICs using U5 assumptions, to assess size of population that can be reached via UC3

Datasource: Desk review

04

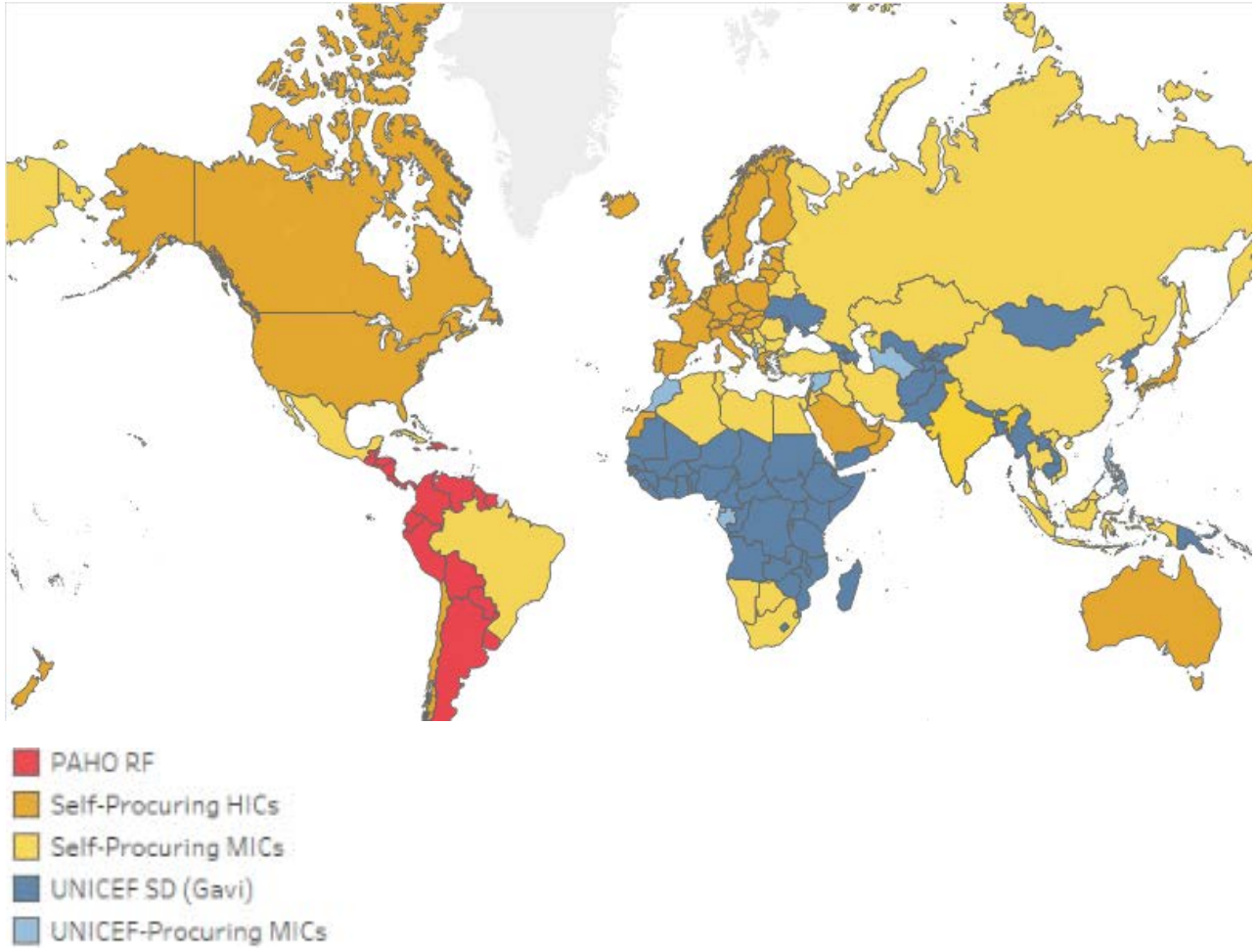
02

MI4A market study for influenza vaccines

Market Information for Access: the missing segments

Vaccine market is **global** – historical focus limited to UN procured vaccines leaves out 60% of the vaccine ecosystem and makes difficult to understand access bottlenecks and risks

- ✓ **All vaccines** – independent of global funding schemes
- ✓ **All countries** – independent of procurement method
- ✓ **All suppliers** – independent of PQ status of their products
- ✓ **All payors** – independent of the public or private status
- ✓ **All populations** – independent of recommendation for use

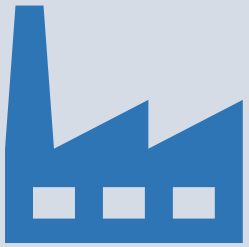


World Health Organization

MI4A MARKET INFORMATION FOR ACCESS TO VACCINES

By engaging with stakeholders, WHO establishes the forum to create and validate this global view

Manufacturers Engagement



Available Supply for Commercialisation

Licensure plans

Clinical Development plans

Advisory Group representing key immunization partners

Member States Engagement

Programmatic doses requirements

Policy requirements

Desired product characteristics

Objectives of the global market studies

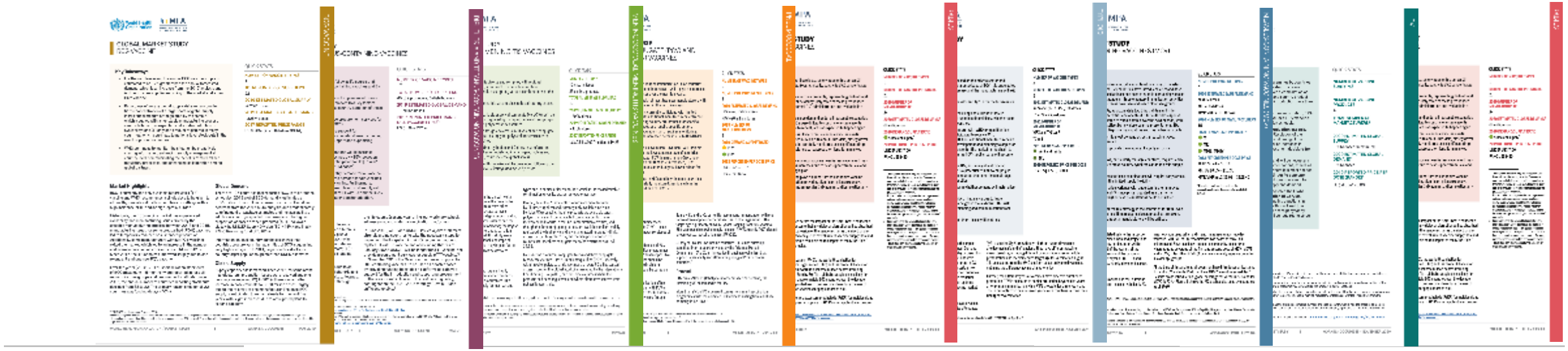
Develop a shared understanding of **global** vaccine demand, supply and pricing dynamics of the selected vaccine(s)

Identify **access risks** linked to availability, affordability and other drivers

Identify **areas for action** where strategies and guidance need to be developed to mitigate identified risks

Ten Global Market Studies performed so far covering key vaccines

- Meningococcal meningitis
- Pneumococcal
- Human rabies
- Typhoid
- Hepatitis A *(ongoing)*
- BCG
- D&T containing
- HPV
- Measles containing
- Malaria



World Health Organization

MI⁴A
MARKET INFORMATION FOR ACCESS TO VACCINES

https://www.who.int/teams/immunization-vaccines-and-biologicals/vaccine-access/mi4a/mi4a-market-studies

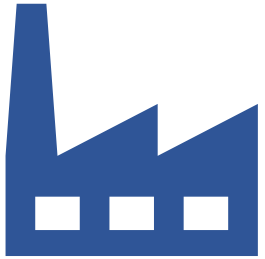
An IVIR-AC* endorsed process and methodology used to estimate the evolving state of demand and supply

Demand Forecasting

Programmatic doses requirements

The estimated number of doses a country would need to procure to meet its immunization program needs, whether these are routine – national or subnational – campaigns/SIAs, or for special risk groups only. This requirement includes wastage and buffer

Supply Forecasting[1]



Available supply for commercialization

The estimated number of doses a manufacturer can make available for sale at global level in one typical year with normal production facilities utilization across the various vaccines (not factoring in special market, regulatory or technical events)"

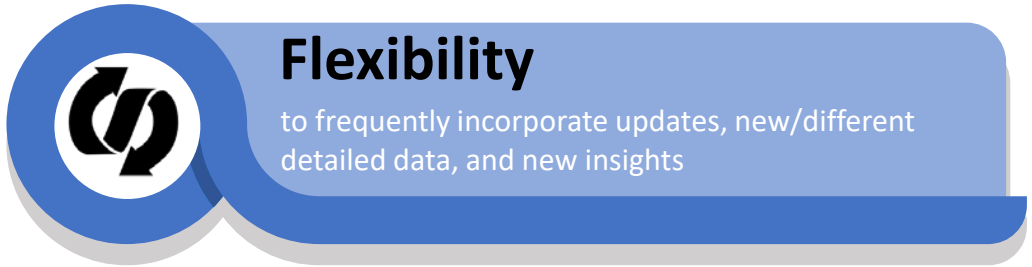
Supply-demand balance

World Health Organization

MI4A MARKET INFORMATION FOR ACCESS TO VACCINES

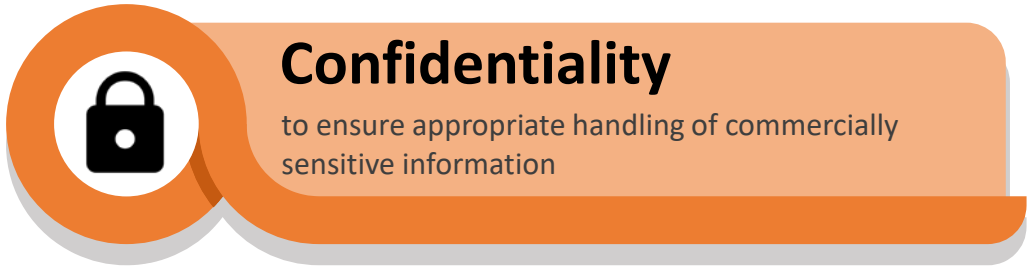
Note: The supply forecasting performed as part of the MI4A global influenza vaccine market study will be informed by and complimentary to the global manufacturing capacity survey carried out annually by WHO's Influenza Programme

Methodology designed to meet MI4A objectives and to address specific analytical constraints



Flexibility

to frequently incorporate updates, new/different detailed data, and new insights

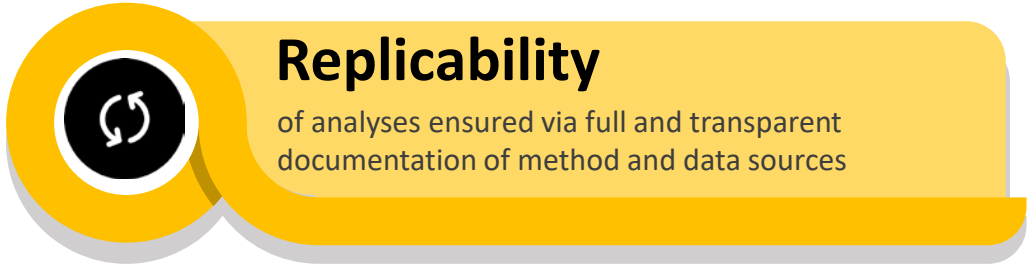


Confidentiality

to ensure appropriate handling of commercially sensitive information

Reliance on existing estimates

from global partners (BMGF, Gavi, UNICEF SD, PAHO RF) complemented with information for self-procuring countries and non-PQ'd products

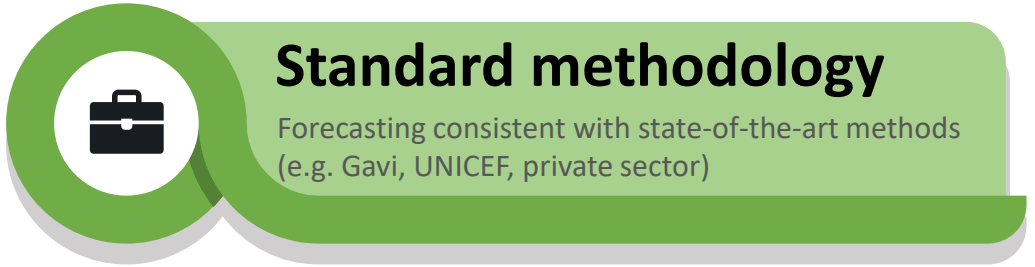


Replicability

of analyses ensured via full and transparent documentation of method and data sources

Expert validation

of methods with market shaping experts/partners and continuous improvements

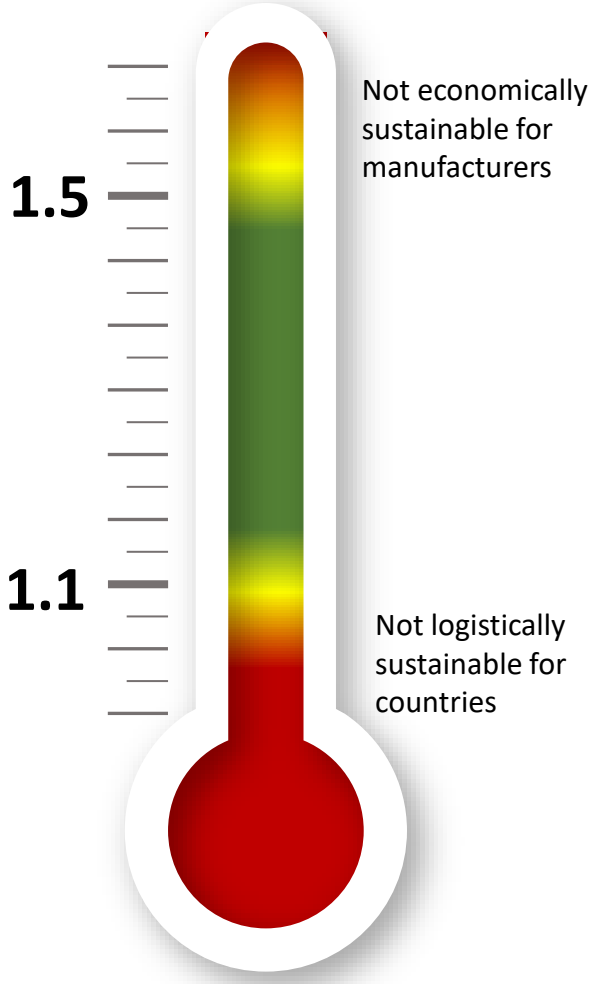


Standard methodology

Forecasting consistent with state-of-the-art methods (e.g. Gavi, UNICEF, private sector)

Supply-demand balance signals the level of risk in accessing supply of specific vaccines

- **Supply** (ASC)* **Risk** results from:
  - **Demand predictability** – because of state of vaccine introduction (established vs. new vaccine) and vaccine interchangeability (do substitute vaccine exist or not?)
  - **Supply status** – because of market concentration and shared antigens (is the vaccine sharing antigens with other vaccines so that an increase in supply for one vaccine will result in a reduction for the other?)
- Appropriate thresholds of **systemic redundancy** to be defined to reflect vaccine specific risk conditions based on expert evaluation.



*Available Supply for Commercialisation (ASC): The number of doses available for sale at global level in one typical year with normal production facilities utilization across the various vaccines (not factoring in special market, regulatory or technical events)

Key areas of attention for the global influenza vaccine market study

1. Evaluate the potential impact of improved influenza vaccines on the influenza vaccine market dynamics
2. Assess the demand dynamics globally, but with emphasis on LMICs/LICs
   a) Develop global demand forecast for current seasonal and improved influenza vaccines (not currently available)
   b) Limited use of current seasonal influenza vaccines in LMICs/LICs
   c) Uncertainty if LMICs/LICs could face access issues should demand for current seasonal influenza or improved influenza vaccines
3. Understand the levers of global supply and demand
   a) Sufficiency of global supply of current seasonal influenza vaccines in the medium- and long-term
   b) Potential implications of new and improved influenza vaccines on global supply and equitable access in all WHO Member States

Evaluating next generation influenza vaccines

Funders:

The team

Investigators

Mark Jit
Professor of Vaccine Epidemiology, LSHTM

Rosalind Eggo
Associate Professor, LSHTM
Honorary position in Vaccine Evaluation, UKHSA
HDR UK Innovation Fellow

Naomi Waterlow
Research Fellow, LSHTM

Sreejith Radhakrishnan
Research Fellow, LSHTM

Key collaborators

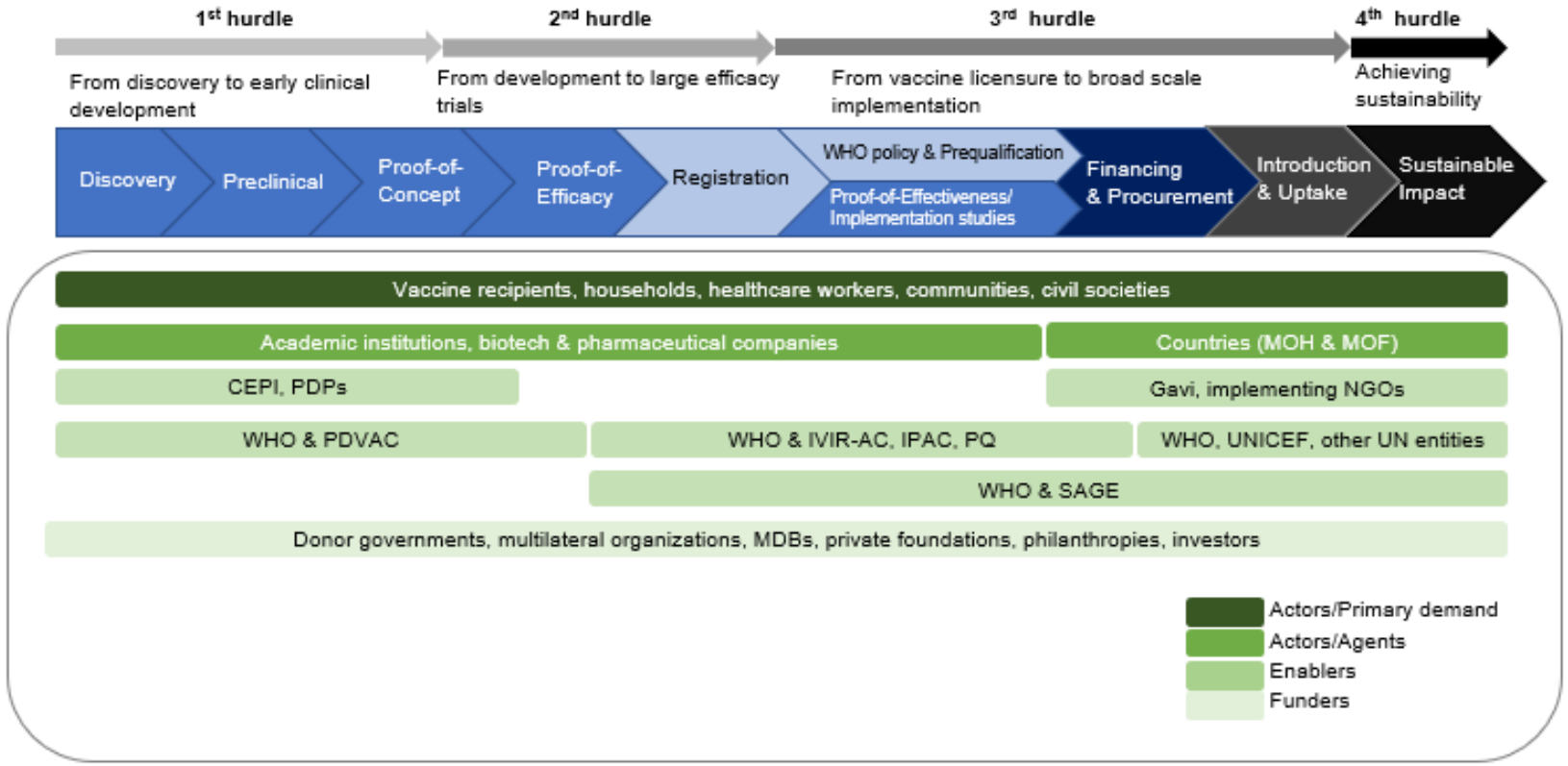
Edwin van Leeuwen
UKHSA & LSHTM

Jeannette Dawa
Washington State University – Global Health Programs, Kenya

Marie Mazur
Taskforce for Global Health

Joseph Bresee
Taskforce for Global Health

Universal flu vaccination: full value of vaccines assessment



Key question

"Should we invest in developing a universal flu vaccine?"

"Should we recommend/fund a universal flu vaccine?"

"Should we introduce a universal flu vaccine?"

From Hutubessy et al. https://ssrn.com/abstract=3841999. Also discussed at Fondation Mérieux consultation, 5-7 December 2016; WHO Product Development for Vaccines Advisory Committee (PDVAC) Consultation, 26-28 June 2019, Wilder-Smith et al. BMC Medicine 2017; 15:138 etc.

The plan

Year 1 (Dec 2021 – Nov 2022)

- Use calibrated models of seasonal influenza in two settings (Kenya + Thailand)
- Compare the impact and cost-effectiveness of current vs. next generation influenza vaccines

Year 2 (Dec 2022 – Nov 2023) subject to funding

- Extrapolate model findings to other parts of the world
- Analyse the impact of next generation vaccines in pandemic situations

Further work in discussion with WHO

- Link epidemiological and economic modelling to supply and demand models to support a full value of vaccines assessment

Next Generation Flu Vaccines: WHO PPC

	Improved influenza vaccines	Universal influenza A vaccines
Projected year of licensure	2022	2027
Target population	Children 6-59 months old	All clinical risk groups including children 6-59 months old
Duration of protection	At least one year/influenza season (equal or better than current vaccines)	At least 5 years
Clinical efficacy	Better than current vaccines for either vaccine-matched or drifted strains	Better than current vaccines for vaccine-matched AND drifted strains

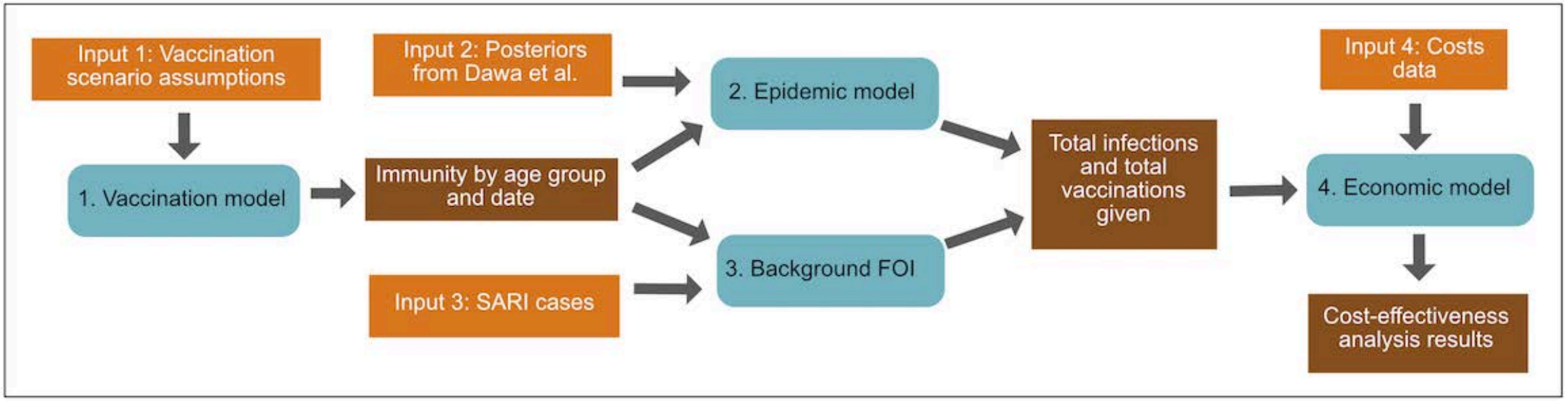
Main vaccine scenarios of interest

- No vaccine
- Current vaccines *(70/40 efficacy, 6months waning)*
- Improved vaccines – Minimal (70/40 efficacy, 1 year waning)
- Improved vaccines - Breadth *(70 efficacy, 3 years)*
- Improved vaccines - Efficacy *(90/70 efficacy, 2 years)*
- Universal vaccines *(90 efficacy, 5 years)*

Sensitivity analysis:

- 75% coverage in target age groups, instead of 50%
- infection-derived immunity modelling

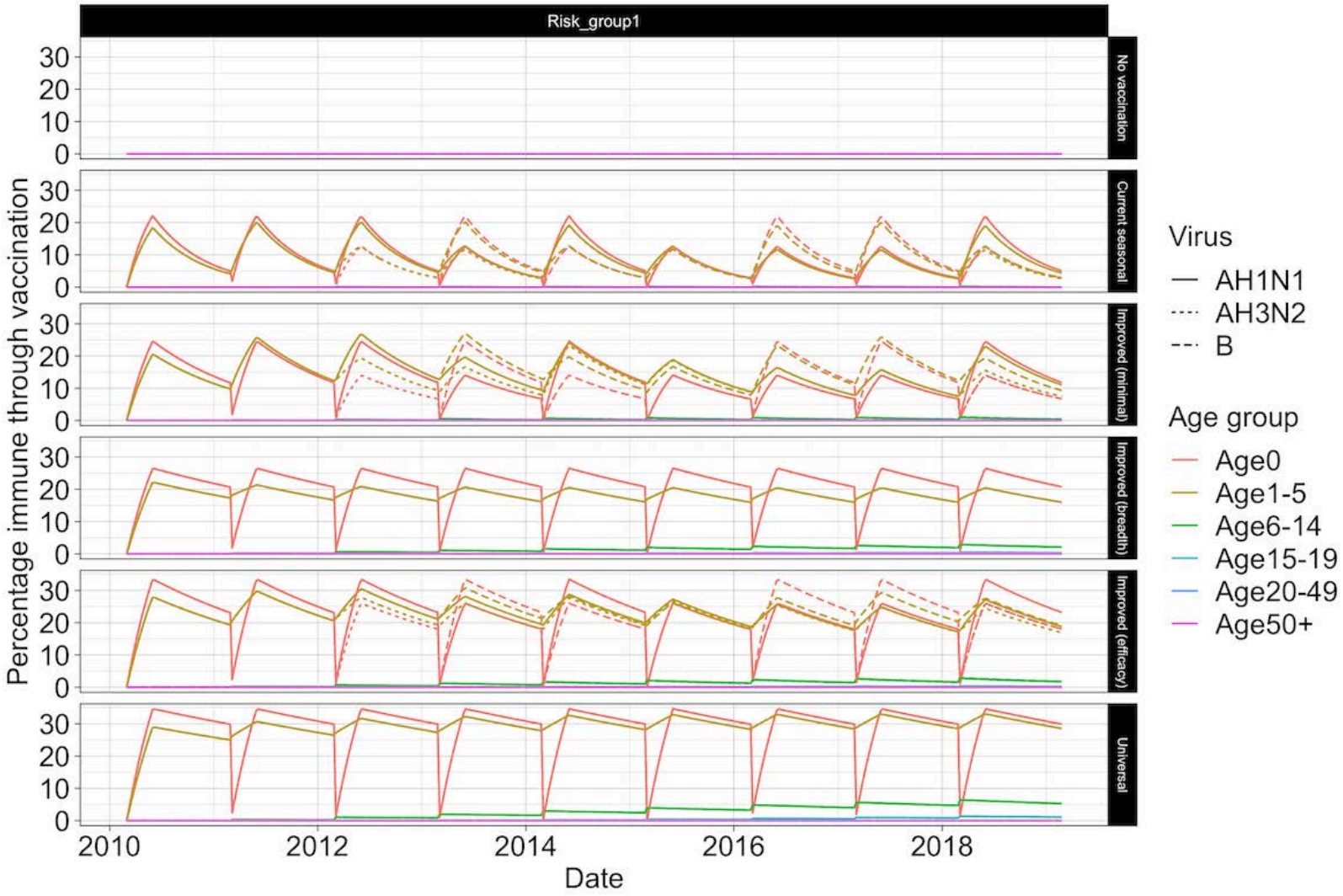
Modelling Overview



2010- 2019, Kenya

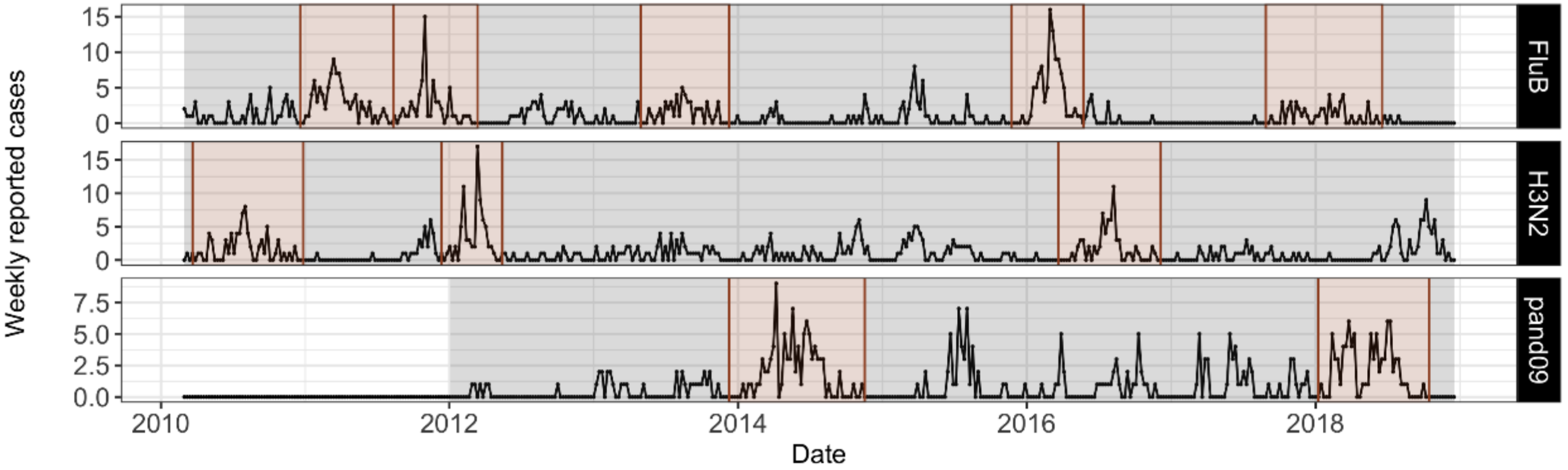
What would have happened if we'd had these vaccines then

1. Vaccine Model



- Vaccine immunity is all-or-nothing
- Assume everyone born susceptible
- Ageing of population

2. Epidemic model (Based on Dawa et al. (2020))



Epidemics fit with *fluevidencesynthesis* R package

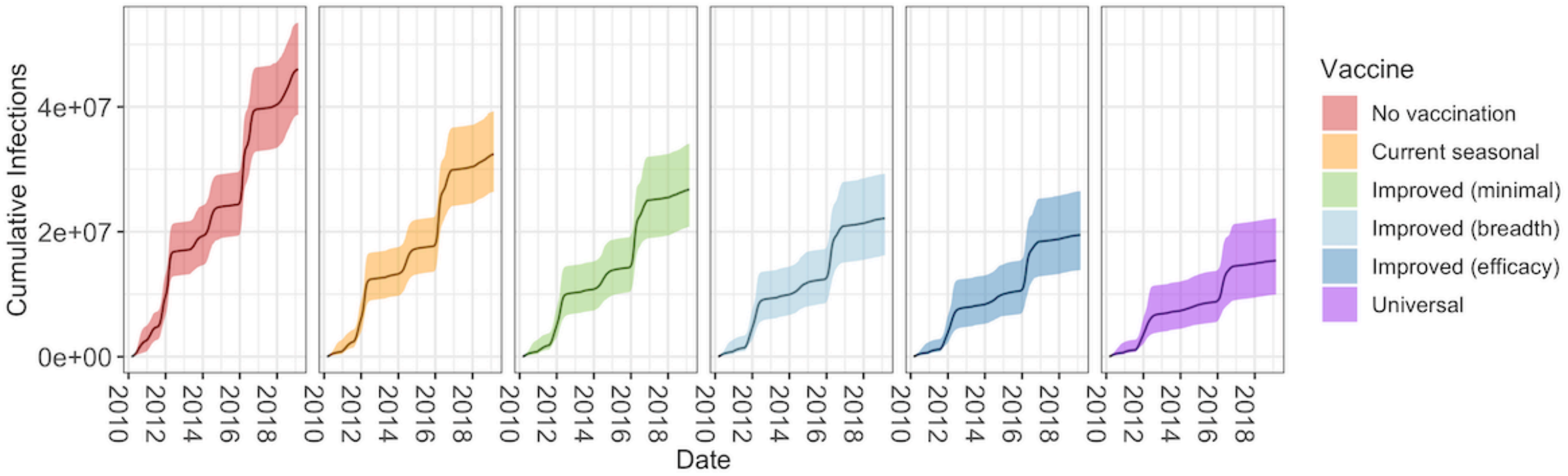
SEEIIR epidemic model, with vaccination.

Parameters estimated: transmissibility, age-specific susceptibility, age-specific ascertainment rates, initial number of infections

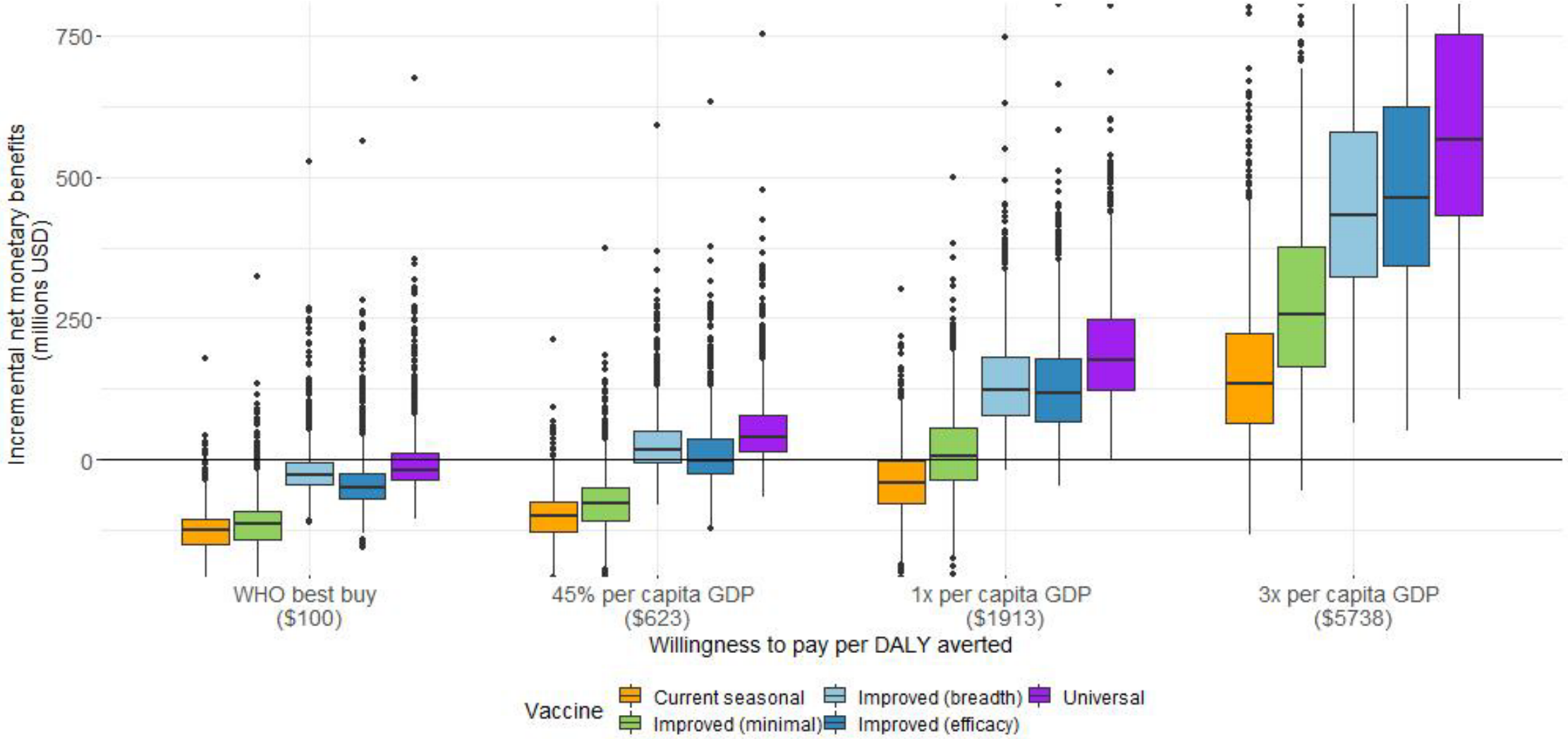
3. Background FOI

In off-season there is a background rate of infection. Poisson distribution fitted to the weekly observed cases in each age group and across subtype. Scaled by the ascertainment rate to get number of infections, and the vaccine-derived immunity calculated from the vaccine model.

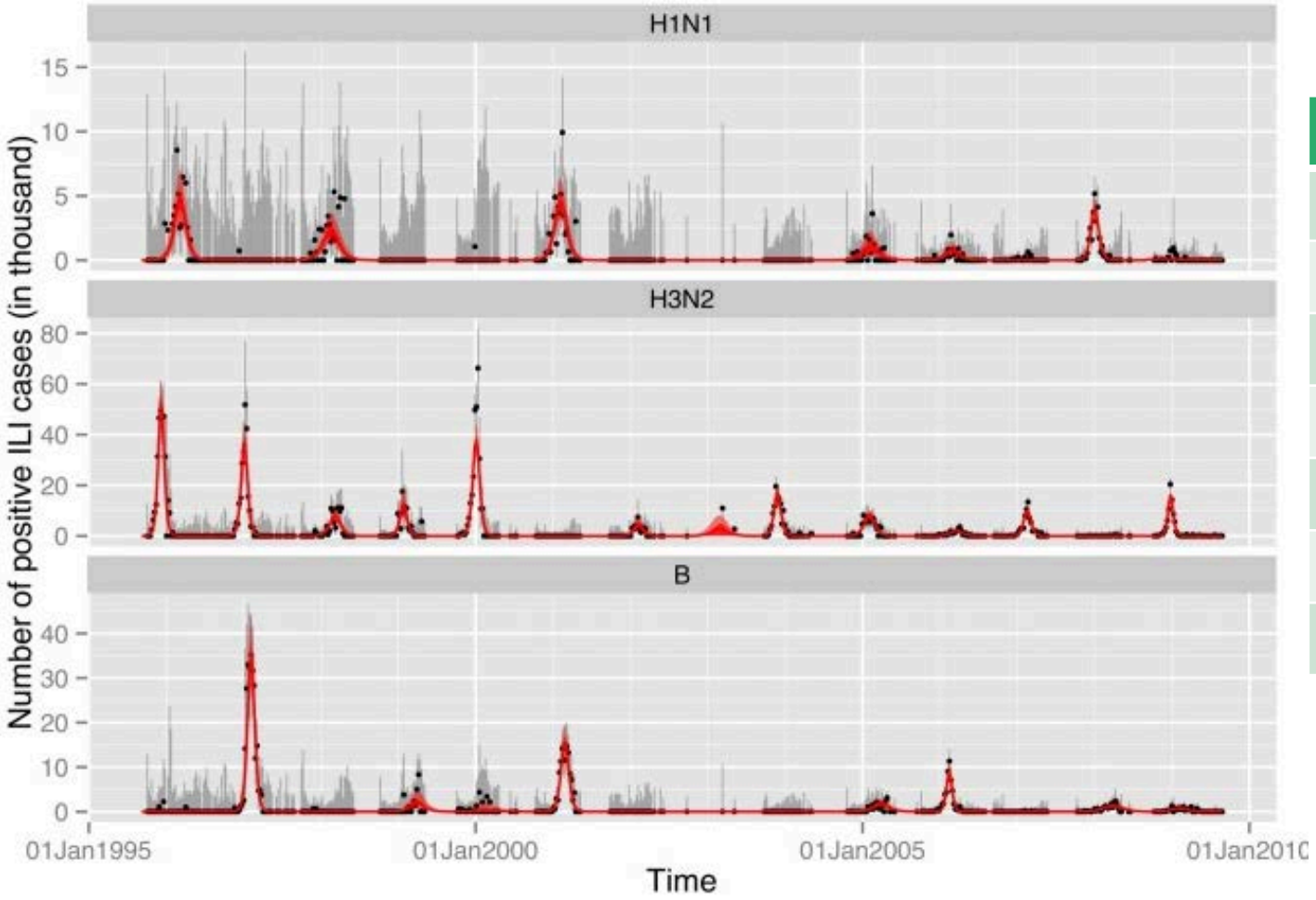
$$Background\ Infections_{t,i,k} = \sum_{i=1}^{n=6} \Lambda_{i,k} * (sus_{t,i,k}/asc_{i,k})$$



4. Economic analysis



Expanding to other countries



(Baguelin 2013)

Age group	Low Risk Coverage	High Risk Coverage
<1	0	0.449
1-4	0.438	0.449
5-14	0.604	0.449
15-24	0.604	0.449
25-44	0	0.449
45-64	0	0.449
65+	0.724	0.724

Conclusions and next steps

- Universal vaccines are cost-effective across a wide range of willingness to pay thresholds and deliver the widest benefits - these vaccines are therefore especially likely to benefit LMICs which may have lower WTPs
- Improved vaccines are also more cost-effective and result in fewer influenza cases than currently available seasonal vaccines, and therefore merit investment

Next steps:

- Extend the framework to select other countries (e.g. Thailand / UK)
- Develop estimation of impact globally
- Extend to looking at the impacts of pandemic influenza.

September 2021

1. Next Generation Influenza vaccines in specific countries	Status: *Funded and in Progress*
• Evaluate pediatric NGI vaccine impact in Kenya by extending an existing dynamic model of seasonal influenza vaccines • Adapt framework to model NGI vaccines in Thailand • Run cost-effectiveness analyses in both countries	Funder: Ready2Respond (CDC/Wellcome Trust)

January 2023

2. Global expansion of Next Generation Influenza vaccine analysis	Status: *Awaiting funding confirmation*
• Extrapolation of results from Kenya and Thailand to the rest of the world. • Construction of model to examine the health and economic benefit of NGI vaccines during an influenza pandemic	Funder: TBD

~ March 2024

3. FVIVA Workstream 3 extension	Status: *Awaiting funding confirmation*

• Conceptual development of an economic model of global supply and demand
• Update of global burden of disease model, including extrapolation of likely long-term impacts of the Covid-19 pandemic
• Projection of the potential demand for vaccines with different characteristics based on country demand
• Estimation of the effect of next generation vaccines with different interactions with human immunity, in terms of health impact and economic value of the vaccines
• Broader assessment of FVIVA including:
  • Savings to health care systems, households (in terms of care, outcome and behaviour-related productivity gains.
  • Community health and economic externalities
  • Insurance value during pandemics
  • Effect on reduction in antibiotic use and antimicrobial resistance
	Funder: *WHO FVIVA*

~ October 2025

World Health Organization

MI4A
MARKET INFORMATION FOR ACCESS TO VACCINES

GLOBAL MARKET STUDY
HPV

Key Takeaways

- Sixteen years after the first marketing authorisation, 60% of WHO Member States have introduced human papillomavirus (HPV) vaccine into their national routine immunization schedule. However, as of 2021, only 13% of girls in the world are fully protected.
- High interest in HPV vaccination by countries across all income groups has led to a sharp increase in demand in the past several years. However, a combination of factors, primarily linked to continued supply constraints, has slowed the pace of introduction, particularly in low-resource settings.
- In the past year, the risk of HPV shortages has significantly decreased, mainly because of active demand management (in response to past supply shortages), delays in programme implementation driven by the coronavirus disease (COVID-19) pandemic and availability of additional supply resulting from increased production capacity. In addition, two new HPV vaccines achieved marketing authorization. One of these has also received WHO prequalification.
- Despite global supply now being sufficient to meet global demand, over the next 3 years access constraints at the individual country level may continue to occur due to limited supply buffers. Careful phasing of multi-age cohorts (MACs) campaigns, particularly in large countries, and country willingness to accept all available HPV vaccines will be critical to minimize the risk of shortages. Implementation of large catch-up campaigns in older-age cohorts and widespread implementation of boys' vaccination will also require attention.
- By 2024, sufficient increases in production capacity will result in a healthy HPV supply situation. This outcome is subject to the success and timing of the clinical development programmes currently in advanced stages as well as completion of manufacturing capacity increases from existing HPV vaccine manufacturers.
- In the long term, HPV supply will not only be sufficient to meet the goals of the Global Strategy to Accelerate the Elimination of Cervical Cancer, but also to significantly outstrip global demand for HPV vaccines. Consequently, active engagement with all manufacturers and management of future supply and demand will be required to ensure market sustainability.
- The potential widespread adoption of a one-dose schedule would lead to higher supply flexibility in the short-term. In the mid-term, it could result either in expansion of the HPV programs (i.e., boys or older age cohorts) or the rapid reduction in programmatic dose requirements. The latter would require careful management to ensure continuity of supply and access.

QUICK STATS

NUMBER OF VACCINE SUBTYPES[1]
3

NUMBER OF VACCINE PRODUCTS
5

TOTAL NUMBER OF MANUFACTURERS[2]
4

2022 ESTIMATED GLOBAL SUPPLY[3]
~80M DOSES (MAXIMUM)

2022 ESTIMATED GLOBAL DEMAND[4]
~80M DOSES

2021 REPORTED PRICE PER DOSE (RANGE)[5]
US$ 4.50 TO US$ 196.32

1 Vaccine subtypes are differentiated by the antigen content of the various HPV vaccines; in this case, three distinct vaccine subtypes are available on the market: HPV2 (16, 18), HPV4 (6, 11, 16, 18) and HPV9 (6, 11, 16, 18, 31, 33, 45, 52, 58).

2 The total number of manufacturers indicates only the companies that have full manufacturing capacity. The number does not include licensors providing a portion of the manufacturing process (e.g., filling and finishing) or distributors that simply commercialize the product in some locations.

3 Supply refers to the "available supply for commercialization", defined as the number of doses available for sale at the global level in one typical year with normal production facility utilization across the various vaccines (not factoring in special market, regulatory or technical events). This differs from the manufacturing capacity or the plant yearly throughput.

4 Demand refers to "programmatic dose requirement", defined as the average estimated number of doses a country would need to procure to meet its immunization programme needs, whether these are routine or campaign. This requirement includes wastage (depending on the presentation) and buffers.

5 The highest publicly reported price is the private market price posted by the US Centers for Disease Control and Prevention (US CDC) (https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html, accessed 20 March 2022).

Disclaimer: This market study incorporates the impact of the COVID-19 pandemic on the HPV vaccination programme. Demand projections assume that programmatic delays or disruptions will be fully absorbed and resolved by 2023.

Purpose & Background

Following the adoption by WHO Member States of a global strategy to accelerate the elimination of cervical cancer in November 2020, increasing introduction and coverage of HPV vaccine worldwide is essential to meeting its targets. Since 2018, WHO has established ongoing monitoring of HPV vaccine supply and demand via the Market Information for Access to Vaccines (MI4A) initiative to help inform decisions, shaping policy, programmes and markets in the face of access challenges.[6]

This study provides the most up-to-date understanding of current and future global trends and drivers of HPV supply and demand to support the resolution of challenges to equitable, unrestricted and flexible access to HPV vaccines across all regions and income groups.

Market Highlights

As of March 2022, 117 countries (60% of WHO Member States, corresponding to approximately one-third of the global target population) have introduced HPV vaccine into their national routine immunization schedules, with 10 new introductions planned by the end of 2022. The rate of introduction (Figure 1) in low and middle-income countries (LICs and MICs), which carry the greatest share of disease burden,[7] remains lower than in high-income countries (HICs). Approximately half of the countries (47%)[8] that have introduced the HPV vaccine are self-procuring. Based on MI4A demand estimates for 2022, approximately 10% of global demand is for use in boys.

Currently, five HPV vaccines have received marketing authorisation and/or WHO prequalification:

- Three bivalent (HPV2) vaccines:
  - » GSK's Cervarix® with proprietary AS04 adjuvant, indicated for girls and women, boys and men between 9-45 years of age.
  - » Innovax's Cecolin® with aluminium-containing adjuvant, indicated for girls and women aged 9-45 years.
  - » Walvax Biotechnology's product with aluminium-containing adjuvant, indicated for girls and women aged 9-30 years (developed by its subsidiary Shanghai Zerun Biotech).
- One quadrivalent (HPV4) vaccine: Merck's Gardasil® with aluminium-containing adjuvant, indicated from 9-45 years of age for girls and women, boys and men.
- One nonavalent (HPV9) vaccine: Merck's Gardasil 9® with aluminium-containing adjuvant, indicated from 9-45 years of age for girls and women, boys and men.

Merck's products represent the great majority of doses procured and have also been commercialized by two licensees: Instituto Butantan in Brazil and Sinergium Biotech in Argentina. Distribution agreements exist in various other countries.

According to the WHO position paper on HPV vaccines, "current evidence suggests that from the public health perspective the bivalent, quadrivalent and nonavalent vaccines offer comparable immunogenicity, efficacy and effectiveness for the prevention of cervical cancer, which is mainly caused by HPV types 16 and 18".[9]

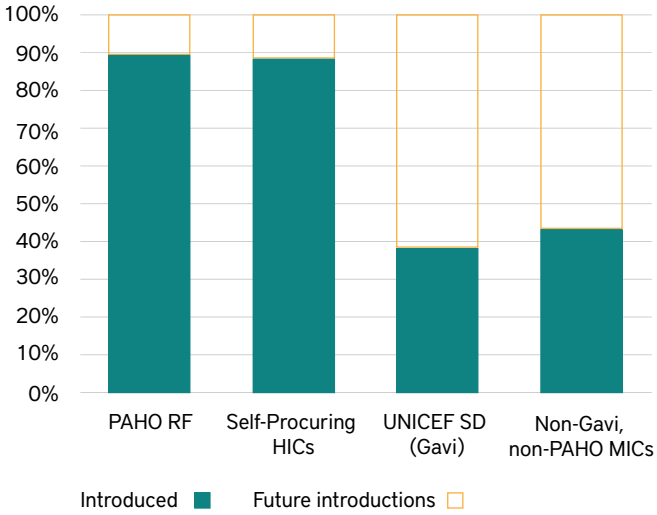
6 In October 2019, SAGE provided guidance to countries regarding the management of the available HPV vaccine supply to limit access constraints. Meeting of the Strategic Advisory Group of Experts on Immunization. Source: Wkly Epidemiol Rec. 2019;94(47):541–60 (https://apps.who.int/iris/handle/10665/329962, accessed 22 March 2022).

7 HPV cases (all cancers), women (2018). Source: Global Cancer Observatory In: International Agency for Research on Cancer; Global Cancer Observatory [website]. Lyon: IARC; 2022 (https://gco.iarc.fr, accessed 22 March 2022).

8 Procurement status of countries informed by 2013–2021 JRF purchase data.

9 Human papillomavirus vaccines: WHO position paper. Wkly Epidemiol Rec. 92(19):241–68 (https://apps.who.int/iris/handle/10665/255354, accessed 22 March 2022).

FIG. 1: HPV VACCINE INTRODUCTION STATUS BY COUNTRY PROCUREMENT GROUP



PAHO RF: Pan American Health Organization Revolving Fund, HICs: high-income countries, UNICEF SD (Gavi): 73 countries eligible for support by Gavi, the Vaccine Alliance;; MICs: middle-income countries;.

Global Demand (Programmatic Doses Requirements)

A global demand forecast for HPV vaccine has been developed for the 10-year period 2022–2031 based on historical procurement data and the latest available information on country introduction plans and other key drivers of demand (e.g. coverage increases and planned MAC campaigns). The base-case scenario of the forecast was developed based on the current WHO-recommended two-dose schedule for girls under 15 years of age.[10] The scenario assumes planned MAC campaigns and continuation of current or near-term planned introductions in boys and older age cohorts; no new MAC campaigns, boys or older-age cohort introductions are included to reflect the 2019 Strategic Advisory Group of Experts on Immunization (SAGE) recommendation to "temporarily pause implementation of boy, older age group (>15 years) and multi-age cohort (MAC) HPV vaccination strategies until vaccine supply allows equitable access to HPV vaccine by all countries."[11]

Global HPV programmatic dose requirements for 2022 will total ~80M doses, including demand from the public and private sectors. Without any supply-related constraints, demand is projected to exceed 130M doses in 2023,[12] reaching ~140M doses in 2026 and stabilizing at ~125M doses by 2031 once MAC campaigns are completed. In the short term, increased demand is expected to be largely driven by potential Gavi-supported MAC campaigns and planned catch-up activities for MACs campaigns in several large HICs.[13] In the medium term, introductions in the national immunization programmes of China and India (estimated for 2024 and after) are expected to drive the most significant increases in global demand; the combined demand of these countries will represent approximately one-third of the market by 2031.

Over the past several years, MI4A has been simulating different scenarios to assess the potential evolution of global demand under different policy options. The most relevant scenarios for ongoing policy and programmatic discussions are shown in Fig. 2.[14]

A. The single dose with single-dose MAC scenario[15] provides insight into the implications of potential policy recommendations for a one-dose schedule on programmatic dose requirements in the short, medium and long term. This scenario results in the lowest dose requirements among the evaluated scenarios, with required doses stabilizing at ~70M in 2028.

B. The scenario detailing a global switch to a one-dose HPV schedule accompanied by a shift to a boys vaccination strategy in all countries assesses the potential use of the availably supply to reach a broader target population; programmatic dose requirements in the medium and long term are comparable to the base demand scenario.[16]

10 Human papillomavirus vaccines: WHO position paper. Wkly Epidemiol Rec. 92(19):241–68 (https://apps.who.int/iris/handle/10665/255354, accessed 22 March 2022).

11 In the same context, SAGE also proposed two alternative approaches to countries, subject to consideration of context and programmatic feasibility: (i) to retain the accelerated impact of MAC campaigns, target girls who are 13 or 14 years old or in the equivalent school grade for two-dose vaccination; or (ii) to temporarily further reduce vaccine supply needs, adopt a 3- to 5-year extended interval between the two doses when the first dose is delivered at 9–10 years of age. This latter strategy constitutes off-label use of the vaccine. Meeting of the Strategic Advisory Group of Experts on Immunization. Wkly Epidemiol Rec. 2019;94(47):541–60 (https://apps.who.int/iris/handle/10665/329962, accessed 22 March 2022).

12 While this projection represents the best estimate of unconstrained demand, it does not correspond to full potential demand for the year; the persistence of supply constraints has already led to postponement of country introductions and MAC campaigns in the past (demand that is now forecasted for subsequent years).

13 A minimum of 24 Gavi-supported countries are forecast to conduct MAC campaigns by 2025 – only planned Gavi MAC campaigns are included in the base demand forecast.

14 Scenarios were developed to give an indication of possible global programmatic dose requirements and do not represent WHO's endorsement of specific schedules in specific groups of countries. All scenarios assume that all countries have introduced the HPV vaccine by 2030 and that MACs are implemented only for vaccination of girls.

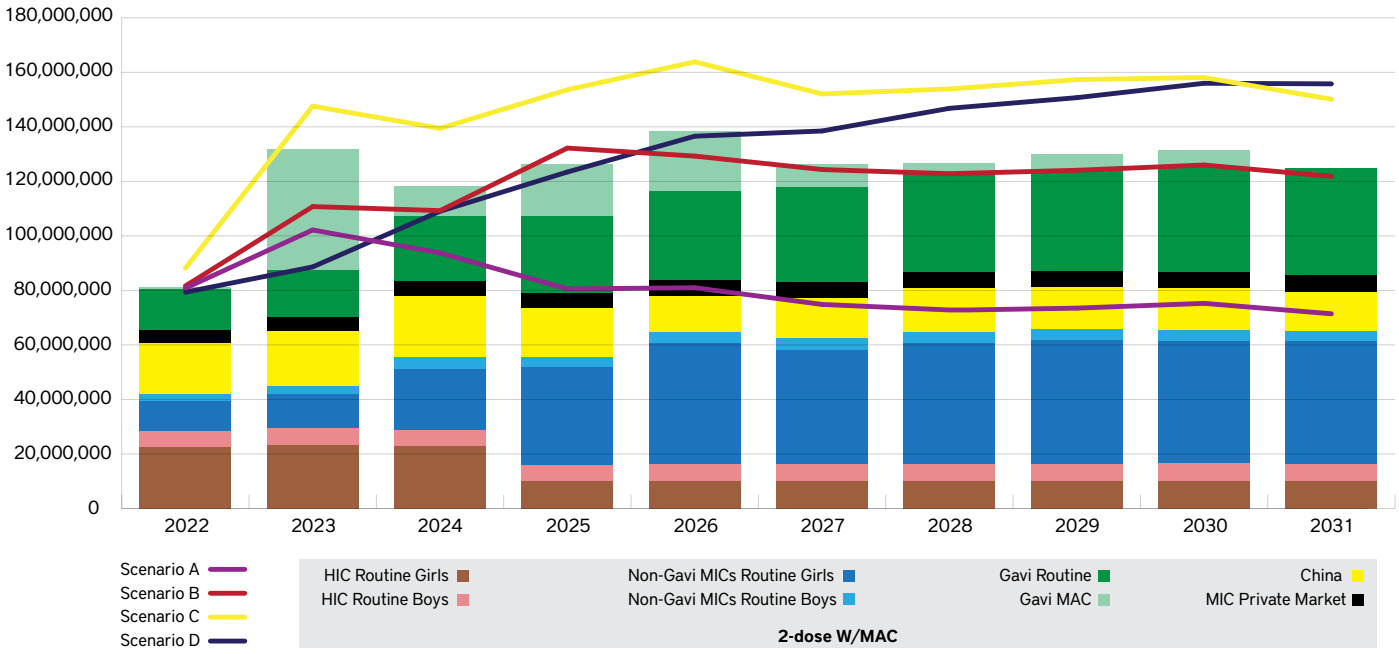
15 The single dose with MAC scenario models a single-dose schedule with increased coverage for all countries. LICs and LMICs are assumed to adopt the single-dose schedule in 2023, and UMICs (upper-middle-income countries) and HICs are assumed to switch in 2025.

16 The single dose with MACs and switch to gender-neutral programme scenario follows the same assumptions as the single dose with MACs scenario. The only exception is that countries adopt a gender-neutral strategy in the year during which a single-dose schedule is implemented.

C. The largest programmatic dose requirements in the short and medium term are required in the scenario that combines the continuation of a two-dose schedule with the implementation of a boys vaccination strategy in all HICs and MICs, including China and India.[17]

D. The programmatic dose requirements to support WHO's cervical cancer elimination goals by 2030[18] are the highest in the long term due to rapid increases in HPV coverage required in all countries,[19] resulting in an additional ~25M doses per year by 2030.

FIG. 2: COMPARISON OF UNCONSTRAINED DEMAND SCENARIOS



Gavi: Gavi, the Vaccine Alliance; HIC: high-income country; MAC: multi-age cohort; MICs: middle-income countries.

Global Supply (Available Supply for Commercialisation)

Consultations with manufacturers and experts, as well as a review of publicly available information on HPV vaccines, provided the basis for an assessment of the current and future global supply of HPV vaccine.

Since the last update, one new HPV vaccine – Cecolin, a bivalent HPV vaccine produced by Innovax – has received WHO prequalification, expanding the global supplier base from two to three suppliers. In addition, Walvax Biotechnology's product received marketing authorization and existing manufacturers are continuing investments to increase manufacturing capacity. Supply has already increased on average by 15% annually in recent years, and new investments are expected to translate into continuing and increased growth in available supply, with significant increases anticipated in the short and medium term (2023–2025).

Two quadrivalent HPV vaccines are currently in Phase 3 clinical development: one from Serum Institute of India and one from the China National Biotec Group (CNBG). All use aluminium-containing adjuvants and are likely to be licensed with an indication for girls 9–14 years old for two- and/or three-dose schedules. The success, timing and capacity of these pipeline vaccine efforts will have a significant impact on the long-term outlook for HPV vaccine supply.

17 The two-dose routine with MAC and switch to gender-neutral programme scenario follows the same assumptions as the base scenario, with the exception that a gender-neutral strategy is implemented from the year of HPV introduction.

18 Modelling the potential increase in demand from the global cervical cancer elimination strategy assumes HPV vaccine introductions across the globe, with all countries reaching at least 90% coverage by 2030.

19 The elimination scenario follows the same assumptions as the base case (two-dose schedule) but estimates that all countries will reach at least 90% coverage by 2030; no MAC is included in this scenario (https://www.who.int/news-room/events/detail/2019/10/08/default-calendar/strategic-advisory-group-of-experts-on-immunization-(sage)---october-2019, accessed 20 March 2022)

The base projection foresees a threefold increase in available supply over the medium term (4–6 years, range 2–4X), from the ~80M doses expected to be available in 2022.

Technology transfers for HPV vaccine are limited. Currently, Merck supplies Instituto Butantan and Sinergium Biotech with HPV drug substance, and each supplier performs the subsequent filling and finishing processes. Both suppliers commercialize the HPV vaccine in Brazil and Argentina, their respective domestic markets. Additional technology transfers involving companies in Russia and Thailand are currently being implemented; the timing and likelihood of these activities contributing to global supply are unclear.

Supply–Demand Balance

In past years, continuing supply constraints particularly affected LICs and MICs and led to the adjustment of introduction plans, especially in Gavi-supported countries, and to the issuing of adapted global policy recommendations. As result of this proactive management of HPV demand, along with declines in immunization coverage because of the COVID-19 pandemic, and increases in the available HPV supply, primarily from one of the existing manufacturers, the supply–demand balance has significantly improved.

Starting from 2022, global supply is expected to be sufficient to meet base demand for a two-dose routine programme[20] targeting girls, inclusive of MACs campaigns (Fig. 3). Nevertheless, given limited buffers, for the next 2–3 years careful phasing of MAC campaigns and country willingness to use any of the available HPV vaccines will be necessary conditions to ensure all countries can access the supply required to achieve the primary goals of the HPV vaccination programme. Attention will also be required to the supply implications of implementing large catch-up campaigns in older-age cohorts and to the widespread adoption of boys vaccination strategies.

The supply–demand balance is expected to **steadily improve from 2023 to 2024, subject to the realization of the following conditions**:

» Sustained committed to existing programmes by existing suppliers, success in expanding capacity and making new capacity available (both in terms of the timing and size of the capacity increases); and
» Successful completion of clinical development programmes by pipeline manufacturers, obtaining required marketing authorisation and making supply available in the expected quantities in all countries where necessary.

The expected increases will improve the flexibility of supply and allow countries more freedom of choice in term of products and vaccination strategies. After 2025, HPV vaccine supply is expected to significantly exceed demand even in the most pessimistic supply scenarios. Therefore, active engagement with all manufacturers and management of future supply and demand will be required to ensure market sustainability.

In this context, the potential adoption of a one-dose schedule would further improve the supply–demand balance in the short term, allowing accelerated implementation of MAC campaigns and more flexibility on product choice. In the medium and long term, the implementation of a one-dose schedule by a large number of countries could (i) either allow for a more generalized adoption of boys and/or older cohorts vaccination strategies or (ii) lead to a rapid reduction in programmatic dose requirements. The latter, coupled with the fact that not all products have data available supporting the switch to one dose or boys vaccination, could impact the sustainability of the HPV market for vaccine manufacturers, including through price changes and/or market exits. Transition to a one-dose schedule would therefore require carefuly management, including through generation of evidence for single-dose efficacy for all products.

FIG. 3: SUPPLY/DEMAND BALANCE[21,22]

Demand Scenarios	Base supply			Low supply		
	Short-Term (1-3)	Mid-Term (4-6)	Long-Term (6-9)	Short Term (1-3)	Mid Term (4-6)	Long-Term (6-9)
2-doses +2ds MACs (base case)						
2-doses +2ds MACs & gender neutral						
2-doses no MACs high coverage (Elimination)						
1-dose +1d MACs						
1-dose +1d MACs & gender neutral						

Excess supply
Supply >2X Demand

No risk of shortages
Supply >1.3X Demand

Some risk of shortages
Supply <1.3X Demand

Insufficient supply
Supply <1.1X Demand

1d: one dose; 2ds: two doses; MACs: multi-age cohorts.

20 In this scenario, boys' vaccination is not expanded further to countries other than the ones that already have them in place.

21 Low supply scenario based on more conservative assumptions concerning manufacturing capacity increases and success in clinical development.

22 One-dose-only scenarios assume that supply is available solely from suppliers that have supporting data for a single-dose schedule.

Price

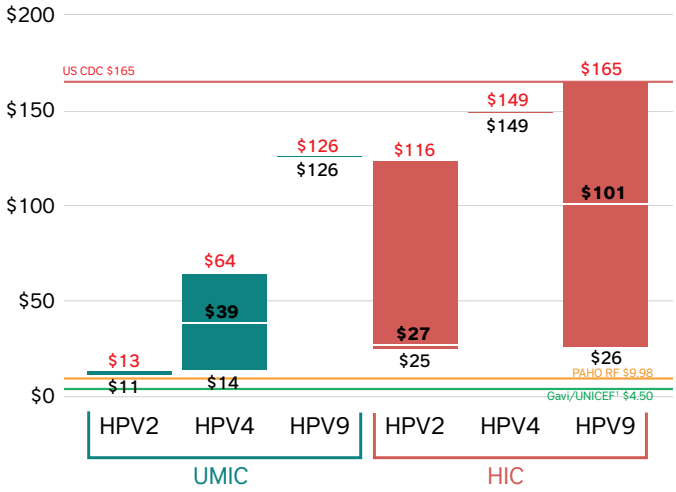
The reported price per dose[23] of HPV vaccines shows a tiered structure by procurement method and income group (Ref. Figure 4), with UNICEF (United Nations Children's Fund) Supply Division (SD)/Gavi and the PAHO (Pan American Health Organization) Revolving Fund (RF) paying the lowest prices, at US$ 4.50 and US$ 9.98,[24] respectively. The UNICEF SD/Gavi price for GSK's HPV2 product will increase to US$ 5.18 starting in 2022, and the price for Merck's HPV4 will continue at US$ 4.50 until 2025. Contracted price for Innovax starting in 2022 is $2.90 per dose though no country is yet to procure the vaccine. The self-procuring MICs' median price for HPV2 is more than twice the Gavi price and slightly higher than the PAHO price. HPV4 median price is instead significantly higher.

Generally, GSK's HPV2 product is lower priced, ranging from US$ 11.17 to US$ 12.53, compared with Merck's HPV4 product, which ranges from US$ 13.81 to US$ 64.16 for self-procuring MICs.[25] HPV prices have generally decreased across all procurement and income groups over the last half-decade. Further reductions in price are expected to materialize as and when a more competitive environment is established by future new market entrants, provided there is reasonable demand for those new products.

Affordability remains a concern for MICs that no longer are or never were supported by Gavi or PAHO RF. Both Merck and GSK have made price commitments (under specific conditions) to countries transitioning out of Gavi support.[26] Some countries are no longer eligible for these time-limited commitments.[27]

The overlap between the reported prices paid by MICs and those paid by HICs indicates space for improvement towards a more equitable tiered pricing. In the context of the current global economic uncertainty and of the ambitious agenda of reaching zero-dose children in the Immunization Agenda 2030 (IA2030), country financing for immunization will be stretched by both vaccine procurement and implementation costs. The impact of HPV vaccine introduction on health and immunization budgets can represent a significant barrier , particularly in countries where HPV vaccine represents a substantial financial burden.

FIG. 4: 2021 HPV SELF-PROCURED PRICE PER DOSE



HPV: human papillomavirus; PAHO: Pan American Health Organization; UMIC: upper-middle-income country; US CDC: US Centers for Disease Control and Prevention; WAP: weighted average price.

- Median values in bold.
- Source: 2021 MI4A Purchase Data (country-reported).
- Note: Reduction in Gavi/UNICEF price is the result of new products being available. Gavi/UNICEF will pay this price when countries elect to introduce the relevant product into their national immunization systems.

23 WHO JRF 2021 data.

24 The PAHO RF price is the 2021 price for HPV4.

25 Excluding outliers.

26 For details of price commitments, see the fact sheet on vaccine pricing for Gavi-transitioning countries: https://www.who.int/publications/m/item/factsheet-on-vaccine-pricing-for-gavi-transitioning-countries.

27 As part of its 5.0 strategy (2021–2025), Gavi is outlining parameters for potential engagement with former Gavi-eligible countries and non-Gavi-eligible countries with gross national income per capita of up to US$ 6000 to support introduction of new vaccines, including HPV. This support would facilitate introduction of HPV in MICs but is not expected to come into play before 2022.

Areas for Action

Careful coordination and investments are required to enhance supply availability towards global cervical cancer elimination goals. Specific actions are recommended as follows:

- ✓ WHO and its partners will continue to convene a global access dialogue engaging all stakeholders to achieve equitable access to supply, including through active management of demand and supply and implementation of WHO recommendations.
- ✓ WHO will continue to explore opportunities to increase access through timely translation of emerging scientific evidence into policy recommendations, particularly with reference to the comparability of immunogenicity, efficacy and effectiveness of the available quality-assured products and on optimized schedules (e.g. one-dose).
- ✓ WHO will continue providing timely support for prequalification of new HPV vaccines and seamless implementation of post-marketing changes of relevance for the programme (e.g. one-dose, boys vaccination).
- ✓ WHO will continue to inform country decision-making regarding HPV vaccine product selection and adoption of WHO recommendations to improve flexibility of demand and support implementation of HPV programmes that can be sustainably financed.
- ✓ WHO and its partners will work with MICs in line with IA2030 and the Gavi 5.0 MICs approach to support introduction of HPV vaccine.

For more information, contact:
MI4A@who.int

Methodology & Sources

MI4A Technical Advisory Group of Experts:

MI4A benefits from the expertise of a standing advisory group for input, review and validation of market analyses. The group includes members from regional technical advisory groups on immunization, UNICEF SD, PAHO RF, Gavi, the Bill & Melinda Gates Foundation, implementation partners and WHO SAGE, along with manufacturers' associations (the Developing Countries Vaccine Manufacturers Network and the International Federation of Pharmaceutical Manufacturers and Associations) and independent experts.

Supply resources:

MI4A annual data collection from manufacturers, high-level validation of outputs of analysis with studies from Gavi and the Bill & Melinda Gates Foundation, bilateral discussions with manufacturers on capacity drivers and pricing prospects, review of clinical trial information, review of available cost of goods studies, review of manufacturing processes documentation (e.g., the European Medicines Agency), analysis of vaccine products registration.

Demand resources:

Historical procurement: WHO MI4A V3P/JRF (2013–2021) and UNICEF SD (2014–2021). Planned/projected country introductions: WHO Joint Reporting Form (JRF), Gavi Operational Forecast, 2020 WHO Estimates on HPV vaccine coverage, 2020 update (Immunization, Vaccines and Biologicals database, July 2021).

Pricing resources:

WHO MI4A V3P/JRF, PAHO RF, UNICEF SD (2020 data).

Other useful public resources

This global study complements market analysis performed by UNICEF SD and Gavi for specific market segments:

Human papillomavirus (HPV) supply and demand update. New York: UNICEF SD; 2020 (https://www.unicef.org/supply/reports/human-papillomavirus-hpv-vaccine-supply-and-demand-update, accessed 20 March 2022).

Supply and procurement roadmap: human papillomavirus vaccine, public summary. In: Gavi/Our alliance [website]. Geneva: Gavi; 2017 (https://www.gavi.org/sites/default/files/document/hpv-supply-and-procurement--roadmappdf.pdf, accessed 20 March 2022).

Vaccine 36 (2018) 498–506

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Bacillus Calmette-Guérin (BCG) vaccine: A global assessment of demand and supply balance

Tania Cernuschi [a,*], Stefano Malvolti [b], Emily Nickels [c], Martin Friede [a]

[a] World Health Organization, Expanded Programme on Immunization, 20 Avenue Appia, 1211 Geneva, Switzerland
[b] MMGH Consulting, Kürbergstrasse 1, 8049 Zürich, Switzerland
[c] Linksbridge SPC, 808 Fifth Ave N, Seattle, WA 98109, United States

ARTICLE INFO

Article history:
Received 4 May 2017
Received in revised form 20 October 2017
Accepted 4 December 2017
Available online 15 December 2017

Keywords:
BCG
Tuberculosis
Shortages
Stock-outs
Supply
Demand

ABSTRACT

Over the past decade, several countries across all regions, income groups and procurement methods have been unable to secure sufficient BCG vaccine supply. While the frequency of stock-outs has remained rather stable, duration increased in 2014–2015 due to manufacturing issues and attracted the attention of national, regional and global immunization stakeholders. This prompted an in-depth analysis of supply and demand dynamics aiming to characterize supply risks. This analysis is unique as it provides a global picture, where previous analyses have focused on a portion of the market procuring through UN entities. Through literature review, supplier interviews, appraisal of shortages, stock-outs and historical procurement data, and through demand forecasting, this analysis shows an important increase in global capacity in 2017: supply is sufficient to meet forecasted BCG vaccine demand and possibly buffer market shocks. Nevertheless, risks remain mainly due to supply concentration and limited investment in production process improvements, as well as inflexibility in demand. Identification of these market risks will allow implementation of risk-mitigating interventions in three areas: (1) enhancing information sharing between major global health actors, countries and suppliers, (2) identifying interests and incentives to expand product registration and investment in the BCG manufacturing process, and (3) working with countries for tighter vaccine management.

© 2017 Published by Elsevier Ltd. This is an open access article under the CC BY IGO license. http://creativecommons.org/licenses/by/3.0/igo/

1. Introduction

Tuberculosis (TB) is one of the major causes of death worldwide, claiming 1.8 million lives in 2015, particularly among communities which already face socioeconomic challenges [1]. Mycobacterium tuberculosis (MTB), the etiological agent of TB, is transmitted via respiratory droplets by patients who are already infected. In 90 percent of infected persons, the bacterium is contained by the host immune response as a latent TB infection (LTBI). Bacillus Calmette-Guérin (BCG) is the only available vaccine to fight the disease, with a duration of protection of at least ten years with some residual vaccine effectiveness up to 20–25 years [2,3]; however, the vaccine only prevents acute forms of childhood TB, and not reactivation of LTBI (the main source for adult pulmonary disease and transmission of MTB) [1]. WHO recommends universal vaccination with a single birth dose of BCG in settings where TB is highly endemic or where there is high risk of exposure to TB [4].[1]

There is evidence that BCG also prevents leprosy [5], a skin-neurological disease caused by Mycobacterium leprae (200,000 cases in 2016, mainly in Southeast Asia) [6]. BCG vaccine is also effective against other mycobacterial infections, such as Buruli ulcer disease [7].

Over the ninety years since its development, the BCG vaccine has been administered to more than three billion children in the Expanded Programme on Immunization (EPI) across all regions [8]. Although reviews show little evidence that revaccination with BCG affords additional protection, several countries do report implementation of a two-dose schedule [9].[2]

All the BCG vaccines currently in use derive from the original strain of BCG produced by Albert Calmette and Camille Guérin in 1924 at the Pasteur Institute. The original strain was distributed to several countries, leading to generation of the many substrains used today [10]. Currently, the main substrains used for vaccine production are Brazilian (Moreau/Rio de Janeiro), Danish (Copenhagen – 1331), Japanese (Tokyo – 172-1), Russian (Moscow – 368) and Bulgarian (Sofia – SL222). Different strains tend to be

* Corresponding author.
E-mail address: cernuschit@who.int (T. Cernuschi).

[1] WHO is currently reviewing its position on BCG and will publish an updated position paper in early 2018.

[2] Reporting countries: Bulgaria, Kazakhstan, Russia, Seychelles, Tajikistan, Turkmenistan, Ukraine.

https://doi.org/10.1016/j.vaccine.2017.12.010
0264-410X/© 2017 Published by Elsevier Ltd.
This is an open access article under the CC BY IGO license. http://creativecommons.org/licenses/by/3.0/igo/

used interchangeably, with no conclusive evidence existing to discriminate for efficacy and safety [11]. The choice of the strains used in the different countries is therefore the result of historical use, production, logistics or other factors [12].

Beyond the open questions on efficacy and interchangeability, continued supply availability has been a main challenge with BCG vaccine. The problem has become more acute in recent years: in 2015, UNICEF reported a supply shortfall of 16.5 million doses due to decreased supply capacity. Large middle-income countries (MICs), typically self-procuring, have also experienced issues in accessing supply [13], as have several high-income countries (HICs); in particular, this was a result of the production problems faced by one historical and large supplier (Statens Serum Institut of Denmark – SSI) [14].[3]

Manufacturing problems, in particular GMP issues, and decisions of suppliers to halt their production are not something new to the BCG vaccine market (as illustrated in Fig. 1) [13–20]. Manufacturing has remained mostly unchanged since the 1920s, with poor characterization and difficulties in maintaining control of the process. The low vaccine price, while affordable for countries, reduced incentives for manufacturers for starting complex and expensive activities for redesign and enhancement of the production process.[4]

This analysis aims to assess the level of risk of BCG vaccine supply in the short- and mid-term and to identify potential areas for intervention. Special attention has been dedicated to maintaining a global perspective: traditional analyses on vaccine availability tend to focus only on segments of the vaccine supply, generally the portion supplied via United Nations (UN) procurement. A global perspective is necessary when assessing vaccine markets, as supply is ultimately allocated on a global basis. In the specific case of BCG vaccine, self-procuring countries account for about 60 percent of total demand.

The analysis investigates BCG vaccine demand and supply dynamics for recent past, present (2017) and near future, with the goal of informing country choices and global policy decisions.

2. Methods

The work has been structured in five areas, as described below.

2.1. Vaccine shortages

A review of the extent and frequency of vaccine shortages over the past decade was conducted. For this work, vaccine shortages are defined as the inability of countries to meet national needs (population needs plus a required buffer). Nevertheless, in the absence of a precise measure of shortages, the analysis reviews country-reported data on national-level stock-outs[5] from the WHO/UNICEF Joint Reporting Form (JRF) for the period 2005–2015 [9]. For more recent years (2016 through early 2017), information on shortages has been obtained through consultations with the WHO regional offices.

2.2. Global demand

Modelling of global BCG vaccine demand was completed. Annual demand is calculated using the formula below:

$$[\text{Target Population} \times \text{Number of Doses} \times \text{Coverage} \times \text{Wastage}] + \text{Buffer}$$

All 194 WHO Member States report EPI schedules through the WHO/UNICEF JRF on an annual basis [9].[6] The currently reported schedules for countries reporting universal vaccination (see Fig. 2) were used to identify country-specific target ages as well as number of doses. The UN Population Division (UNPD) population forecast by year of life was used as the country target population for BCG vaccination [21].[7] The target population was multiplied by the WHO/UNICEF estimated national immunization coverage (WUENIC) [9] and the standard WHO wastage by vial size (in cases of BCG vaccine where the predominant presentations are 10 and 20 dose vials, a factor of 50 percent has been used). The standard buffer stock level (25 percent of the difference in demand between years (positive values only)) was added. The result was a forecast of BCG vaccine demand, per country, per year, for the period 2017–2030 [22].

In addition, data on historical BCG vaccine procurement was available for 146 countries (JRF and UNICEF [23]). This data was compared to the demand forecast for the same 146 countries to inform estimates.

Given the evidence that BCG vaccine can prevent leprosy [24],[8] we analyzed the EPI schedules for the 22 highest burden countries [9]. In addition, the 17 countries with the next highest case detection rates were also included in our assessment, for a total of 39 countries.[9] For these countries, we reviewed recommendations for BCG vaccination to estimate potential additional demand.

Finally, to assess the potential impact of migration flows on global demand of BCG vaccine, we looked at the estimates of the number of refugees/migrants arriving in countries/regions with BCG vaccination for high-risk groups; e.g., Canada (in 2015 and 2016, ~250,000 annually [25]). Vaccination of the entire migrant population with one dose of BCG vaccine was then assumed, given lack of comprehensive data on BCG vaccination practices for these populations. In connection with the recent migrant crisis in the European Union, we estimated the influx of migrants (in 2016, estimates range from 362,000 to 1.2 million [26,27]) and assumed one dose for each, independent of country policy.

2.3. Global supply

A list of manufacturers with available supply of BCG vaccine (and product characteristics) has been compiled with the help of PAHO Revolving Fund, International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) and Developing Countries Vaccine Manufacturers Network (DCVMN), as well as through a review of published literature [12,28–33], UNICEF Supply Division market updates [13],[10] and internal reports from Bill & Melinda Gates Foundation (BMGF) and Clinton Health Access Initiative (CHAI).

All manufacturers were contacted to obtain information on available products and their characteristics (presentation, shelf-life, route of administration, strain, disease and age indication), as well as information on countries of registration and manufactur-

[3] SSI completed divestment of its BCG vaccine business to AJ Biologics in 2016 after having experienced repeated production and GMP issues.

[4] Analysis of BCG vaccine price by income, region, manufacturer, volume and procurement method can be generated from the V3P website at http://apps.who.int/immunization/vaccineprice (last accessed 07 April 2017).

[5] Stock-out of a vaccine for at least one month indicates that "safety stocks have been depleted and vaccine availability for the national immunization programme could be compromised" [42].

[6] WHO/UNICEF JRF data includes country-reported EPI schedules and estimated coverage (WUENIC) and can be viewed or downloaded here: http://www.who.int/immunization/monitoring_surveillance/data/en/.

[7] The total birth cohort for 153 countries with BCG in EPI is 131 million [21].

[8] Of note: as of October 2017, WHO recommends universal birth dose vaccination with BCG in high burden leprosy settings regardless of the TB incidence (SAGE report: http://apps.who.int/iris/bitstream/10665/259533/1/WER9248.pdf?ua=1).

[9] Data on leprosy case detection rates provided by the WHO Global Leprosy Programme (GLP).

[10] All UNICEF Supply Division market updates are available here: https://www.unicef.org/supply/index_54214.html.

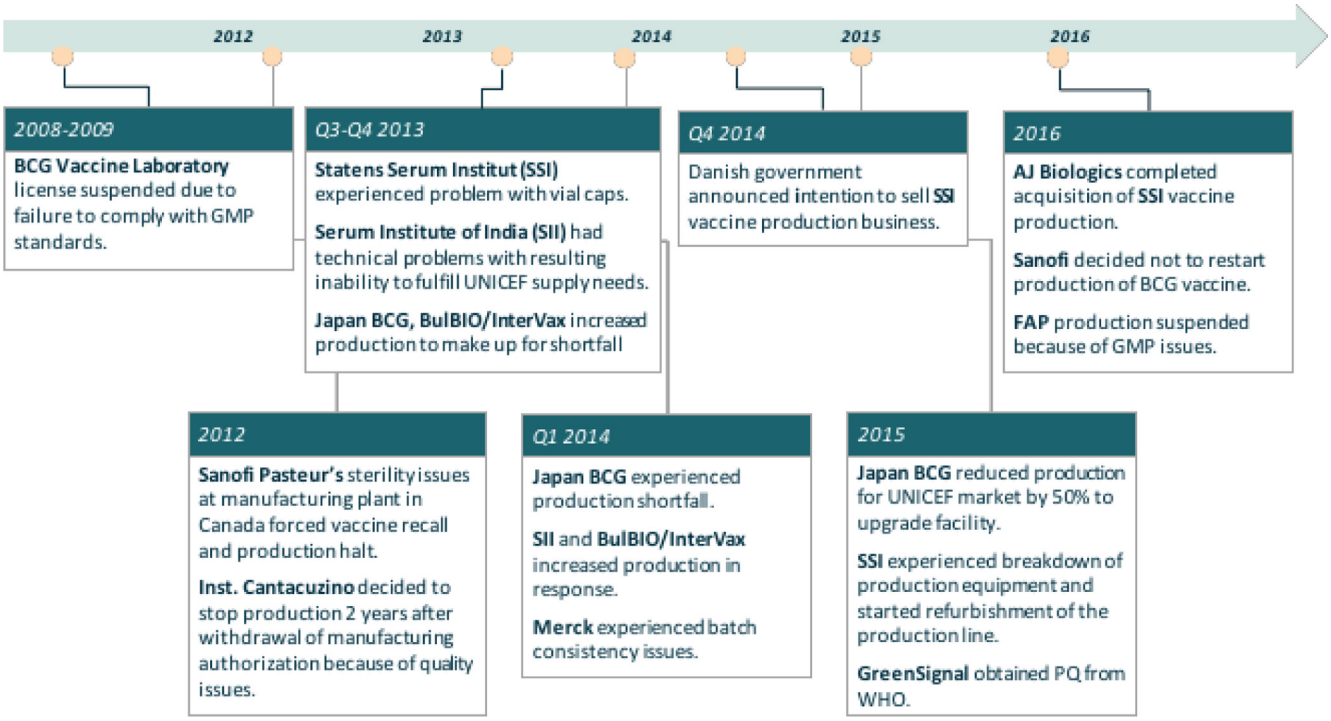


Fig. 1. Chronology of key events for BCG vaccine in the period 2008–2016. (Based on unpublished Bill & Melinda Gates Foundation work modified with recent manufacturer, WHO, and UNICEF press releases [13–19].)

ing capacity. Nine interviews took place, including all five WHO prequalified (PQ'd) producers.[11]

This process allowed for building of three supply estimates: the historical view of 2015 supply, the current available supply for 2017 and a future short-term projection for 2019. The available information indicates that no new major vaccine is to be expected into the market before 2020 and therefore new product availability is unlikely to impact the current BCG vaccine market.

2.4. Product registration

For each of the identified products, information has been collected from manufacturers on their registration status in different countries. This data was combined with information on source of procurement (JRF) and on country ability to accept the collaborative procedure between WHO and NRAs for the assessment and accelerated national registration of WHO PQ'd pharmaceutical products and vaccines [34]. This information was used to estimate countries' ability to readily access alternative products in case of supply failure.[12]

2.5. Global demand-supply balance

Finally, demand and supply estimates were compared to validate historical dynamics and to identify ongoing and future challenges for access.

Results were discussed as part of the proceedings of the WHO Strategic Advisory Group of Experts Working Group on BCG vaccine. They are presented in this paper at the aggregate level to ensure compliance with confidentiality agreements and anti-trust regulations.[13]

3. Results

3.1. Vaccine shortages

The analysis confirms that several BCG stock-outs were reported through the JRF across all regions and income groups: an average of 43 out of 194 countries per year experienced stock-outs from 2005 to 2015.[14] The average duration of stock-outs for those countries was 1.4 months for the period 2005–2013. In 2014 and 2015, the average duration increased to 2.6 and 2.8 months, respectively. Stratification of the data provides useful insights:

- The African region has been most affected – annually, an average of 41 percent of countries in the region experienced stock-outs versus 12 to 22 percent of countries in other regions.
- Low-income countries (LICs) and lower-middle-income countries (LMICs) were also more affected, with an average of 41 and 34 percent of countries in these income groups experiencing stock-outs yearly, versus 17 and 4 percent for upper-middle-income countries (UMICs) and high-income countries (HICs), respectively.[15]
- Different procurement methods seem not to modify risk of stock-out.

As mentioned, we cannot attribute each stock-out to a shortage of vaccine supply. Consultation with WHO regional offices con-

[11] Capacity of manufacturers that did not respond (all focused on supplying local markets) has been estimated based on the corresponding local market size. Based on the input from manufacturers, doses allocated for oncological use have been excluded.

[12] This data is unpublished and available through WHO Global Polio Eradication Initiative.

[13] The SAGE WG on BCG vaccine was established in October 2016. For more information, please consult WHO's website at: http://www.who.int/immunization/policy/sage/sage_wg_bcg_oct2016/en/ (last accessed 07 April 2017).

[14] These also include producing countries.

[15] According to the 2016 World Bank income classification.

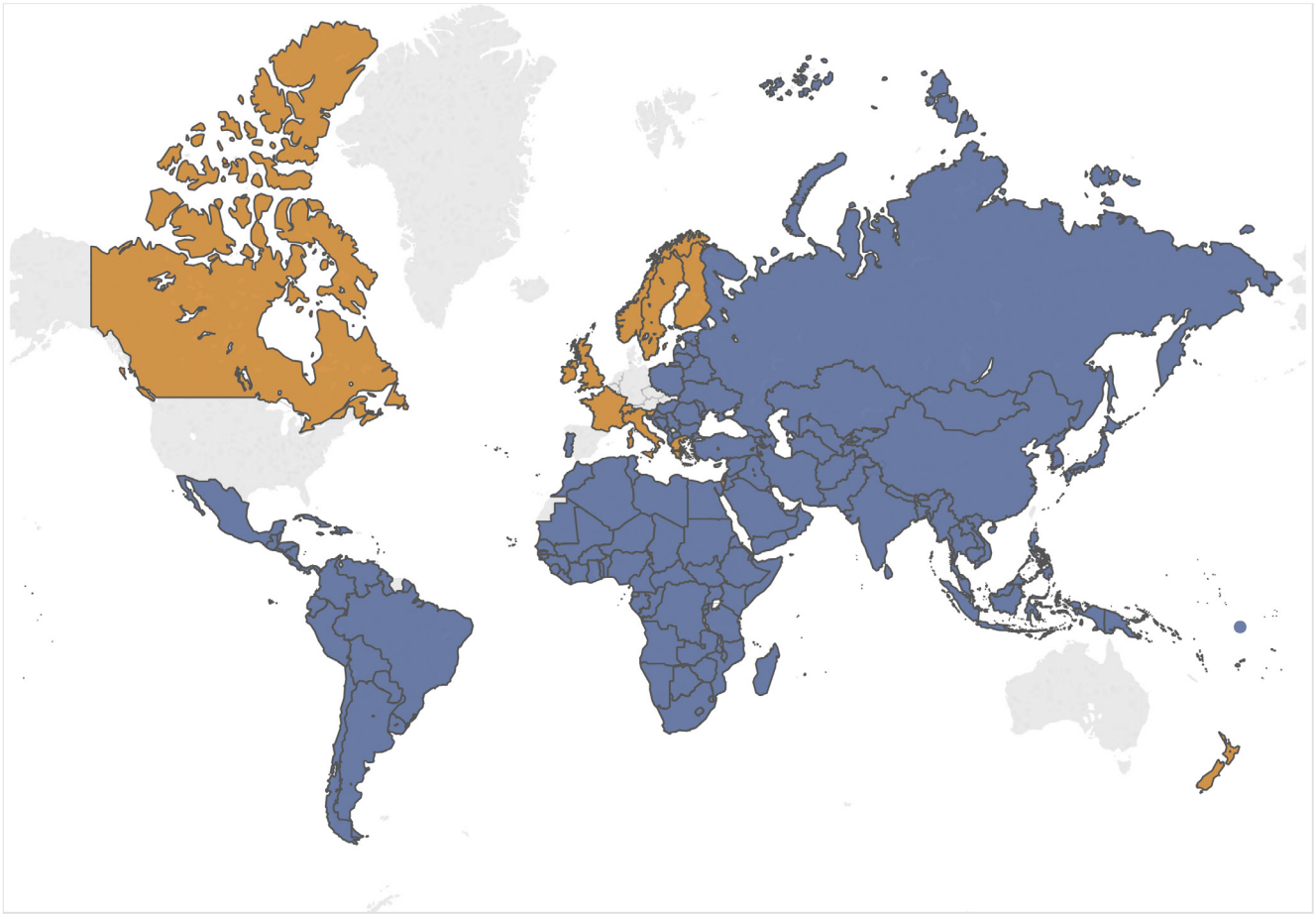


Fig. 2. Country-reported BCG use [9].

firmed that at times, availability of financing, national or external, was an issue. Local procurement shortcomings and ineffective vaccine management were also quoted among reasons for stock-outs. Nevertheless, supply issues are also an important factor behind countries' inability to meet supply needs.

Countries and international agencies leveraged various coping strategies to deal with the unavailability of supply:

- UNICEF worked with manufacturers (with and without PQ'd products) to access supply not yet allocated. Vaccine distribution was prioritized using a process established by WHO and UNICEF [35]. WHO worked with manufacturers on prequalification expectations and a new product was PQ'd in 2015.[16]
- In countries, different strategies were implemented to ensure uninterrupted supply, from reducing shipment size to tighter stock management and changes in vaccination practices to reduce wastage. Alternative suppliers were also sought and used where possible: temporary import licenses from manufacturers were arranged for products not registered. Despite these efforts, over the years, some countries had to suspend vaccination for a few months until vaccine became available.

3.2. Global demand

The result of the global demand forecast was an annual average demand of 227 million doses.[17] However, comparison with historical procurement data suggested this was an underestimate. While on average about 290 million doses of BCG vaccine were procured in the period 2006–2015 for the 146 countries with data available in JRF,[18] modeled demand for these same 146 countries accounted for an average of approximately 190 million doses per year. The amount of JRF-reported procured doses is 1.5 times greater than forecasted demand, with the greatest differences recorded in the self-procuring LMICs. Accounting for larger than expected past pur-

[16] WHO determines the acceptability, in principle, of vaccines from different sources for supply to United Nations agencies. The detailed procedure can be found here: http://www.who.int/immunization_standards/vaccine_quality/pq_system/en/ (last accessed 04 April 2017).

[17] The 2017 modelled demand for the 153 countries with BCG vaccine in the EPI schedule is 229 million doses. The target population is 128 M and includes live births and booster doses in seven countries. The seven countries with booster doses have a total birth cohort of ~3 M.

[18] Historical procurement data was submitted for 48 countries through the JRF.

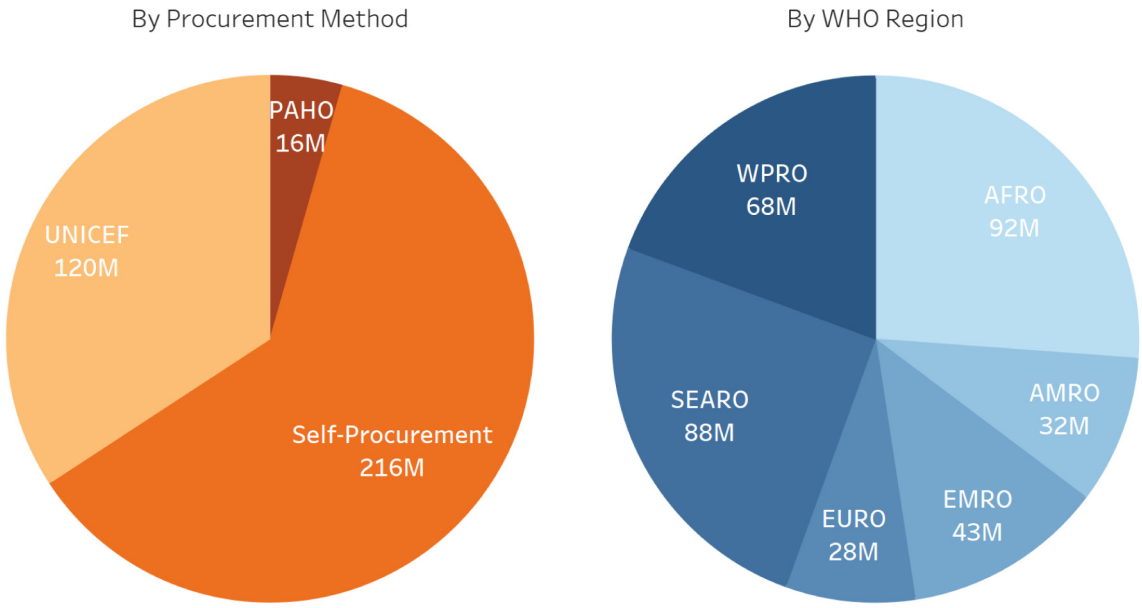


Fig. 3. 2017 Adjusted Global Demand (352 million doses) by Procurement Method and WHO Region. (For reference, the birth cohorts, by procurement method, are: Self-procuring – 78 M, UNICEF – 47 M, PAHO – 5 M [21].)

chases, the annual global demand forecast of 229 million doses was increased by 1.5 times to an estimated 350 million (Fig. 3).

Since all 39 countries with high leprosy burden recommend universal BCG vaccination for prevention of TB [9], no additional BCG demand for prevention of leprosy was included in the global demand forecast.

Finally, the additional demand due to migration was estimated to be negligible (less than 1 percent of forecasted global demand).

Review of demand analysis shows that the largest share (60 percent) of demand for BCG vaccine is from countries self-procuring supply. UNICEF Supply Division procures for many countries, representing about 35 percent of demand, while the PAHO Revolving Fund accounts for the remaining five percent (see Fig. 4). Over 60 percent of forecasted BCG vaccine demand for 2017 is for 20-dose vials: UNICEF procures 20-dose vials only, PAHO procures 10-dose vials, China produces/procures 5-dose vials, and self-procurement is split between 10- and 20-dose vials [9,36,37]. UN agency procurement is exclusively of WHO PQ'd products; self-procuring countries procure both PQ'd and non PQ'd products.

3.3. Global supply

Twenty-two manufacturers (as listed in Table 1) were identified as having manufacturing capacity available for BCG vaccine for prevention of tuberculosis, including two manufacturers belonging to the same corporate group.[19] It is important to notice that all but two currently active manufacturers are in countries with National Regulatory Authorities (NRAs) deemed functional by WHO.[20]

For 2017, the global capacity is estimated to be approximately 500 million doses — a 30 percent increase compared to 2015 and well above expected demand. Capacity is split into two groups:

- Four producers with PQ'd products (Serum Institute of India, GreenSignal, Japan BCG Laboratory and InterVax/BB-NCIPD) that can reach 169 countries where their products are registered or UN procurement is accepted; and
- Fifteen producers with non-PQ'd products that can serve 52 countries where their product is registered.

Consultations with manufacturers suggest a potential for further increase of 35 percent in the next two years, allowing supply to reach 700 million doses, thanks to the return of the three manufacturers currently not supplying the market (Table 1) and flexibility in capacity of some of the manufacturers already supplying the market.

3.4. Product registration

Results show that more than half of the world's countries accept WHO PQ'd product either via direct UN procurement or through the collaborative procedure between WHO and NRAs for regulatory approval. Consequently, these countries have the potential for quick access to a large supplier base (all four PQ'd products and, in some cases, also non-PQ'd products with local licenses) which provides a safety net in case of supply issues.

About 20 countries require local licensure (are not accepting PQ'd products) and have two or three products licensed. These countries can switch between the in-country licensed products in case of supply issues.

Importantly, over 40 countries require local licensure and have only one product registered. In these countries, discontinuation or reduction in supply from the manufacturer of their only licensed product can lead to supply issues. This high-risk group can be further stratified by looking at (a) whether countries have local BCG vaccine production — and are therefore better informed about and in control of potential issues — and (b) whether countries without local production have BCG vaccine in their EPI schedule — thus requiring large supplies. This latter group is composed of about 20 countries.

A second group with high risk is a set of 12 countries that, at the time of the analysis, appear to have no product registered. All are HICs whose preferred supplier has withdrawn from the market.

[19] Chengdu Institute for Biological Products and Shanghai Institute for Biological Products both belong to China National Biotech Group (CNBG).

[20] WHO has developed a benchmarking system using a benchmarking tool with established standard criteria for evaluating NRAs in the area of vaccine regulation, and has identified six key regulatory functions that NRAs need to perform within a regulatory system defined by law. http://www.who.int/immunization_standards/national_regulatory_authorities/role/en/.

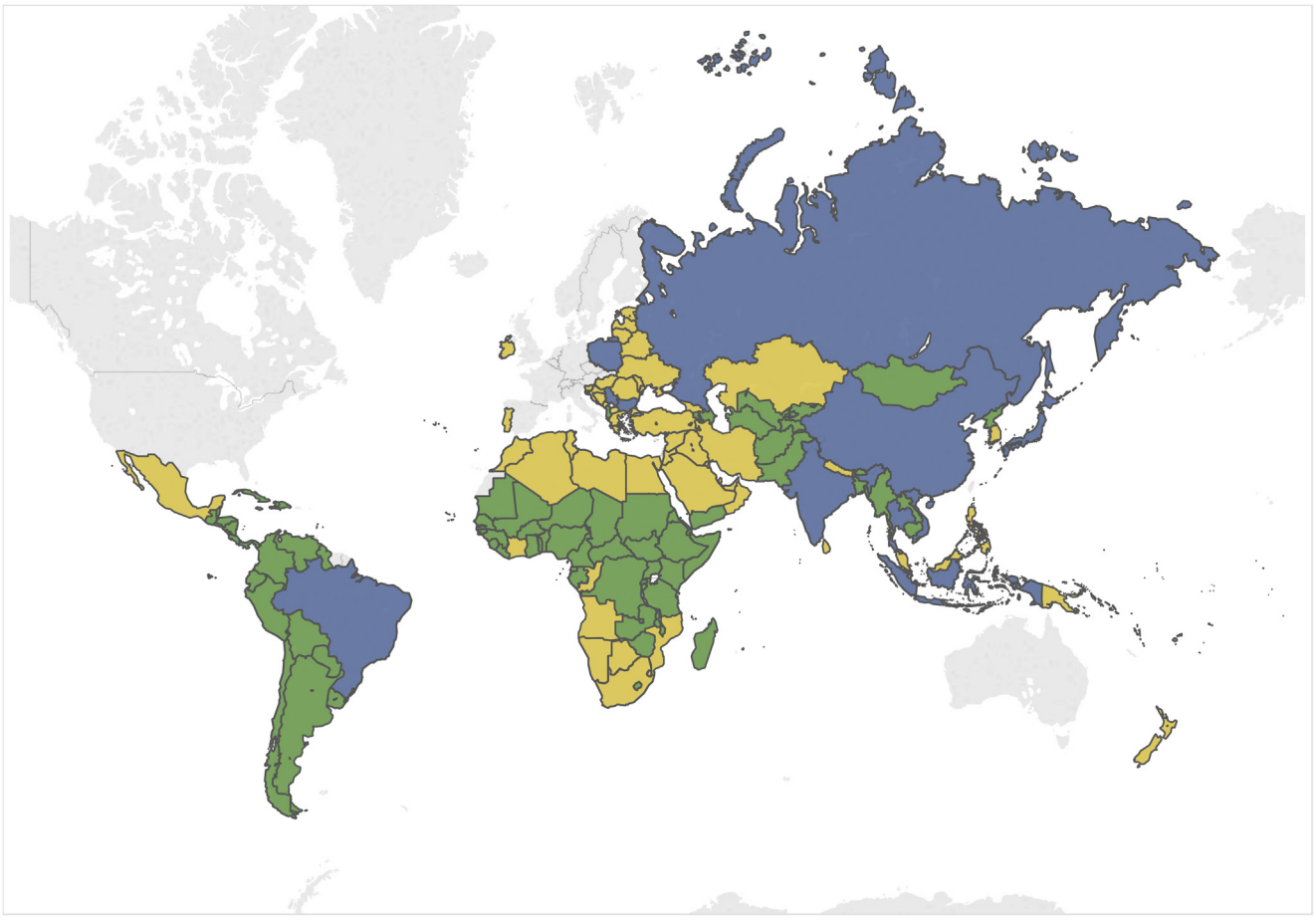


Fig. 4. Reported country BCG procurement and production. (For reference, the 2017 birth cohort of self-producing countries is 55.3 million [21].)

None of these countries use BCG vaccine in their EPI schedule and could procure with a temporary import license to address needs. While some risk remains, there are certainly more resources and established processes to access information and more quickly address supply needs than in lower-income countries.

4. Discussion

4.1. Historical procurement and estimated demand

Results of demand analysis show 2016 country-reported procurement is 1.5 times greater than 2017 forecasted demand. Several hypotheses have been formulated on the potential drivers; one of these is that actual wastage may be higher than 50 percent based on recent information on country immunization sessions.[21] Other possible explanations: countries may be holding stocks larger than the recommended buffer, reported country data may also be including uses beyond prevention of tuberculosis (e.g., oncology).

4.2. Global demand-supply balance

In 2017, available supply of BCG vaccine (~500 M doses) is forecasted to be 1.5 times greater than forecasted demand (~350 M doses) and countries are not reporting supply access issues.

Despite the manufacturer exits of the past 20 years, BCG vaccine has an unusually large number of suppliers, if we consider that most of the currently produced vaccines count on low (single-digit) numbers of producers. This large supplier base is the result of a simple production process that has allowed several countries to maintain production for self-sufficiency. Also, given the low economic attractiveness of the BCG vaccine market, small manufacturers have been able to survive longer and no consolidation efforts from larger producers are noted.

Unfortunately, this large supply base has been very unstable: as a result of the outdated production processes and limited investments, manufacturing issues, often quality and GMP related, have

[21] Also, a recent analysis of the use of 20-dose vials of BCG vaccine in Guinea-Bissau indicates that only 13 to 15 doses can be withdrawn from this very common presentation, leading to a larger need than usually forecasted [43].

Table 1
Current BCG vaccine manufacturers (March 2017).[a]

Manufacturer	Country	Strain	Supplying beyond domestic market	PQ Status	Releasing NRA functionality	Vial size	Route of administration	Supplying in 2017
ANLIS	Argentina	Pasteur 1173 P2 strain	N	N	N	10ds/ 20ds	Unknown	Y
Fundação Ataulpho de Paiva	Brazil	Moreau, Rio strain	Y	N	Y	10ds	Unknown	N
BulBio-NCIPD[b]	Bulgaria	Bulgarian substrain (Sofia) SL222	Y	Y	Y	10ds/ 20ds	Intradermal	Y
China National Biotec Group (Shanghai)	China	Chinese substrain Shanghai D2PB302 (derived from Danish strain 823)	Y	N	Y	5ds	Intradermal	Y
China National Biotec Group (Chengdu)	China	Chinese substrain Shanghai D2PB302 (derived from Danish strain 823)	Y	N	Y	5ds	Intradermal	Y
Shaanxi Pharmaceutical Holding Group	China	Chinese substrain Shanghai D2PB302 (derived from Danish strain 823)	N	N	Y	20ds	Unknown	Y
AJ Biologics	Denmark	Danish 1331 strain	Y	Y	Y	10ds/ 20ds	Intradermal	N
Serum Institute of India	India	Russian (Moscow) – 368	Y	Y	Y	10ds/ 20ds	Intradermal	Y
Green Signal Biopharma	India	Danish 1331 strain	Y	Y	Y	20ds	Intradermal	Y
BCG Vaccine Laboratory, Chennai	India	Danish 1331 strain, Madras Working Seed Lot (MWSL)	Y	N	Y	10ds/ 20ds	Intradermal	N
Taj Pharma Ltd	India	Russian (Moscow) – 368	N	N	Y	20ds	Unknown	Y
BioFarma	Indonesia	Pasteur 1173P strain	Y	N	Y	5ds/ 10ds	Intradermal	Y
Pasteur Institute of Iran	Iran	Pasteur 1173P2 strain	N	N	Y	20ds	Intradermal	Y
Japan BCG Laboratory (JBL)	Japan	Tokyo 172-1 strain	Y	Y	Y	10ds/ 20ds	Intradermal/ percutaneous (multipuncture device)	Y
Biomed Lublin	Poland	Moreau strain	Y	N	Y	10ds	Intracutaneous	Y
Microgen	Russia	Russian (Moscow) – 368	Y	N	Y	10ds/ 20ds	Intradermal	Y
Inst. Of Virology, Vaccines and Sera Torlak	Serbia	Pasteur 1173P2 strain	Y	N	N	10ds/ 20ds	Intradermal	Y
NIIDV	Taiwan	Tokyo 172 strain	N	N	Y	20ds	Intradermal	Y
Queen Saovabha Mem. Inst (Thai Red Cross)	Thailand	Japanese strain	N	N	Y	10ds	Intradermal	Y
Inst. Pasteur Tunis	Tunisia	Pasteur 1173P2 strain	N	N	Y	20ds	Intradermal	Y
Merck & Co (former Organon)	United States	TICE strain	N	N	Y	1ds	Percutaneous (multipuncture device)	Y
IVAC – Institute of Vaccines and Medical Biologicals	Vietnam	Pasteur 1173P2 strain	N	N	Y	20ds	Unknown	Y

[a] Compiled with the help of PAHO Revolving Fund, International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) and Developing Countries Vaccine Manufacturers Network (DCVMN), as well as through a review of published literature [12,28–33], UNICEF Supply Division market updates [13], and internal reports from the Bill & Melinda Gates Foundation (BMGF) and Clinton Health Access Initiative (CHAI).
[b] BulBio vaccine is also distributed by InterVax.

forced manufacturers to frequently suspend production or exit the market.

Given the instability of the BCG vaccine manufacturing process, this extra supply is sufficiently reassuring and shows important progress relative to the bleaker supply/demand balance of recent years.

4.3. Risk identification

Despite some progress, the BCG vaccine market is not risk free; this analysis identified several issues of concern around access to BCG vaccine supply.

First, two suppliers continue to represent more than half of global vaccine supply and, importantly, 75 percent of supply PQ'd by WHO. The complete loss of a major supplier will not automatically lead to a supply/demand imbalance, but it will certainly create a situation of constrained supply, requiring tight and careful management. In such a circumstance, since those large suppliers are critical both to self-procuring countries and countries procuring through UNICEF, it will be necessary to carefully manage information sharing and supply allocations across these two groups.

Second, results show a large dependency on one NRA: the two largest BCG vaccine suppliers are currently released by the same NRA (India). While WHO currently deems this NRA functional, this situation should not be overlooked. The return to market of AJ Biologics in the near future could reduce this risk.

Third, countries with only one product registered that do not accept the collaborative procedure between WHO and NRAs for PQ'd products present an issue; these tend to be middle- and upper-income countries. For these countries, a production issue by the only manufacturing source could easily lead to a shortage. Similarly, the higher-income countries with one or no product registered that also do not recommend use of BCG may face challenges in obtaining larger BCG supply to vaccinate migrants from high TB-burden countries. Countries for which concern is higher are those where the BCG vaccine is in the EPI schedule and thus have the lar-

gest demand — in particular, those countries that import products and do not have much visibility on possible production issues — as well as large countries that have less flexibility in coping with shortages through small shipment sizes and stock management.

These identified threats to sustainable access to BCG vaccine supply are important, considering the historical record of BCG vaccine manufacturing issues. Despite some recent small investments in manufacturing aimed at addressing continued GMP issues, it is not evident that production issues will be less likely in the future. Similarly, given the low economic attractiveness of the BCG vaccine market, the risk of further manufacturer exit remains, particularly in light of the apparent abundance of supply.

Finally, while a systematic review of published trials did not find differences in protection against TB between different strains of BCG [38], there is currently no consensus on this issue and further studies are warranted [39–41]. Results from such studies, as well as evolution of the BCG vaccine pipeline, would certainly influence supply and demand dynamics. A close and continuous monitoring of those studies is warranted to ensure that policies and procurement practices allow sufficient time for supply adjustments.

4.4. Opportunities for action

The identified risks also represent valuable opportunities. As consultations with manufacturers, immunization agencies and countries were carried out, it became apparent that global information collection and sharing could help to address and sometimes prevent some issues, such as countries lacking information on the potential capacity to address imminent shortages, or foreseeing the possible impact of supply constraints on a particular group of countries.

A few key investments can also be explored based on identified risks: (i) offering financial/other incentives for strengthening production processes, thus enhancing the overall stability of supply and (ii) creating a 'BCG vaccine registration fund' encouraging manufacturers to register products in more locations despite regulatory burden – in the context of longer term efforts to harmonize registration requirements among countries.

One final consideration: the analysis shows that historical demand seems to be much larger than what would be forecasted based on available information on target population, coverage and wastage rates. While this deserves further study – particularly on actual wastage rate – it is possible that some countries could reduce stock levels and improve forecasting and procurement to reduce demand to what is strictly necessary. This could also enhance use of scarce national resources for immunization.

Activities could possibly target specific regions (such the African region) or income groups (LICs and LMICs) which have suffered the most from access issues for this vaccine.

4.5. Limitations of study

Some limitations to this analysis should be highlighted. Firstly, while stock-outs remain the most useful information currently available to measure shortages, they can be caused by a range of issues (e.g., supply shortages, but also financing delays, inaccurate forecasting and inefficient stock management or procurement). Furthermore, supply shortages do not always lead to stock-outs.[22] Secondly, supply data are fully relying on manufacturers' input and have not been validated through other independent sources nor facility assessments. Thirdly, product licensure information has not been validated with each country, with a risk of information being incomplete. Finally, country-reported data through the WHO/UNICEF JRF was heavily leveraged for the analysis: data quality varies, particularly in relation to historical procurement, but remains the only available data at present.

[22] A country could have sufficient in-country stock to continue vaccinating during the shortage period.

5. Conclusion

The BCG vaccine market experienced several national stock-outs over the past decade across all regions, income groups and procurement methods. While the frequency has remained rather stable, duration of stock-outs increased in 2014–2015 due to manufacturing issues and attracted the attention of national, regional and global immunization stakeholders. This analysis shows an important increase in global capacity in 2017, with sufficient supply to meet forecasted BCG vaccine demand and possibly buffer market shocks. However, risks remain that are related to supply concentration and limited demand flexibility in a market characterized by high instability and low investment. Through a collaboration among immunization partners, various avenues can be explored to address identified risks, particularly by enhancing information sharing, working with countries to improve vaccine management, and working with manufacturers and donors to understand options to tackle production risks and registration issues.

Acknowledgements

The authors would like to acknowledge Dana Armstrong for proofreading the article, and Thomas Cherian, Heather Deehan, Philippe Duclos, Laure Dumolard, Malin Finkernagel, Gian Gandhi, Laura Gillini, Andrew Jones, Alireza Khadem Broojerdi, Ivana Knezevic, Souleymane Kone, Patrick Lydon, Drew Meek, Sonia Pagliusi, Monica Pereira, P.V. Ranganadha Rao, Daniel Rodriguez, Carmen Rodriguez Hernandez and Robin Schofield for useful input and discussions during the analysis period. Finally, countries, WHO regional offices and vaccine manufacturers that have shared important information for this analysis should also be acknowledged for their collaboration.

Funding sources

This publication is based on research funded in part by the Bill & Melinda Gates Foundation. The findings and conclusions contained within are those of the authors and do not necessarily reflect positions or policies of the Bill & Melinda Gates Foundation.

Conflict of interest

All authors declare no conflict of interest.

References

[1] World Health Organization. Global Tuberculosis Report. WHO. <http://www.who.int/tb/publications/global_report/en/>; 2016.
[2] Abubakar I, Pimpin L, Ariti C, Beynon R, Mangtani P, Sterne J, et al. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette–Guérin vaccination against tuberculosis. Heal Technol Assess 2013;17:1–372. https://doi.org/10.3310/hta17370.
[3] Mangtani P, Nguipdop-Djomo P, Keogh RH, Trinder L, Smith PG, Fine PE, et al. Observational study to estimate the changes in the effectiveness of bacillus Calmette-Guérin (BCG) vaccination with time since vaccination for preventing tuberculosis in the UK. Health Technol Assess (Rockv) 2017;21:1–54. https://doi.org/10.3310/hta21390.
[4] World Health Organization. BCG Vaccine: WHO position paper. Wkly Epidemiol Rec 2004;79:27–38.
[5] World Health Organization. WHO Expert Committee on Leprosy: eighth report. vol. 968. Geneva; 2012.

[6] World Health Organization. Global leprosy update, 2015: time for action, accountability and inclusion. Wkly Epidemiol Rec 2016;91:405–20.
[7] Zimmermann and Curtis et al. Does BCG vaccination protect against non-tuberculous mycobacterial infection? Parkville, Australia; 2017.
[8] Zwerling A, Behr MA, Verma A, Brewer TF, Menzies D, Pai M. The BCG world atlas: a database of global BCG vaccination policies and practices. PLoS Med 2011;8:e1001012. https://doi.org/10.1371/journal.pmed.1001012.
[9] WHO/UNICEF. Joint Reporting Form (JRF). <http://www.who.int/immunization/monitoring_surveillance/data/en/>; 2016.
[10] Seki M, Honda I, Fujita I, Yano I, Yamamoto S, Koyama A. Whole genome sequence analysis of Mycobacterium bovis bacillus Calmette-Guérin (BCG) Tokyo 172: a comparative study of BCG vaccine substrains. Vaccine 2009;27:1710–6. https://doi.org/10.1016/j.vaccine.2009.01.034.
[11] Abdallah AM, Hill-Cawthorne GA, Otto TD, Coll F, Guerra-Assunção JA, Gao G, et al. Genomic expression catalogue of a global collection of BCG vaccine strains show evidence for highly diverged metabolic and cell-wall adaptations. Sci Rep 2015;5:15443. https://doi.org/10.1038/srep15443.
[12] Ritz N, Curtis N. Mapping the global use of different BCG vaccine strains. Tuberculosis 2009;89:248–51. https://doi.org/10.1016/j.tube.2009.03.002.
[13] UNICEF Supply Division. Bacillus calmette-guérin vaccine supply & demand outlook. <https://www.unicef.org/supply/files/BCG_Supply_Status_December_2015.pdf>; 2015.
[14] Statens Serum Institut. AJ Biologics agrees to acquire SSI vaccine production business from the Danish state. http://www.ssi.dk/~/media/Indhold/EN - engelsk/News/Saturn press release_1 June 2016 UK.ashx; 2016 [accessed February 28, 2017].
[15] Romania Insider. Romanian vaccine producer Cantacuzino Institute on the verge of collapse, employees demand manager's dismissal. Romania-Insider.com. <http://www.romania-insider.com/romanian-vaccine-producer-cantacuzino-institute-on-the-verge-of-collapse-employees-demand-managers-dismissal/>; 2012 [accessed February 28, 2017].
[16] Statens Serum Institut. Statens Serum Institut has procured a tuberculosis vaccine from Japan. <http://www.ssi.dk/English/News/News/2016/2016 - 01 - EPI-NEWS 4 BCG vaccine Japan.aspx>; Febr 3, 2017 n.d. [accessed February 28, 2017].
[17] World Health Organization. WHO prequalified vaccines – BCG vaccine (Freeze Dried) – Intradermal. <https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=294&AspxAutoDetectCookieSupport=1>; 2017 [accessed April 14, 2017].
[18] American Society of Health-System Pharmacists. BCG Vaccine Live Intravesical. <https://www.ashp.org/Drug-Shortages/Current-Shortages/Drug-Shortage-Detail.aspx?id=915>; 2016 [accessed February 28, 2017].
[19] Pharmafile. Dutch government sells off vaccine facility. <http://www.pharmafile.com/news/149629/netherlands-vaccine-institute-bilthoven-sale>; 2011 [accessed February 28, 2017].
[20] Governo do Brasil. Anvisa suspende fabricação de vacinas BCG e Imuno BCG. Portal Bras. <http://www.brasil.gov.br/saude/2016/12/anvisa-suspende-fabricacao-de-vacinas-bcg-e-imuno-bcg>; 2016 [accessed February 28, 2017].
[21] UN Population Division (UNPD). World population prospects. <https://esa.un.org/unpd/wpp/>; 2015.
[22] Linksbridge SPC. Global vaccine market model (GVMM) demand module. 2017.
[23] UNICEF Supply Division. Total number of doses (Millions doses) for each vaccine procured by year for 1996–2015. <https://www.unicef.org/supply/files/Table_of_Vaccine_Procurement_1996__2015_Volume.pdf>; 2016.
[24] World Health Organization Regional Office for South East Asia. Global leprosy strategy 2016–2020: accelerating towards a leprosy-free world – 2016 operational manual. New Delhi; 2016.
[25] Government of Canada. Admissions of permanent residents by country of citizenship. Perm Resid – Mon IRCC Updat – Open Gov Portal. <http://open.canada.ca/data/en/dataset/f7e5498e-0ad8-4417-85c9-9b8aff9b9eda?_ga=2.175751589.622797135.1508266615-1491582383.1508266615>; 2017 [accessed October 17, 2017].
[26] Eurostat. Asylum statistics. <http://ec.europa.eu/eurostat/statistics-explained/index.php/Asylum_statistics>; 2017 [accessed October 4, 2017].
[27] UNHCR. UNHCR Global Report – Regional Summaries: Europe; 2016.
[28] Luca S, Mihaescu T. History of BCG vaccine. Maedica (Buchar) 2013;8:53–8.
[29] Joung SM, Ryoo S. BCG vaccine in Korea. Clin Exp Vaccine Res 2013;2:83–91. https://doi.org/10.7774/cevr.2013.2.2.83.
[30] Orduña P, Cevallos MA, de León SP, Arvizu A, Hernández-González IL, Mendoza-Hernández G, et al. Genomic and proteomic analyses of Mycobacterium bovis BCG Mexico 1931 reveal a diverse immunogenic repertoire against tuberculosis infection. BMC Genomics 2011;12:493. https://doi.org/10.1186/1471-2164-12-493.
[31] Yamamoto S, Yamamoto T. Historical review of BCG vaccine in Japan. Jpn J Infect Dis 2007;60:331–6.
[32] Stefanova T, Chouchkova M, Hinds J, Butcher PD, Inwald J, Dale J, et al. Genetic composition of Mycobacterium bovis BCG substrain Sofia. J Clin Microbiol 2003;41:5349. https://doi.org/10.1128/JCM.41.11.5349.2003.
[33] Voronina OL, Kunda MS, Aksenova EI, Semenov AN, Ryzhova NN, Lunin VG, et al. Mosaic structure of Mycobacterium bovis BCG genomes as a representation of phage sequences' mobility. BMC Genomics 2016;17:1009. https://doi.org/10.1186/s12864-016-3355-1.
[34] World Health Organization. Revised procedure for expedited review of imported prequalified vaccines for use in national immunization programmes. WHO. <http://www.who.int/immunization_standards/vaccine_quality/expedited_review/en/>; 2015 [accessed October 17, 2017].
[35] World Health Organization, UNICEF Supply Division. Guidance on how to prioritize globally constrained BCG vaccine supply to countries. <http://www.who.int/immunization/diseases/tuberculosis/BCG-country-prioritization.pdf>; 2015.
[36] PAHO Revolving Fund. Vaccine prices for 2017. <http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&gid=38122&Itemid=270&lang=en>; 2017.
[37] UNICEF Supply Division. BCG vaccine price data. 2015.
[38] Mangtani P, Abubakar I, Ariti C, Beynon R, Pimpin L, Fine PEM, et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. Clin Infect Dis 2014;58:470–80. https://doi.org/10.1093/cid/cit790.
[39] Favorov M, Ali M, Tursunbayeva A, Aitmagambetova I, Kilgore P, Ismailov S, et al. Comparative tuberculosis (TB) prevention effectiveness in children of bacillus calmette-guérin (BCG) vaccines from different sources, Kazakhstan. PLoS One 2012;7:e32567. https://doi.org/10.1371/journal.pone.0032567.
[40] Shann F. Editorial commentary: different strains of bacillus calmette-guérin vaccine have very different effects on tuberculosis and on unrelated infections. Clin Infect Dis 2015;61:960–2. https://doi.org/10.1093/cid/civ454.
[41] Comstock GW. Simple, practical ways to assess the protective efficacy of a new tuberculosis vaccine. Clin Infect Dis 2000;30. https://doi.org/10.1086/313870.
[42] Lydon P, Gasca A, Dumolard L, Urfer D, Senouci K. Vaccine stockouts around the world: are essential vaccines always available when needed? Vaccine 2017;35:2121–6. https://doi.org/10.1016/j.vaccine.2016.12.071.
[43] Schaltz-Buchholzer F, Frankel HN, Benn CS. The real-life number of neonatal doses of Bacille Calmette-Guérin vaccine in a 20-dose vial. Glob Health Action 2017;10:1267964. https://doi.org/10.1080/16549716.2017.1267964.

Potential health and economic impact of paediatric vaccination using next generation influenza vaccines in Kenya: a modelling study

Authors: Naomi R Waterlow[1,*], Sreejith Radhakrishnan[1], Jeanette Dawa[2,3], Edwin van Leeuwen[1,4], Philipp Lambach[5], Joseph Bresee[6], Marie Mazur[7], Rosalind M Eggo[1], Mark Jit[1]

[1] Centre for Mathematical Modeling of Infectious Disease, London School of Hygiene and Tropical Medicine, London WC14 7HT, United Kingdom

[2] Center for Epidemiological Modelling and Analysis, University of Nairobi, Nairobi, Kenya

[3] Washington State University - Global Health Kenya, Nairobi, Kenya

[4] Statistics, Modelling and Economics Department, UK Health Security Agency, London NW9 5EQ, United Kingdom

[5] Immunization Vaccines and Biologicals Department, World Health Organization, Geneva, Switzerland

[6]The Task Force for Global Health, Decatur, GA, USA

[7]Ready2Respond c/o Taskforce for Global Health, Decatur, GA, USA

[*]corresponding author. naomi.waterlow1@lshtm.ac.uk

Abstract:

Background: Influenza is a major year-round cause of respiratory illness in Kenya, particularly in children under 5. Current influenza vaccines result in short-term, strain-specific immunity and were found in a previous study not to be cost-effective in Kenya. However, next generation vaccines are in development that may have a greater impact and cost-effectiveness profile.

Methods: We expanded a model previously used to evaluate cost-effectiveness of seasonal influenza vaccines in Kenya to include next generation vaccines by allowing for enhanced vaccine characteristics and multi-annual immunity. We specifically examined vaccinating children under 5 years of age with improved vaccines, evaluating vaccines with combinations of increased vaccine effectiveness, cross protection between strains (breadth) and duration of immunity. We evaluated cost-effectiveness using incremental cost-effectiveness ratios (ICERs) and incremental net monetary benefits (INMBs) for a range of values for the willingness-to-pay (WTP) per DALY averted. Finally, we estimated threshold per-dose vaccine prices at which vaccination becomes cost-effective.

Results: Next generation vaccines can be cost-effective, dependent on the vaccine characteristics and assumed WTP thresholds. Universal vaccines (assumed to provide long-term and broad immunity) are most cost-effective in Kenya across three of four WTP thresholds evaluated, with the lowest median value of ICER per DALY averted ($263, 95% Credible Interval (CrI): $-1698, $1061) and the highest median INMBs. At a WTP of $623, universal vaccines are cost-effective at or below a median price of $5.16 per dose (95% CrI: $0.94, $18.57). We also show that the assumed mechanism underlying infection-derived immunity strongly impacts vaccine outcomes.

Conclusion: This evaluation provides evidence for country-level decision makers about future next generation vaccine introduction, as well as global research funders about the potential market for these vaccines. Next generation vaccines may offer a cost-effective intervention to reduce influenza burden in low-income countries with year-round seasonality like Kenya.

Keywords: influenza; vaccination; cost-effectiveness; mathematical modelling; next-generation vaccines; health economics

Background

Influenza is a major cause of respiratory illness in Kenya, particularly in children under 5 years old (1,2). Current influenza vaccines result in short-term, strain-specific immunity (3) which is particularly problematic in tropical and subtropical settings where multiple peaks and identifiable year-round activity make it challenging to decide if, who and when to vaccinate, as well as which formulation (northern or southern hemisphere) to use (4–7). Existing vaccines have been evaluated for cost-effectiveness in Kenya, looking at the potential impact of vaccinations in 2010 to 2018 (2). This analysis showed that vaccinating children in Kenya with currently available vaccines was not cost-effective, given current willingness-to-pay thresholds (2). Barriers to cost-effectiveness of influenza vaccination include inconsistent seasonality (with high burden across the year in some years), multiple subtypes of influenza, varying vaccine effectiveness depending on match to circulating influenza strains and the need for annual revaccination(8).

Many of these obstacles could be addressed by next generation vaccines on the near horizon, with 18 vaccines in clinical trials (10 in phase I, 6 in phase II and 2 in phase III trials), and over 100 in preclinical trials (9,10). Newer technologies are being trialled, for example mRNA vaccines and self-assembling nano-particles, and many of these vaccines aim to overcome the immunodominance of the haemagglutinin (HA) head, instead focusing on more conserved proteins across influenza strains and often aiming to stimulate a T-cell response (9).

The World Health Organisation (WHO) Preferred Product Characteristics (PPC) (11) describes next generation influenza vaccines in two categories: improved vaccines, which have increased vaccine efficacy (VE) or strain cross-protection (breadth) and which generate immune protection lasting at least a year; and universal vaccines, which have increased efficacy against influenza A phylogenetic HA group viruses and which generate immune

protection lasting at least 5 years.These descriptions are based on the likelihood of development in the near to mid future. The US National Institute of Allergy and Infectious Diseases (NIAID) uses similar but slightly varying definitions (12). Such next generation vaccines may hold promising benefits for countries like Kenya, but their potential population impact and cost-effectiveness have yet to be evaluated. Such evaluations could inform country-level decision makers about potential future vaccine introduction, as well as global research funders about the potential market for these vaccines.

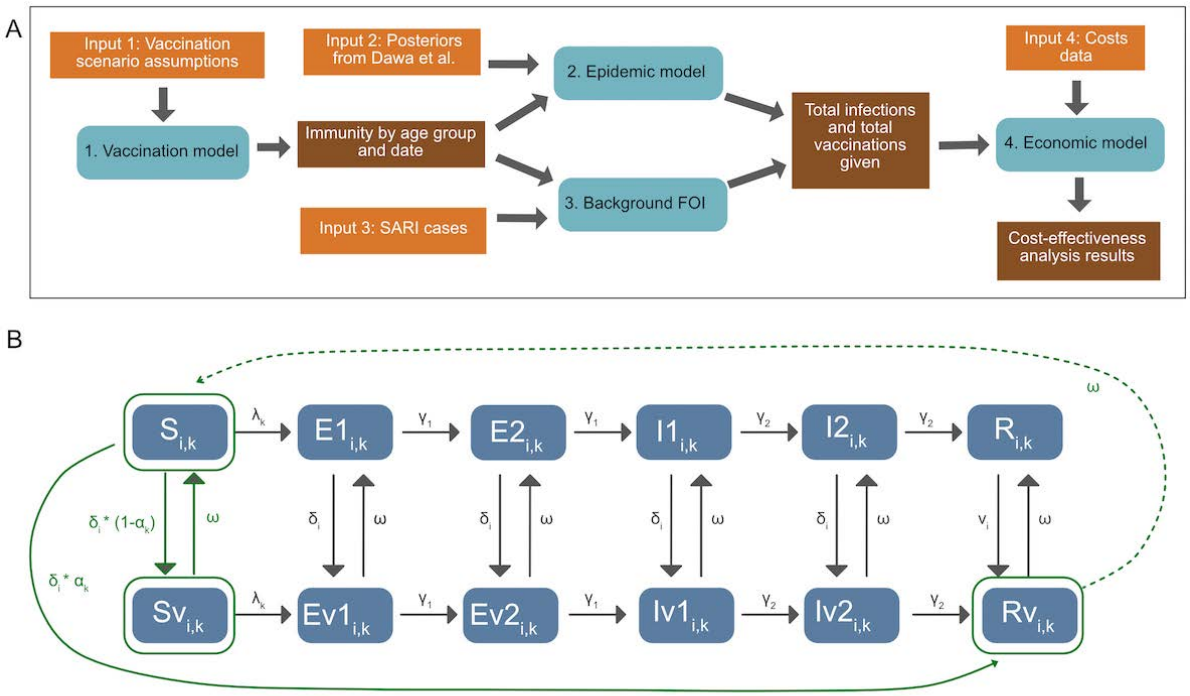
Mathematical models are ideal tools for evaluating their cost-effectiveness, as they allow analysis and comparison of potential hypothetical interventions and strategies. Specifically, transmission dynamic models have the additional advantage of including both direct and indirect benefits of vaccination. This allows evaluation of optimal control strategies including coverage and timing of vaccination campaigns and vaccine characteristics,such as subtype broadness vs efficacy considerations.

We expand the model previously used to evaluate cost-effectiveness of current influenza seasonal vaccines in Kenya to evaluate the cost-effectiveness of next generation vaccines.

Methods

Overview

We utilise a transmission model from Baguelin *et al.* (2013) (13) that was fitted to Kenya severe acute respiratory illness (SARI) data from 2010 - 2018 by Dawa *et al.* (2013) (2) and extend it to include next generation influenza vaccines with longer durations of immunity, higher efficacy and/or broader sub-type cross-protection (Figure 1). Code is available at https://github.com/NaomiWaterlow/NextGenFlu_Kenya



105

106

107 *Figure 1 - Modelling overview: A) Methods overview, depicting inputs, models and outputs.*
108 *B) Model diagram, including both the epidemic and the vaccination model. Elements in solid*
109 *green are included in both models. Transitions in grey are included only in the epidemic*
110 *model, and transitions in dotted green are included only in the vaccination model. States are:*
111 *Susceptible (S), Exposed (E), Infectious (I) and Recovered (R), and their vaccinated*
112 *counterparts (Sv, Ev1, Ev2, Iv1, Iv2, Rv). v denotes the vaccinated equivalent of the*
113 *compartments. See Table S3 for parameter details.* δ *is the rate of vaccination in age group*
114 i, α *is the efficacy by subtype (*k*),* ω *is vaccine derived immunity waning. The model is run*
115 *separately for each subtype. For the epidemic model, in both vaccinated and unvaccinated*
116 *compartments, susceptibles who are infected with the viral subtype enter the first Exposed*
117 *(E) compartment. They then progress through the E and Infectious (I) compartments. After*
118 *ceasing to be infectious they enter the R compartment, whereupon they cannot be re-*
119 *infected during the same epidemic period. Both the E and I populations consist of two*

compartments, in order to get a gamma distributed waiting time. Each compartment is also subdivided by age (i).

Model 1 - Vaccination model

The vaccination model (Figure 1B - green compartments) tracks the dynamics of vaccine-induced immunity for each virus subtype without considering prior infection or vaccination status. This is a conservative assumption, assuming vaccination status in the population is unknown and hence people are vaccinated independent of whether they were recently infected or vaccinated. At the time of vaccination the population can be in 1 of 3 compartments: Susceptible (*S*), Susceptible-vaccinated (*Sv*) and Recovered-vaccinated (*Rv*) (Figure 1A, green). Vaccination is assumed to be all-or-nothing, with a proportion defined by the efficacy for each subtype entering the *Rv* compartment where they are immune, and the inverse proportion entering the *Sv* compartment, where they are susceptible. Waning of vaccination from compartments *Sv* and *Rv* occurs exponentially at a rate, ω, determined by the duration of vaccine-induced immunity, returning the population to the *Sv* compartment.

We consider scenarios where vaccines have characteristics matching either currently available seasonal influenza vaccines, or next generation vaccines in line with WHO Preferred Product Characteristics (11) (input 1). In the first year, all 0-5 year olds are vaccinated across all vaccine scenarios. Following this, vaccination occurs every x years, calculated as a proportion of the age group, where x is the mean duration of vaccine derived immunity. We generate 5 vaccine scenario examples, corresponding to four categories of Preferred Product Characteristics: current seasonal vaccines, minimally improved vaccines, improved efficacy vaccines, improved breadth vaccines, and universal vaccines (Table 1). We consider vaccines to be either ‘matched’ or ‘mis-matched’ to circulating strains each season, and a different efficacy is given in these cases (see supplement for more details).

Table 1: Illustrative vaccine scenarios. "Mis-matched seasons" refers to the possibility that the vaccine is not well matched to a particular season's influenza strain and therefore has reduced efficacy. Immunity duration is assumed to be exponential. All vaccines are given as a campaign, across March, April and May.

Scenario name	**Mis-matched seasons?**	**Efficacy (Matched/Mis-matched)**	**Immunity Duration**	**Coverage**	**Age-groups vaccinated**
No Vaccine	-	-	-	-	-
Current Seasonal Vaccines	Yes	70% / 40%	6 months	50%	All 0-5
Improved vaccines (Minimal)	Yes	70% / 40%	1 year	50%	All 0-5
Improved Vaccines (Efficacy)	Yes	90% / 70%	2 years	50%	All individuals aged 0-5 in the first year of vaccination, followed by age 0, 2 and 4 in subsequent years
Improved Vaccines (Breadth)	No	70% / 70%	3 years	50%	All individuals aged 0-5 in the first year of vaccination, followed by age 0, 2 and 4 in subsequent years
Universal Vaccines	No	90% / 90%	5 years	50%	All individuals aged 0-5 in the first year of

					vaccination, followed by age 0 and 5

We also run sensitivity analyses where vaccination coverage is 75% for all vaccines, allowing for higher uptake upon new vaccine development (Supplement Section 9).

We run the model from 1 March 2010, where 1 March each year is considered the start of the southern hemisphere (SH) influenza season. The model runs with given inputs until 31 August, as we define 1 September as the start of the Northern Hemisphere (NH) influenza season. VE can differ between seasons to take account of vaccine matched or mis-matched strains. As in Dawa *et al*. (2020) we identify each season's strain as matched or mis-matched to vaccination based on published VE data (Table S1) and assume that a VE >= 50% is a matched vaccine, and < 50% is a mis-matched vaccine. Following the NH season, the population size is updated (see Supplement section 1), and ageing of the population occurs, to allow for a build up of immunity in the relevant age groups. The model runs from 1 March 2010 to 28 February 2019. We model transmission of each influenza subtype separately (A(H1N1), A(H3N2), B) to allow different vaccine efficacies across subtypes. We assume all individuals are born susceptible to infection.

This vaccination model outputs the proportion of the population that is vaccinated, and of this the proportion that is immunised for each subtype every week over the modelled period.

Model 2 - Epidemic Model

We model the 11 subtype-specific epidemic time periods that were identified and fitted in Dawa *et al*. (2020) (Figure 2A). As in Dawa *et al*. (2020) we define influenza epidemics to start at the first week of a time period consisting of "≥2 successive weeks where the

proportion of subtype-specific test-positive cases was greater than the average weekly proportion during the entire study" (Figure 2A). Where an epidemic was previously defined to last less than 8 months, we follow it for the full 8 months to allow capturing the consequences of a slower epidemic progression as the result of vaccination. At the start of each epidemic the proportion of the population in the *S*, *Sv* and *Rv* compartments is taken from the output of the vaccination model, in the matching week and for the relevant virus subtype.Vaccine efficacy is split into NH and SH time frames as in the vaccination model. For each epidemic we run an independent transmission model (with structure of Figure 1B) with the estimated transmission rate, susceptibility for three age groups (<= 14, 15-49, 50+), initial number of infections and the probability of identifying an influenza-positive patient within the catchment population for 3 age groups (<1, 1-5, 6+) from Dawa *et al*. (2020). Influenza immunity is assumed to be leaky. Supplement section 2 contains the model equations, parameters and values.

For key transmission parameters (transmission rate, susceptibility, number of infections at the start of the season, number of imports and ascertainment rates), we use the estimated values by Dawa *et al*. 2020 for each of the 11 strain/subtype-specific peaks in influenza activity identified between 2010 - 2018 (input 2). The parameter values for each strain/subtype-specific peak are estimated independently, using the *fluEvidenceSynthesis* R package. We also use the same age groups ($<$ 1, 1–5, 6–14, 15–19, 20–49 and $\geq$ 50 years old) contact patterns and population sizes. For more details see Dawa ***et al.*** (2020) .

In our main analysis we assume that the previous season's vaccination has no effect on the proportion of people who have infection-derived immunity at the start of the next season. This is supported by statistical analyses indicating that susceptibility at the start of each

season (based on the model fit in Dawa *et al*. (2020)) is not strongly dependent on infections in the previous season (Supplement section 4). To explore the possibility that there is some dependency, we run sensitivity analyses with two different assumptions on changes in susceptibility (Supplement section 9).

Model 3 - Background FOI

To characterise influenza epidemiology in Kenya, we use weekly numbers of hospitalised patients with SARI from 2010-2018 from the Kenyan National SARI surveillance system (input 3). Data from a subset of 5 large hospitals that have a bed capacity of over 200 and a well-established surveillance system in place is used. The case definition of SARI was a hospitalised patient with acute illness onset presenting with fever or cough. A random sample of these patients underwent virological analysis to identify the presence or absence of influenza. For further details and data access, see Dawa *et al*. (2020).

To account for infections in the inter-epidemic periods, we include a background rate of infection with a Poisson distribution with shape parameter $\Lambda_{i,k}$, fitted to the weekly observed cases in each age group and of each subtype across all inter-epidemic periods. We then calculate the weekly number of background infections per age group, i, and subtype, k, across the whole time period:

$$Background\ Infections_{t,i,k} = \sum_{i=1}^{n=6} \Lambda_{i,k} * (sus_{t,i,k}/asc_{i,k})$$

Where $sus_{t,i,k}$ is the proportion susceptible each week (t) for age group i and influenza subtype s outputted from the vaccination model, $asc_{i,k}$ is the mean ascertainment rate by age group as estimated in the Dawa *et al.* (2020) paper.

Model 4 - Economic analyses

We estimate the incremental cost-effectiveness of each of the vaccine scenarios in Table 1 (compared to no vaccination), following WHO recommendations for economic evaluations of vaccines (14). The analytic time horizon used in the economic analyses is the same as the epidemiological model (2010-2019 inclusive), except that life years lost due to death are counted until the full normal life expectancy. Information on input costs used in these analyses (input 4) can be found in the Supplement section 8. We adopt a societal perspective on costs, and both costs and health outcomes are discounted at 3% per annum, with 0% discounting for health outcomes in a sensitivity analysis. All costs (except vaccine costs) are expressed in terms of 2019 USD and costs from other years are adjusted using Kenya gross domestic product (GDP) deflator values (15) before calculating cost-effectiveness measures.

Uncertainty is captured using probabilistic sensitivity analysis. This is done by drawing 1000 random samples per vaccine scenario of the total number of influenza infections generated from 2010 to 2019 by all virus subtypes across all age groups and charting disease and hospitalisation outcomes for each infection. Adopting the same approach as Dawa *et al.* (2020), we use a decision tree (Supplement section 8) to project health-related outcomes associated with influenza infections. Samples of probability parameters are drawn from a beta distribution (16) whose shape parameters were calculated first by fitting the mean and 95% confidence intervals for each probability parameter (drawn from the literature) to a beta distribution (2).

We further divide symptomatic infections into mild (upper respiratory tract infections, URTI) or severe (lower respiratory tract infections, LRTI) illness. Patients with mild illness will receive medical attention at outpatient clinics and eventually recover. Severely ill patients go on to be

hospitalised, and further progress to recover from illness or die. The mean durations of influenza-associated illness and length of hospital stay are assumed to be 4 days (17,18).

A range of influenza-related healthcare utilisation events such as seeking medical care at outpatient clinics, hospitalisation as inpatients and purchase of over-the-counter medication are assumed to incur healthcare costs. To capture uncertainty around these costs, random samples of cost parameters are drawn from a gamma distribution (16). Direct medical costs include the price of influenza vaccines, assumed to be $3 per dose, and vaccine wastage, assumed to be 15% (2). Healthcare related costs include transportation costs for hospital visits to seek medical care for influenza-associated illness or for influenza vaccination. Similarly, indirect costs include lost wages and childcare costs due to influenza-related illness (see supplement section 8, and Figure 1 and Tables 2 and 3 in Dawa *et al.*, (2020) for parameter values and references).

For health outcomes, we calculate disability-adjusted life years (DALYs) using disability weights for mild URTI, moderate and severe LRTI and death (GBD, 2019). In contrast to Dawa et al. (2020), no age-weighting of DALYs is done, as this is no longer recommended (14).

We determine cost-effectiveness of vaccination scenarios by calculating median incremental cost-effectiveness ratios (ICERs) per DALY averted and median incremental net monetary benefits (INMBs) across all ten years for each vaccine scenario compared to the no vaccination scenario. The most cost-effective scenario is the one with the lowest ICER value and the highest INMB value. In the absence of locally-determined cost-effectiveness thresholds for health interventions in Kenya, ICERs are evaluated against a WHO ‘best buy’ threshold of $100 per DALY averted in LMICs as well as cost-effectiveness thresholds derived using two broad approaches - marginal productivity thresholds calculated by the University of York (19) and those based on global analyses by the Commission for Macroeconomics and Health (20). While results using four WTP thresholds (Table 2) are presented in the main

paper, details of the full range of thresholds used and corresponding results are presented in the supplement (section 8). These thresholds are also used to calculate vaccine prices at or below which a vaccination scenario is deemed cost-effective.

All results presented in the main text are calculated using discounted costs and DALYs. In sensitivity analyses, undiscounted costs are also used. We also analyse the effect of changing the vaccine price to $1.50, $6 and $10 per dose.

Table 2: Selected willingness to pay (WTP) thresholds used in this study

WTP threshold (USD)	Description*	Reference
100	WHO best buy	(21)
623	45% Kenya pc GDP (2015)	(19)
1912.65	1x Kenya pc GDP (2019)	(22)
5737.95	3x Kenya pc GDP (2019)	(22)

*pc GDP - per capita gross domestic product

Results

Cases averted and doses used

While all modelled vaccine types increased the proportion of the population with some immunity, *Universal vaccines* resulted in the highest levels of immunity across the whole period (Supplemental section 7). In addition, this resulting immunity was generated with fewer vaccine doses due to slower waning, with a total of 14 million vaccine doses used for the *Universal vaccine* scenario over the whole time period. The same number of vaccines were used for *Improved vaccine (breadth*) scenarios, 19 million for *Improved vaccine*

(efficacy) scenarios and 30 million for the *Current seasonal vaccines* and the *Improved vaccines (Minimal)* scenario.

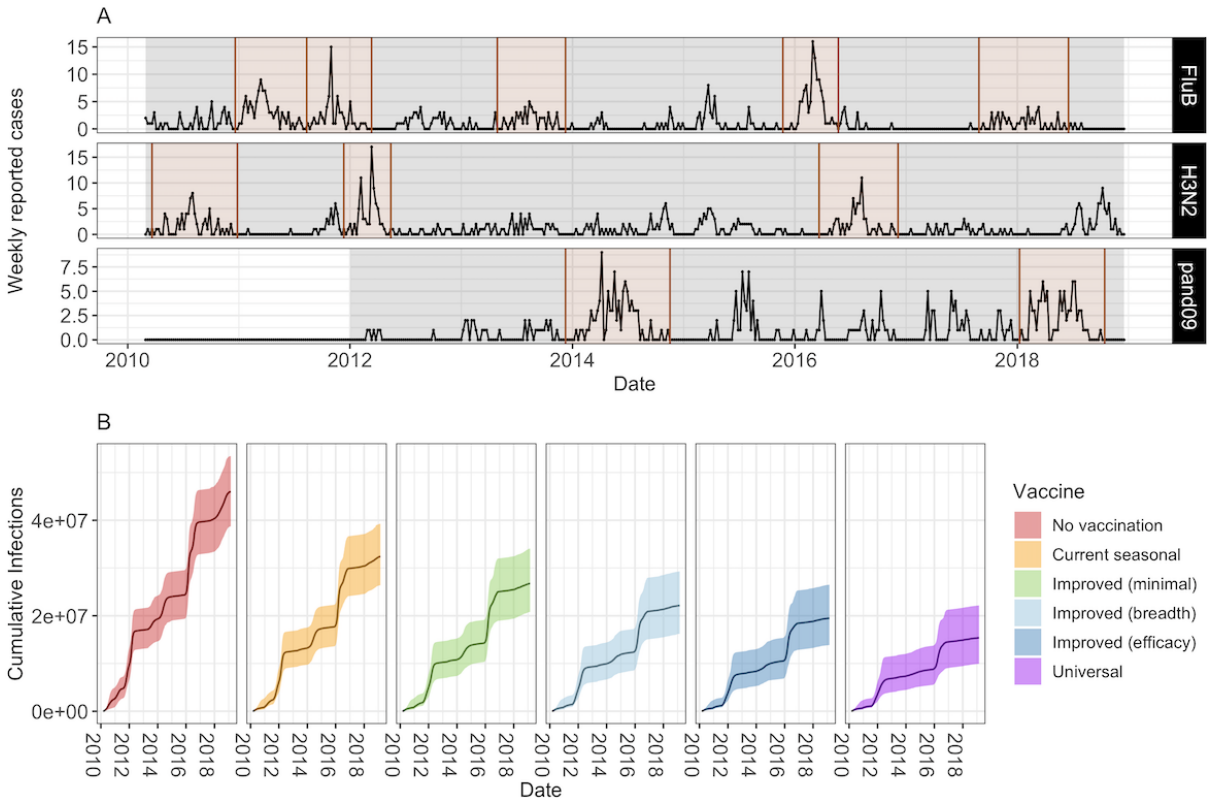


Figure 2: A) Number of weekly reported cases during epidemic and inter-epidemic time periods. Epidemic periods are highlighted in brown, and periods used to estimate the background force of infection are shown in grey. B) Model projections of cumulative number of infections (median and 95% CrI) by vaccine scenario.

The high immunity from *Universal* vaccines translated into the biggest projected reduction in cumulative infections across the 10 year period with a median total of 66% of infections averted (95% Credible Interval (CrI) 56%-74%) as compared to the no vaccination scenario. This compared to the *Improved (Efficacy)* of 57% (95% CrI 47 - 67%), *Improved (Breadth)* of 51% (95% CrI 42%- 61%), *Improved (Minimal)* 41% (95% CrI 33% - 49%) and *Current seasonal* of 29% (95% CrI 23% - 35%) infections averted. The mean R_0 of influenza across epidemics was 2.2 (range 1.2 - 6.7, Supplement section 8 for further details) and across

vaccination scenarios the average number of cases averted per vaccine dose ranged from 0.33 to 2.6.

Cost-effectiveness

Programmes using *Universal* and *Improved (Breadth) vaccines* incurred the lowest total vaccine purchase and administration costs across the entire period, assuming per-dose vaccine costs are the same for all vaccines ($3), because they required the fewest doses. These amounted to a median total value of $78.86 million (95% CrI: $60.96, $125.18 (in millions)), compared to $108.54 million for *Improved (Efficacy)* and $167.91 million for both *Improved (Minimal)* and *Current seasonal* (Supplement section 8). After accounting for these costs and the costs of travel to seek vaccination, programmes using universal vaccines incurred the lowest total societal costs (direct medical, healthcare-related and indirect costs) and thereby incremental total costs, compared to when no vaccination was conducted (Figure 3A). Median discounted incremental total costs for *Universal* vaccines were $27.67 million (95% CrI: $-174.38, $78.21 (in millions)). In contrast, median discounted incremental costs were higher for all *Improved* vaccines and highest for *Current seasonal* vaccines ($128.64 million (95% CrI $35.62, $228.43 (in millions)) (Supplement section 8).

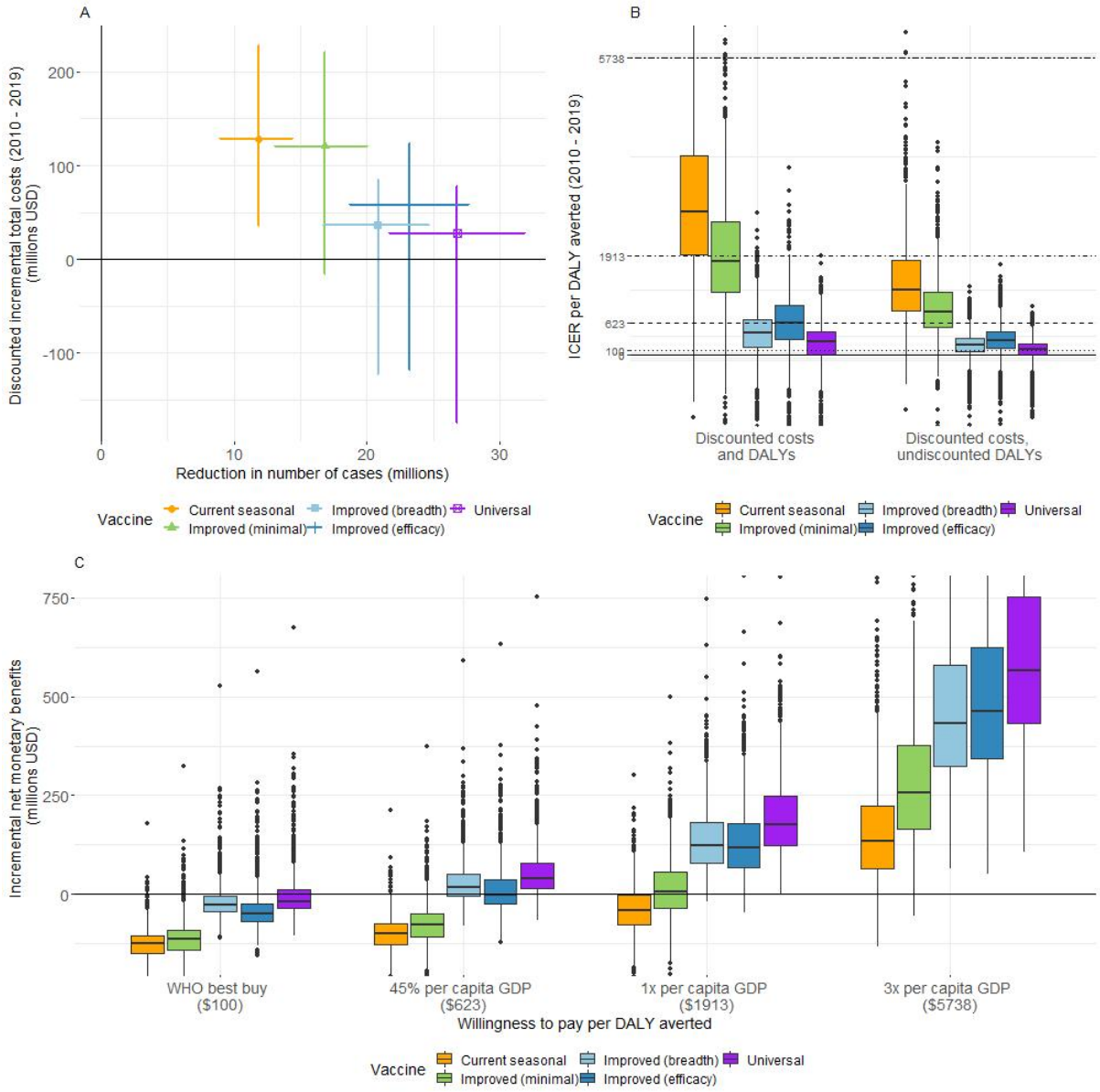


Figure 3: A) Mean (with 95% CrI) discounted incremental total costs (in millions of USD) vs. mean (with 95% CrI) reduction in number of cases (in millions) for each vaccine (2010 – 2019). B) Boxplot of ICER per DALY averted for each vaccine (2010 - 2019). Horizontal lines represent different willingness-to-pay thresholds per DALY averted. C) Boxplot of INMB (in millions of USD) (2010 to 2019) at four selected thresholds of WTP per DALY averted.

None of the vaccines were cost-effective at the WHO best buy threshold of $100 per DALY averted when evaluating cost-effectiveness using discounted costs and DALYs (Figure 3). While there was overlap between uncertainty ranges of ICER values calculated for all five

vaccines, *Universal* vaccines were cost-effective across three of the four WTP thresholds evaluated in this study, with a median ICER per DALY averted of $263 (95% CrI: $-1698, $1061) (Figure 3B). Similarly, *Improved (breadth)* vaccines were cost-effective across three of four WTP thresholds with a median ICER value of $422 per DALY averted, while *Improved (Efficacy)* vaccines had a median ICER value of $626, being cost-effective across two of four thresholds. In contrast, *Current seasonal* vaccines had a median ICER value of $2764 per DALY averted, being cost-effective only at a WTP threshold of 3 times the 2019 per capita GDP of Kenya of approximately $5738 (Figure 3B, Supplement section 8). Thus, median ICER values for *Improved (Breadth)*, *Improved (Efficacy)* and *Current seasonal* vaccines were 1.60, 2.38 and 10.51 times higher than for *Universal* vaccines, respectively.

Similarly, *Universal* vaccines had the highest median INMB values across all WTP thresholds (Figure 3C). At a threshold of $623 (45% of Kenya's 2019 per capita GDP), the median INMB value of *Universal* vaccines ($39.6 million) was 2.29 times higher than that of *Improved (Breadth)* ($17.26 million) vaccines (Supplement section 8). At this threshold, *Universal* vaccines had a high probability (>75%) of being cost-effective, at or below a median price of $5.16 per vaccine dose (95% CrI: $0.94, $18.57) (Table 3, Fig. S7, supplement section 8). Calculated threshold per-dose vaccine prices were consistently higher for *Universal* vaccines across all WTP thresholds. *Universal* vaccines had median INMB values 4.21 times higher than that of *Current seasonal* vaccines ($134.63 million) at a WTP threshold of $5738.

Table 3: Median (and 95% CrI) values of threshold per-dose vaccine prices (2019 USD) at or below which each vaccination scenario is cost-effective, calculated using discounted costs and DALYs, at four selected thresholds of willingness-to-pay per DALY averted. These are calculated while including a median vaccine administration cost of $1.31 per dose (gamma distributed).

Vaccine	WHO best buy ($100)	45% per capita GDP ($623)	1x per capita GDP ($1913)	3x per capita GDP ($5738)
Current seasonal	-0.87 (-3.74, 1.85)	-0.14 (-2.92, 2.63)	1.54 (-1.43, 5.79)	6.51 (1.54, 16.66)
Improved (minimal)	-0.58 (-3.48, 3.29)	0.45 (-2.49, 4.38)	2.86 (-0.69, 8.77)	9.97 (3.52, 23.2)
Improved (breadth)	0.98 (-2.05, 10.85)	3.77 (0.03, 14.02)	10.4 (4.05, 25.4)	29.47 (13.83, 64.04)
Improved (efficacy)	0.46 (-2.42, 8.38)	2.67 (-0.71, 10.9)	7.99 (2.69, 19.89)	23.31 (10.78, 50.57)
Universal	1.59 (-1.51, 14.2)	5.16 (0.94, 18.57)	13.67 (5.99, 31.68)	37.8 (18.74, 79.06)

*pc GDP - per capita gross domestic product

In our sensitivity analyses, increased coverage of vaccination made only slight differences to the cost-effectiveness of any of the vaccines across the different WTP thresholds evaluated (supplement, section 9). The number of cases averted per vaccine dose was slightly lower than in the 50% coverage scenario, ranging from 0.31 - 2.16. In addition, we found that assumptions around susceptibility had a large impact on impact and cost-effectiveness. If we assumed that greater reduction in infections in one season increased susceptibility in the next season, then vaccines were less impactful and cost-effective (see supplement section 10 for details).

Discussion

Our study indicates that next generation vaccines are likely to have much greater impact and an improved cost-effectiveness profile than currently available influenza vaccines. This is true even for incrementally improved vaccines with slightly greater breadth or duration. These are evidenced by the scale of reduction in influenza infections and improvements in cost-effectiveness measures, particularly for universal vaccines. Universal vaccines result in the most substantial reduction in influenza infections utilising the least vaccine doses, averting 66% of infections compared to no vaccination. In contrast, our model predicts that current vaccines avert only 29% of infections, while even improved (minimal) vaccines avert 41% of infections. Similarly, ICER values are higher for improved (1.60 to 2.38 times) and current seasonal (10.51 times) vaccines than for universal vaccines. Universal vaccines also have the highest INMB values - 2.29 times higher than Improved (breadth) vaccines at a WTP threshold of $623, and 4.21 times higher than current seasonal vaccines at a WTP threshold of $5738, the only threshold at which current vaccines are cost-effective. Thus our results suggest that universal vaccines result in the highest immunity per vaccine dose and subsequently, the least number of infections, as well as having the most favourable cost-effectiveness profile among all the vaccines evaluated.

Our conclusions are influenced by vaccine dose costs and cost-effectiveness thresholds. We assumed that vaccine per-dose costs are the same for all vaccines ($3), which is unlikely to be true. More advanced vaccines may cost more per dose. As a comparison, SARS-Cov-2 AstraZeneca vaccines, which were sold without profit, cost between $2.15 and $5.25 per dose, compared to mRNA SARS-CoV-2 vaccines costing $14.70 to $23.50 per dose (23). Nevertheless, our estimates of the threshold per-dose vaccine price (prices at or below which vaccination programs are cost-effective) suggest that universal vaccines are cost-effective even when priced higher than current seasonal or improved vaccines and irrespective of the WTP threshold. At the same time, we find that improved vaccines can

405 also be cost-effective at comparatively low WTP thresholds and result in fewer influenza
406 cases than currently available seasonal vaccines, even if priced higher per dose. The
407 development and use of universal vaccines are very likely to benefit low-and-middle-income
408 countries which may only be willing or able to pay less for health benefits than more
409 advanced economies. However, universal vaccines are unlikely to be immediately available
410 for widespread use, but improved vaccines offer substantial value as an achievable and
411 satisfactory alternative to current influenza vaccines, especially since these may be available
412 in the near future.
413
414 Our analyses demonstrate the importance of assumed cost-effectiveness thresholds when
415 determining whether health interventions are cost-effective or not. Kenya does not have an
416 official cost-effectiveness threshold, but Dawa *et al*. (2020) reported that vaccination with
417 current seasonal influenza vaccines in Kenya had a low probability of being cost-effective
418 given WTP thresholds of 1-51% of per capita GDP. To address uncertainty around
419 thresholds, we used a wide range of values ranging from extremely low WHO “best buys”
420 threshold reserved for evaluating some of the most cost-effective programmes that WHO
421 has ever evaluated (21), to very high 1-3 times GDP per capita thresholds representing the
422 potential value of human capital associated with disability (24). Like Dawa *et al*., we find that
423 current vaccines are cost-effective only at a very high threshold of 3 times the per capita
424 GDP of Kenya and at a maximum threshold price of $6.51 per dose, which is much lower
425 than prices at which most influenza vaccines are available in the US (25) or UK (26).
426 Conversely, both universal and improved influenza vaccines are cost-effective at lower
427 thresholds.
428
429 A key strength of our epidemiological model is the direct incorporation of vaccine-derived
430 immunity waning over multiple years, with ageing of the population, which is required to
431 evaluate next generation vaccines with benefits that last several years. This contrasts to
432 many seasonal vaccination models where vaccine-derived immunity is not tracked across

seasons (2,13). In contrast with the marked annual seasonality of influenza in temperate regions (27), influenza epidemics in Kenya do not have a regular seasonal pattern, with substantial transmission in between epidemics, which we included by separately modelling the inter-epidemic periods. However we used a relatively simple approach for this and we do not capture indirect effects of vaccination between epidemics. In addition, while we include 3 influenza subtypes (AH1N1, A H3N2 and B), we do not allow for any interaction between these subtypes, which may contribute to the dynamics of transmission (28–33). However, as our modelling is based on fitted models, this should not have major impacts on our economic analysis. Therefore the main practical disadvantage is that we are unable to investigate vaccines with different efficacies within the influenza B viruses.

Country decisions to invest in health interventions can be influenced by considerations other than cost-effectiveness (34), for example due to competing options for implementation or due to widespread vaccine hesitancy. Whilst our modelling indicates that next generation vaccines can be cost-effective, their implementation will be competing against other public health interventions. In Kenya, separate studies have shown both rotavirus and pneumococcal childhood vaccination to be cost effective, with between $25 and $59 (35) and $38 (36) per DALY averted respectively, and programmes covering these vaccines have been introduced. However, these estimates are substantially lower than for even the universal influenza vaccines calculated here. Equity in vaccine distribution (37) is also a key consideration for vaccine programme implementation. The availability of financing options such as from Gavi, the Vaccine Alliance (38), is also important, but Kenya is already starting to transition out of Gavi support.

Our study has a number of other limitations. We have assumed that vaccination occurs independent of current vaccine status, meaning that individuals can receive multiple vaccinations and therefore some vaccinations will be ‘wasted’ on individuals already immune. This is a conservative assumption, likely making the vaccine scenarios appear less

cost-effective, and is more likely to have an effect at higher coverage levels. It is also recommended that children between 6 months and 8 years of age, or those who have only ever received one dose, should receive two vaccine doses at least 4 weeks apart (39,40). Administration of a second vaccine dose will incur additional costs for vaccine purchase, transport and administration, although these additional costs may be off-set by vaccinating independent of vaccine status. In reality, there may also be challenges to administer vaccines twice due to limited access. We also do not consider adverse vaccine reactions (40,41) in our DALY calculations. These would influence cost-effectiveness and vaccine threshold prices, particularly at lower cost-effectiveness thresholds.

Immune protection to influenza virus infection and vaccination are poorly understood and we found that assumptions on infection-derived immunity have a large impact on incidence and resulting cost-effectiveness estimates. However, such assumptions could not be empirically informed, because in this setting the previous season does not have an impact on estimated susceptibility levels in the following season and our sensitivity analyses with different infection-susceptibility assumptions show different behaviour than observed for current seasonal vaccines. Therefore our main analysis presents the most likely assumptions. Another important consideration is the potential population-level effects of universal vaccines on vulnerability to newer influenza virus variants. Previous mathematical modelling studies suggest that universal vaccines can prevent the development of cross-protective immunity developed through natural infection. In the absence of sufficiently high vaccination coverage, it was thus suggested that universal vaccines can increase the risks of emergence of vaccine escape variants that could cause influenza pandemics (42,43). These studies suggest that combining administration of seasonal and universal vaccines may help to mitigate these risks (42), a strategy which we have not explored in our study.

Conclusions

Our study provides the first formal evaluation incorporating both direct and indirect (herd) protection, of the effectiveness and cost-effectiveness of a range of next generation influenza vaccines meeting WHO PPCs. In doing so it bolsters the case for investing in development of these vaccines, while highlighting the benefits to be derived from improved vaccines. This provides proof-of-principle for similar studies to be conducted in other LMICs, so that a global picture of potential demand for these vaccines can be built.

List of Abbreviations

CrI – Credible Interval

DALY – disability-adjusted life years

E – Exposed

GDP – gross domestic product

HA - haemagglutinin

I – infectious

ICER – incremental cost-effectiveness ratio

INMB – incremental net monetary benefits

LMIC – lower middle-income countries

LRTI – lower respiratory tract infections

NH - Northern Hemisphere

NIAID – National Institute of Allergy and Infectious Diseases

PPC – Preferred product characteristics

R – recovered

Rv – Recovered-vaccinated

S - Susceptible

SARI – severe acute respiratory illness

SH - Southern Hemisphere

Sv – Susceptible-vaccinated

URTI – upper respiratory tract infections

USD – US Dollars

VE – Vaccine efficacy

WHO – World Health Organisation

WTP – Willingness-to-pay

Declarations

Ethics Approval

Not applicable.

Consent for publication

Not applicable

Availability of data and materials

The datasets analysed during the current study are available in the Supplement of Dawa *et al.* (2020). (https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-020-01687-7#Sec18)

All code is available at https://github.com/NaomiWaterlow/NextGenFlu_Kenya.

Competing Interests

The authors declare that they have no competing interests.

Funding

This work was funded by the Wellcome Trust (224690/Z/21/Z) and Centers for Disease Control and Prevention (CDC-RFA-IP21-2103). JB was funded by PIVI and CDC. EvL and RME were also supported by the National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Modelling and Health Economics, a partnership between UK HSA, Imperial College London, and LSHTM (grant number NIHR200908) and EvL was also supported by the European Union's Horizon 2020 research and innovation programme - project EpiPose (101003688).

Authors contributions

RME, MJ, JB and MM contributed to the conception of the project. RME, MJ, JD, NRW, SR and EvL contributed to the design of the work. NRW, SR, JD and EvL contributed to the analysis of the work. NRW, SR, JD, EvL, JB, MM, PL, RME and MJ contributed to the interpretation of the data. NRW, SR and JD contributed to the creation of the new software in the work. NRW and SR drafted the manuscript and NRW, SR, JD, EvL, JB, MM, PL, RME and MJ reviewed and edited the manuscript.

Acknowledgments

We thank Ready2Respond, the Partnership for Influenza Vaccine Introduction and the Taskforce for Global Health for their support in securing funding, project management and scientific input into this work. We would also like to acknowledge the advice received from Sandra Chaves, Marc-Alain Widdowson and Gideon Emukule.

References

1. McMorrow ML, Emukule GO, Njuguna HN, Bigogo G, Montgomery JM, Nyawanda B, et al. The Unrecognized Burden of Influenza in Young Kenyan Children, 2008-2012. PLoS ONE. 2015 Sep 17;10(9):e0138272.
2. Dawa J, Emukule GO, Barasa E, Widdowson MA, Anzala O, van Leeuwen E, et al. Seasonal influenza vaccination in Kenya: an economic evaluation using dynamic transmission modelling. BMC Med. 2020 Aug 20;18:223.
3. Gomez Lorenzo MM, Fenton MJ. Immunobiology of Influenza Vaccines. Chest. 2013 Feb;143(2):502–10.
4. Hirve S. Seasonal Influenza Vaccine Use in Low and Middle Income Countries in the Tropics and Subtropics [Internet]. World Health Organization; 2015 [cited 2022 Jul 27] p. 99. Available from: https://www.who.int/publications-detail-redirect/9789241565097
5. Lambach P, Alvarez AMR, Hirve S, Ortiz JR, Hombach J, Verweij M, et al. Considerations of strategies to provide influenza vaccine year round. Vaccine. 2015 Nov 25;33(47):6493–8.
6. Hirve S, Lambach P, Paget J, Vandemaele K, Fitzner J, Zhang W. Seasonal influenza vaccine policy, use and effectiveness in the tropics and subtropics - a systematic literature review. Influenza Other Respir Viruses. 2016 Jul;10(4):254–67.
7. Vaccine in tropics and subtropics [Internet]. [cited 2022 Aug 17]. Available from: https://www.who.int/teams/global-influenza-programme/vaccines/vaccine-in-tropics-and-subtropics
8. Matheka DM, Mokaya J, Maritim M. Overview of influenza virus infections in Kenya: past, present and future. Pan Afr Med J. 2013 Apr 8;14:138.
9. Universal Influenza Vaccine Technology Landscape | CIDRAP [Internet]. [cited 2022 Apr 5]. Available from: https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape
10. Moore KA, Ostrowsky JT, Kraigsley AM, Mehr AJ, Bresee JS, Friede MH, et al. A Research and Development (R&D) roadmap for influenza vaccines: Looking toward the future. Vaccine. 2021 Oct 29;39(45):6573–84.
11. WHO Preferred Product Characteristics for Next-Generation Influenza Vaccines [Internet]. [cited 2022 Jan 6]. Available from: https://www.who.int/publications-detail-redirect/9789241512466
12. Erbelding EJ, Post DJ, Stemmy EJ, Roberts PC, Augustine AD, Ferguson S, et al. A Universal Influenza Vaccine: The Strategic Plan for the National Institute of Allergy and Infectious Diseases. J Infect Dis. 2018 Jul 2;218(3):347–54.
13. Baguelin M, Flasche S, Camacho A, Demiris N, Miller E, Edmunds WJ. Assessing Optimal Target Populations for Influenza Vaccination Programmes: An Evidence Synthesis and Modelling Study. PLoS Med [Internet]. 2013;10(10). Available from: http://researchonline.lshtm.ac.uk/1273063/
14. WHO. WHO guide for standardization of economic evaluations of immunization programmes [Internet]. 2nd ed. Geneva PP - Geneva: World Health Organization; 2019 p. 137–137. Available from: https://apps.who.int/iris/handle/10665/329389
15. Inflation, GDP deflator (annual %) - Kenya | Data [Internet]. Available from: https://data.worldbank.org/indicator/NY.GDP.DEFL.KD.ZG?locations=KE
16. Briggs AH, Claxton K, Sculpher MJ. Decision modelling for health economic evaluation. Oxford: Oxford University Press; 2006. 237 p. (Oxford handbooks in health economic evaluation).
17. Carrat F, Vergu E, Ferguson NM, Lemaitre M, Cauchemez S, Leach S, et al. Time Lines of Infection and Disease in Human Influenza: A Review of Volunteer Challenge Studies. Am J Epidemiol. 2008 Apr 1;167(7):775–85.
18. Emukule GO, Ndegwa LK, Washington ML, Paget JW, Duque J, Chaves SS, et al. The cost of influenza-associated hospitalizations and outpatient visits in Kenya. BMC Public Health. 2019 May;19(3):1–10.
19. Ochalek J, Lomas J, Claxton K. Estimating health opportunity costs in low-income and middle-income countries: a novel approach and evidence from cross-country data. BMJ Glob Health. 2018 Nov;3(6):e000964.

20. Loganathan T, Ng CW, Lee WS, Hutubessy RCW, Verguet S, Jit M. Thresholds for decision-making: informing the cost-effectiveness and affordability of rotavirus vaccines in Malaysia. Health Policy Plan. 2018 Mar 1;33(2):204–14.
21. Organization WH. Tackling NCDs: 'best buys' and other recommended interventions for the prevention and control of noncommunicable diseases [Internet]. Geneva PP - Geneva: World Health Organization; 2017 p. 25–25. Available from: https://apps.who.int/iris/handle/10665/259232
22. GDP per capita (current US$) - Kenya | Data [Internet]. [cited 2022 Jun 13]. Available from: https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?end=2020&locations=KE&start=2018
23. Light DW, Lexchin J. The costs of coronavirus vaccines and their pricing. J R Soc Med. 2021 Nov 1;114(11):502–4.
24. Tan-Torres Edejer T, Baltussen RMPM, Adam T, Acharya A, Evans DB, Murray CJL. Making choices in health : WHO guide to cost-effectiveness analysis [Internet]. World Health Organization; 2003 [cited 2022 Jul 27]. Available from: https://apps.who.int/iris/handle/10665/42699
25. VFC | Current CDC Vaccine Price List | CDC [Internet]. 2022 [cited 2022 Jul 7]. Available from: https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html
26. Medicinal forms | Influenza vaccine | Drugs | BNF content published by NICE [Internet]. [cited 2022 Jul 7]. Available from: https://bnf.nice.org.uk/drugs/influenza-vaccine/medicinal-forms/
27. Lofgren E, Fefferman NH, Naumov YN, Gorski J, Naumova EN. MINIREVIEW Influenza Seasonality: Underlying Causes and Modeling Theories. J Virol. 2007;81(11):5429–36.
28. Andreasen V, Lin J, Levin SA. The dynamics of cocirculating influenza strains conferring partial cross-immunity. J Math Biol. 1997 Aug;35(7):825–42.
29. Sonoguchi T, Naito H, Hara M, Takeuchi Y, Fukumi H. Cross-Subtype Protection in Humans During Sequential, Overlapping, and/or Concurrent Epidemics Caused by H3N2 and H1N1 Influenza Viruses. J Infect Dis. 1985 Jan;151(1):81–8.
30. Koutsakos M, Illing PT, Nguyen THO, Mifsud NA, Crawford JC, Rizzetto S, et al. Human CD8+ T cell cross-reactivity across influenza A, B and C viruses. Nat Immunol. 2019 May;20(5):613–25.
31. Yang W, Lau EHY, Cowling BJ. Dynamic interactions of influenza viruses in Hong Kong during 1998-2018. Viboud C, editor. PLOS Comput Biol. 2020 Jun;16(6):e1007989–e1007989.
32. Lin J, Andreasen V, Levin SA. Dynamics of influenza A drift: the linear three-strain model. Math Biosci. 1999 Nov;162(1–2):33–51.
33. Waterlow NR, Flasche S, Minter A, Eggo RM. Competition between RSV and influenza: limits of modelling inference from surveillance data. Epidemics. 2021 Mar 26;100460.
34. Jit M. Informing Global Cost-Effectiveness Thresholds Using Country Investment Decisions: Human Papillomavirus Vaccine Introductions in 2006-2018. Value Health. 2021 Jan 1;24(1):61–6.
35. Sigei C, Odaga J, Mvundura M, Madrid Y, Clark AD. Cost-effectiveness of rotavirus vaccination in Kenya and Uganda. Vaccine. 2015 May 7;33:A109–18.
36. Ayieko P, Griffiths UK, Ndiritu M, Moisi J, Mugoya IK, Kamau T, et al. Assessment of Health Benefits and Cost-Effectiveness of 10-Valent and 13-Valent Pneumococcal Conjugate Vaccination in Kenyan Children. PLoS ONE. 2013 Jun 24;8(6):e67324.
37. Vaccine equity [Internet]. [cited 2022 Jul 8]. Available from: https://www.who.int/campaigns/vaccine-equity
38. Gavi, the Vaccine Alliance [Internet]. [cited 2022 Jul 8]. Available from: https://www.gavi.org/
39. CDC. Children & Influenza (Flu) [Internet]. Centers for Disease Control and Prevention. 2021 [cited 2022 Jul 7]. Available from: https://www.cdc.gov/flu/highrisk/children.htm
40. Influenza vaccine | Drugs | BNF content published by NICE [Internet]. [cited 2022 Jul 7].

669 Available from: https://bnf.nice.org.uk/drugs/influenza-vaccine/
670 41. Seasonal Influenza Vaccine Safety: A Summary for Clinicians | CDC [Internet]. 2021
671 [cited 2022 Jul 7]. Available from:
672 https://www.cdc.gov/flu/professionals/vaccination/vaccine_safety.htm
673 42. Arinaminpathy N, Riley S, Barclay WS, Saad-Roy C, Grenfell B. Population implications
674 of the deployment of novel universal vaccines against epidemic and pandemic influenza.
675 J R Soc Interface. 2020 Mar;17(164):20190879.
676 43. Subramanian R, Graham AL, Grenfell BT, Arinaminpathy N. Universal or Specific? A
677 Modeling-Based Comparison of Broad-Spectrum Influenza Vaccines against
678 Conventional, Strain-Matched Vaccines. Regoes RR, editor. PLOS Comput Biol. 2016
679 Dec 15;12(12):e1005204.

WHO Full Value of Vaccines Assessment (FVVA)

Draft template

'Vaccines should be seen not only, or even primarily, as a cost that increases public health budget needs, but as an investment with sustainable, long term, and large-scale impact.

Accurately measuring the full public health value of vaccines will increase the likelihood of adopting this approach by increasing political will and allowing for more accurate prioritization of available resources' (Gessner et al. 2017).

The purpose of this WHO Full Value of Vaccines Assessment (FVVA) is to describe the global public health rationale for developing vaccines against **pathogen(s) X**, to inform decision making regarding short- and long-term investment in their development. The FVVA can be used as a basis for the development of more detailed investment or business cases.

This template has suggested headings and sections. For some vaccines, a partial FVVA can be performed and other sections can be added.

Guidance notes on possible content for each section are in brown italics and can be reduced in length.

Table of Contents

1 Executive summary and public health value statement 3
1.1 Public health value statement 3
2 WHO public health value assessments for vaccines in early stage development 4
2.1 Target audiences and use of WHO FVVAs 5
2.2 Criteria for selecting vaccines for FVVAs 5
2.3 Methodology for FVVA development 5
3 The global public health need for the vaccine 6
3.1 Disease description 6
3.2 Current methods of surveillance, diagnosis, prevention and treatment 7
3.3 Key gaps in knowledge or research evidence 8
4 **X vaccine - a strategic priority for WHO 9**
4.1 WHO Preferred Product Characteristics (PPCs) 9
5 Stakeholder analysis and involvement 10
5.1 Key gaps in knowledge or research evidence 10
6 Development of the vaccine 11
6.1 Biology of the vaccine 11
6.2 Technical platforms under consideration 11
6.3 Preclinical development: key issues 11
6.4 Clinical development and regulatory pathway: key issues 11
6.5 Vaccine efficacy: key issues 12
6.6 Vaccine safety; key issues 13
6.7 Implementation: key issues 13
6.8 Key gaps in knowledge or research evidence 13

7 Assessment of the vaccine development pipeline 14
7.1 Pipeline summary 14
7.2 Pathway and timescale to licensure 15
7.3 Benchmarking against other vaccines 15
7.4 Probability of success 16
7.5 Key gaps in knowledge or research evidence 16
8 Estimation of disease burden and transmission 17
8.1 Public health inputs and output for modelling 17
8.2 Transmission modelling 17
8.3 Key gaps in knowledge or research evidence 17
9 Defining the market for the vaccine 18
9.1 Potential market segments 18
9.2 Market validation 18
9.3 Strategic vaccine demand forecast 20
9.4 Key gaps in knowledge or research evidence 20
10 Impact of the vaccine on burden of disease and transmission 22
10.1 Measurement of vaccine benefits 22
10.2 Key gaps in knowledge or research evidence 22
11 Economic analysis of the value of the vaccine 23
11.1 Economic analysis: methodology 23
11.2 Economic analysis: summary of findings 23
11.3 Impact of investment 25
11.4 Estimation of cost effectiveness 27
11.5 Key gaps in knowledge or research evidence 28
12 Financing the development of the vaccine 29
12.1 Likely gaps in funding for development for use in LMICs 29
12.2 Key gaps in knowledge or research evidence 30
13 Conclusions and recommendations 31
13.1 Next steps 31
14 References 32
14.1 Further reading 32
Appendix 1. Abbreviations 33
Appendix 2. Glossary 34
Appendix 3. Overview of the product development process 38
Appendix 4. Draft target product profile (TPP) 39
Appendix 5. Authors, advisors and stakeholders interviewed 40

1 Executive summary and public health value statement

Summarise key points and conclusions from the FVVA.

1.1 Public health value statement

Summarize the vaccine(s) in question.

Table 1.Key characteristics, features, values and beneficiaries of **X vaccine**

	Vaccine **X**	Notes
Vaccine characteristics		*Some WHO PPCs and FVVAs will list more than one vaccine and/or more than one indication.*
Value		*Include which groups will benefit from the vaccine.*
Status of development		*Include whether the vaccine is being developed or tested in LMICs.*
Market features		

2 WHO public health value assessments for vaccines in early stage development

This will become standard text for future WHO Initiative for Vaccine Research (IVR) FVVAs. FVVAs developed in collaboration with other groups might have different content and focus. WHO FVVAs are evidence based and not uncritical advocacy documents. The definition and methodology for their creation is new for WHO and it is likely that they will evolve over the next few years.

World Health Organisation's (WHO's) FVVAs for vaccines are published by WHO Initiative for Vaccine Research (IVR).

The mission of WHO IVR is to accelerate the development and optimal use of safe and effective vaccines and related technologies. Priority research focus areas include

- Promotion and acceleration of vaccine candidates in early development, towards licensure;
- Research to generate evidence to inform policy recommendations for candidate vaccines at advanced stages of development.

WHO FVVAs describe for candidate vaccines in **early development**, the value of a vaccine for a wide range of possible stakeholders, with a particular focus on public health value, especially in low- and middle-income countries (LMICs). For WHO FVVAs, early development is defined as 'up to and including phase II clinical trials'.

Evaluation of the public health value considers the population impact of a vaccine and encompasses measures of community benefits against a range of outcomes. (Gessner et al. 2017) These values might be broader than the claims of efficacy in a vaccine's license.

Like most WHO preferred product characteristics (PPCs) for vaccines, WHO FVVAs for vaccines aim to summarise:

- The unmet public health **need** for a vaccine, but with more quantification and stratification (for example by gender, occupation, at country level) than is contained in the PPCs, especially for LMIC populations;
- The type of vaccines that are likely to be of highest value for global public health use, especially in LMICs, but FVVAs might contain a more detailed analysis;
- The value for different stakeholders, but with additional quantification and stratification of potential markets for the vaccine;
- The pipeline of vaccines in development, but FVVAs might include more detail than the PPC regarding the technical feasibility of development, including estimating timescales to licensure and considerations for uptake;
- Key issues in the development of the vaccine and important gaps in knowledge, but for different stakeholders. FVVAs can also describe research studies and analyses that might address some of these gaps.

Unlike PPCs, FVVAs aim to:

- Estimate the cost of vaccine R&D and then the costs of implementation for the vaccine;
- Provide some guidance about possible pricing of vaccines, based on stakeholder feedback and economic analysis;
- Estimate potential vaccine impact in relation to the PPCs.

WHO FVVAs complement, but do not supersede, existing WHO guidance on vaccine development.

WHO FVVAs **do not** necessarily aim to be as comprehensive and detailed as value assessments compiled by other organisations. They do aim to assess the global value assessments by including the value of LMIC markets.

They do not name, compare or rank individual candidate products or product developers.

2.1 Target audiences and use of WHO FVVAs

The primary target audience for WHO PPCs and FVVAs is any entity intending to eventually seek WHO policy recommendation and prequalification (PQ) for their products.

Communication of the potential value of vaccines, including public health value, can be useful to all those involved in vaccine development activities. This can include academic groups, small biotech companies and funders. If WHO FVVAs use only data and opinions in the public domain, WHO FVVAs can be shared widely and published online.

The WHO PPCs and WHO FVVAs, taken together, aim to encourage innovation and the development of vaccines for use in settings most relevant to global unmet public health need. They can help raise further interest and funding to address key gaps in knowledge and to support vaccine development, especially for LMIC use.

2.2 Criteria for selecting vaccines for FVVAs

Selected disease areas for WHO PPC and FVVA development are identified by the WHO Product Development for Vaccines Advisory Committee (PDVAC) based on an unmet public health need for vaccines, and a brief assessment of technical feasibility and suitability for use in LMICs.

2.3 Methodology for FVVA development

For most vaccines, a WHO PPC will have been prepared beforehand. FVVAs complement and extend the scope of WHO PPCs (see above) and will likely refine the guidance to be included in future PPC iterations.

WHO FVVAs are drafted by a WHO secretariat, based on literature review, input from meetings of experts and stakeholders, working groups and wider consultation, including by WHO committees such as PDVAC. WHO FVVAs can also be informed by specially commissioned short projects to address key and amenable gaps in knowledge. The detailed analysis, including methodology, to support the conclusions in a FVVA can be in standalone documents and, ideally, shared in the public domain including in peer-reviewed publications.

Both PPCs and FVVAs can be updated in the event of product or technology innovations, or any other change in the identified need or R&D landscape.

3 The global public health need for the vaccine

This section summarises the unmet public health need (i.e. burden of disease and available healthcare), where it is located, and important trends over time. It can introduce the level of complexity of the problem to be addressed by the vaccine.

It should summarise the problems to be addressed (referring to PPCs) and take note of expected future trends. It should cross-reference to the detailed analysis, including modelling, in later sections.

3.1 Disease description

The main features of the burden of disease with mechanisms and heterogeneity. For more detailed analysis, see Section 8.

Is this a candidate for eradication or elimination?

Table 2. Main features of the infection and disease

Suggested features are shown in the table. The notes could include whether the data are current and from the most appropriate sources or whether they need updating.

Feature	Summary and evidence	Notes
Age distribution		*Comment on heterogeneity, including in transmission.*
Anti-microbial resistance (AMR) issues		*This might be in associated infections.*
Disruption of health systems		*Include humanitarian emergencies if relevant.*
Epidemic and outbreak potential		
Gender distribution		*Comment on heterogeneity, including in transmission.*
Herd immunity		
Morbidity		*Include severity and sequelae*
Mortality		*Include case fatality ratio (CFR).*
Natural immunity		*Include duration of protection.*
Predictability of disease occurrence		
Transmission		*Include heterogeneity.*
Types, strains and serotypes		*After use of a vaccine, could there be pathogen replacement?*

3.1.1 Key interactions with other infections or diseases/conditions

Short statement of pathogens and conditions linked to the vaccine-preventable infection or disease, including

- *Socio-cultural determinants that have a significant impact on the condition. Refer to any systematic analyses of these;*
- *Causal associations that might be addressed by vaccination, e.g. viruses that predispose to bacterial disease; or associations between the infection and malnutrition or chronic diseases.*

3.1.2 Other non-healthcare impacts of the infection, including equity

If possible, introduce non-healthcare impacts of the infection or conditions, e.g. loss in productivity, requirements for additional childcare. These will be described in more detail in Section 11.3.

Equity is a fair opportunity for everyone to attain their full health potential regardless of demographic, social, economic or geographic strata.[1] Vaccination is also an essential element for promoting equity. (Gessner et al. 2017)

Table 3. Equity issues

Equity	Evidence	Notes
Health equity		
Economic equity		*Such as reducing medical and nonmedical costs associated with cases of vaccine-preventable diseases.*
Social equity		*Such as. access to the health care system.*
Vertical equity		*Such as vaccines for diseases of poverty.*

3.1.3 Geographic differences in burden of disease and where need is unrecognised

Summarize what is known.

Does climate change play a role in epidemiology?

3.2 Current methods of surveillance, diagnosis, prevention and treatment

Brief introduction to the healthcare use that is currently linked to the infection or associated condition. This can include surveillance; vaccine use or other prevention (could be anti-microbial use); treatment and care (of all kinds including chemotherapeutic prevention, palliative); behaviour change that requires healthcare input etc. Cross-reference to Section 0 where these will be covered in more detail.

Comment if they are effective alternatives to the vaccine or could be used alongside it. Are they likely to be, able to address needs in LMICs?

[1] http://www.who.int/gender-equity-rights/understanding/equity-definition/en/

If there are existing or related vaccines, why can't they address all need (or not in specific contexts), especially in LMICs?

Table 4. Surveillance, diagnosis, prevention and treatment of **X**

	Status in LMICs	Status HICs	Extent to which they meet the global need
Surveillance of infection and conditions			
Prevention of acquiring infection			
Prevention of transmitting infection			
Diagnostics			
Treatment of symptoms			

3.3 Key gaps in knowledge or research evidence

Table 5. Gap analysis and prioritization

Area	Gap in knowledge	Notes and prioritization
	State the gap and comment on the impact on the development or use of the vaccine.	*Include references where possible.*

4 **X** vaccine - a strategic priority for WHO

This section summarises why the vaccine is important to the WHO and should include links to relevant global public health initiatives and documents. It might be useful to refer to the stakeholder analysis (Section 5).

*Are there any strategic global health goals established for **X**?*

Have any of the following activities been completed, or are they underway or in planning:

- *Portfolio management processes;*
- *Programmes for elimination or eradication;*
- *Prioritisation by other global organisations;*
- *Product development partnerships;*
- *Advanced market commitments;*
- *Other relevant WHO initiatives;*
- *Other relevant PPCs or FVVAs.*

4.1 WHO Preferred Product Characteristics (PPCs)

Summarize key messages of the WHO PPCs for the vaccines, including over-arching goals, prioritised indications, target populations and prioritised outcomes. These could form an appendix.

Will the scope of this FVVA go beyond that of the PPCs and, if so, why? It might be because of a strong high-income country (HIC) market or the development of related vaccines with non-prioritised indications or target groups, for example travel vaccines.

5 Stakeholder analysis and involvement

List types of stakeholders likely to have special interests in the vaccine, and if known, strategies to engage with them in the process of defining PPCs or FVVAs. This can help WHO, and others, to identify key groups and individuals to contact. It can also help people define key messages and routes of communication.

Typical stakeholders for R&D (for vaccines) include

- *Public and private funders and donors;*
- *Developers (large pharma, biotech and academic) and manufacturers;*
- *Global and national policymakers including WHO;*
- *National/global advocacy groups including in countries with high disease burden.*

Other stakeholders:

- *Households;*
- *Third-party payers;*
- *Government (such as ministries of health, finance, military);*
- *Donors;*
- *Innovators;*
- *Society as a whole.*

Stakeholders can be sub-divided into:

- *Global;*
- *WHO regional;*
- *Sub-regional;*
- *HICs, UMIC, LMIC and LICs;*
- *Individual countries.*

Stakeholder interests can include

- *Development of the vaccine;*
- *Procurement (in some cases including for stockpiles) and introduction;*
- *Sustaining the current investment;*
- *Demonstrating the vaccine's return on investment.*

5.1 Key gaps in knowledge or research evidence

Table 6. Gap analysis and prioritization

Area	Gap in knowledge	Notes and prioritization
	State the gap and comment on the impact on the development or use of the vaccine.	*Include references where possible.*

6 Development of the vaccine

*This section should review **briefly** the scientific feasibility of developing an effective vaccine of public health value. The next section will evaluate the status of the technology area. For both sections, it might be informative to refer to knowledge gained from related 'benchmark' vaccines.*

6.1 Biology of the vaccine

This might include

- *Does natural infection impart immunity (see Section 3.1)?*
- *Knowledge of pathology of the infection (see Section 3.1);*
- *Complexity of interactions with other pathogen (see Section 3.1.1);*
- *Mechanisms of protective immunity;*
- *Knowledge of molecular biology of the pathogen;*
- *Knowledge of target antigens;*
- *Future approaches, and general advances in vaccinology expected or possible.*

6.2 Technical platforms under consideration

Summarize the advantages and disadvantages of different vaccine technology platforms that might be used for the vaccine (e.g. live-attenuated compared with inactivated vaccines; subunit compared with nucleic acid). Are adjuvants likely to be needed? Cross reference to Section 7, for assessment of the vaccine pipeline.

6.3 Preclinical development: key issues

Briefly identify some of the key strengths and challenges in preclinical development of the vaccine, for example:

- *Animal models – are they good or bad models of disease, and useful as predictors of efficacy?*
- *Availability of harmonised assays and standard reagents.*

6.4 Clinical development and regulatory pathway: key issues

Discuss the key factors that might assist or hinder clinical development of the vaccines, see Table 7.

Table 7. Key issues in clinical development

	Issues and evidence	Notes
Biomarkers		
Clinical endpoints		*For example, will some clinical endpoints require very large trial design.*
Correlates of protection		

	Issues and evidence	Notes
Diagnosis		
Human challenge models		*For example, vaccine probe studies and community randomized trials.*
Novel trial designs		
Regulatory process and challenges		*Could alternative regulatory pathways be beneficial? For example, licensing on immunogenicity and safety (e.g. using serological correlates of protection) and post-licensure effectiveness studies; integrated/hybrid phase III/IV strategies.*
Surveillance		

6.5 Vaccine efficacy: key issues

Summarise factors that might affect the efficacy of vaccines as measured in randomised controlled trials (RCTs; Table 8), (Gessner et al. 2017).

Table 8. Factors that can affect vaccine efficacy

Factor	Issues and evidence	Notes
Age		
Diagnostic methods		
Local epidemiological situation		
Geography		*For example, rotavirus vaccine trials in HICs compared with LMICs.*
Inclusion and exclusion criteria		
Microbial flora or parasite burden		*Especially for enteric vaccines.*
Pre-existing immunity		
Serotype distribution of the pathogen		

6.6 Vaccine safety; key issues

Briefly summarize possible safety concerns, including potential rare safety issues that might not be identified in early-stage or short-term clinical trials, but might require post-marketing surveillance.

6.7 Implementation: key issues

Who are the likely target populations?

What are assumptions on use case? For example, will the vaccine be used for routine childhood immunisations, in mass vaccination (including campaigns and outbreak response), for adolescents, pregnant women, adults, travellers or older people (refer to Section 9).

What target coverage rates are needed to achieve desired outcomes? What are the challenges for reaching target coverage (refer to Section 9)?

What are the likely formulation, presentation and dosing schedules? What are the implications of these for use (cross-reference to later sections on costs)?

Will new or existing diagnostic tests be required?

Would the vaccine be best used as part of an integrated management strategy, for example with environmental control and hygiene measures (Gessner et al. 2017)? Might need to refer to Sections 10 and 11.

6.8 Key gaps in knowledge or research evidence

Table 9. Gap analysis and prioritization

Area	Gap in knowledge	Notes and prioritization
	State the gap and comment on the impact on the development or use of the vaccine.	*Include references where possible.*

7 Assessment of the vaccine development pipeline

This section should review the status of the current vaccine development pipeline. Vaccines in clinical development should be included. It might also be appropriate to review the portfolio of candidates in preclinical development.

Describe the pipeline in only general terms. WHO does not aim to rank or prioritise individual vaccines in development. Target product profiles (TPPs) are not required but might be available and, if so, could be included or referenced, so they can be referred to by other sections.

Comparisons can be made:

- *By strategy within the general area of vaccine development;*
- *By vaccine type for the indication, for example live compared with subunit vaccine, or by antigen selected;*
- *By indications: for example, prophylactic vaccines for infant or adolescent use compared with therapeutic vaccines for mainly adults.*

It should identify, where possible:

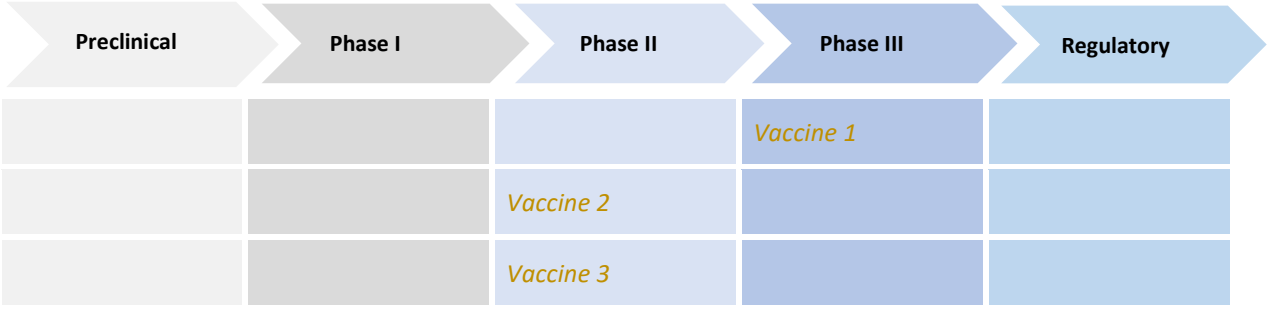
- *The number of candidates at each stage of the pipeline;*
- *Diversity and robustness of the portfolio;*
- *Have the current candidates been informed by what was learned in earlier studies?*

In general terms, discuss who the developers are:

- *Do they have capacity to take the vaccine to license and supply at scale?*
- *Are they all in HICs?*
- *The likely timeframe to license, and, where relevant to WHO PQ;*
- *The probability of success;*
- *The major risks and challenges in development and commercialization;*
- *What could de-risk development, e.g. further development of correlates and biomarkers; see also Section 11.5.*

7.1 Pipeline summary

Figure 1. Current vaccine landscape by stage of development



It might also be informative to summarize the progress and stage of failure of candidates no longer in development.

Table 10. Summary of vaccine candidates no longer in development

Vaccine name	Type and composition	Development stage reached	Summary of results	Notes

It might also be informative to briefly discuss/illustrate the location of developers involved to highlight (lack of) LMIC involvement:

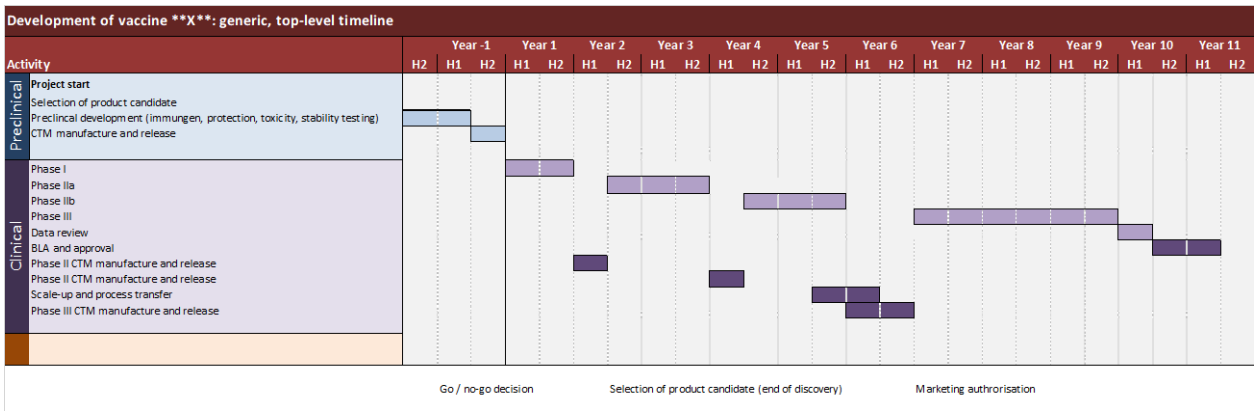
Table 11. Portfolio of vaccines in development by country

Vaccine name	Developer	Country involved and if in HIC or LMIC	Development stage

7.2 Pathway and timescale to licensure

Estimating the steps and time to licensure can provide an indication of the time horizons that might need to be considered for activities such as vaccine impact modelling (Section 9). This could be as a simple, top-level GANTT chart (Figure 2). It might be useful to briefly comment on benchmark vaccines and timelines for current or previous vaccines in the pipeline as supporting data for the timeline.

Figure 2. Top-level illustrative timelines for vaccine **X development**



7.3 Benchmarking against other vaccines

Predicting development timelines is difficult. It can be useful, therefore, to see if lessons can be learned from other relevant vaccines. For some vaccines, where there might be limited direct data, it might be helpful to use benchmark vaccines as examples, explaining why they have been chosen and their possible strengths and weaknesses (Table 12). For example:

- *Refer to examples of vaccines that are relatively difficult to manufacture but are still produced at scale and are affordable;*
- *Refer to vaccines that have a similar mechanism of action, even if for a different pathogen, that have been developed and approved;*
- *Refer to vaccines that were initially expensive but are now much more affordable.*

Table 12. Development of other vaccines with issues in common with vaccine **X**

Vaccine	Rationale for comparison	Notes

7.4 Probability of success

Briefly list major (and general) risks and challenges in development. Many of the risks will be candidate-specific so outside the scope of this WHO analysis.

Depending on the stage of development, it might be appropriate to list ways of de-risking development including

- *Funding the earliest stages of development to increase the numbers and breadth of candidates that could enter the later stages;*
- *Developing novel clinical trials designs;*
- *Portfolio development to share and prioritize critical resources for the most promising candidates and to reduce the number of similar candidates being tested at the same time.*

A qualitative discussion of the key hurdles facing development will probably be sufficient. If required, a quantitative method for estimating the probability of a candidate vaccine progressing through the various stages of development could be used or cited; for example, the Monte-Carlo simulation analysis tool. (AERAS and Tuberculosis Vaccine Initiative 2012)

7.5 Key gaps in knowledge or research evidence

Table 13. Gap analysis and prioritization

Area	Gap in knowledge	Notes and prioritization
	State the gap and comment on the impact on the development or use of the vaccine.	*Include references where possible.*

8 Estimation of disease burden and transmission

In addition to the introductory description of total disease burden in Section 3, more detailed data and/or estimates of the burden of disease could be included, relevant to the prioritised indications in the PPCs and in this FVVA.

The burden of disease can be reported in a number of ways, including deaths, cases, long-term sequelae or 'outbreaks'.

The data can be stratified by geographic regions of interest or target populations, as informed by stakeholders.

8.1 Public health inputs and output for modelling

Inputs could include data from 183 countries (if appropriate) and for each year from 2020 to 2050.

8.2 Transmission modelling

This is used for some studies of the impact of vaccines (see Section 9).

8.3 Key gaps in knowledge or research evidence

Table 14. Gap analysis and prioritization

Area	Gap in knowledge	Notes and prioritization
	State the gap and comment on the impact on the development or use of the vaccine.	*Include references where possible.*

9 Defining the market for the vaccine

A strategic market assessment, over a period of 10 to 20 years, could be provided. (AERAS and Tuberculosis Vaccine Initiative 2012) This is usually based on stakeholder interviews. It can describe potential LMIC markets, which might not be familiar to some developers used to targeting very defined markets, especially in only HICs. This information might be referred to in Section 12.

When available, quantitative data from market analysis can be useful in modelling the impact of use of the vaccine and for cost analyses.

To predict the market globally, or by WHO region, or individual country it can be useful to have:

1. *A draft target product profile (see Appendix 4);*
2. *Location of developers of the vaccine – and their intentions for trial settings and licensing;*
3. *Possible acceptability issues, including safety;*
4. *Disease burden (Section 8);*
5. *Demographics;*
6. *The status of its health systems including capacity for introduction and use of the vaccine;*
7. *Awareness of the health issue, advocacy and political will;*
8. *Its history of adoption of similar vaccines;*
9. *Its gross national income per capita;*
10. *Its access to donor support (e.g. GAVI).*

9.1 Potential market segments

World Bank income-based categories, and LMIC markets are typically used and can be further categorized into public and private. For some vaccines, other segments might include routine use, and travel and military markets. The vaccine characteristics might differ between markets and be different to those described in WHO PPCs.

9.2 Market validation

Validation of the concept of the vaccine against a number of potential markets is useful. Typically, public and private healthcare providers and their customers are interviewed (by survey, as individuals or in focus groups) and in several different countries of interest. This will develop an evidence base to encourage investment in R&D and, at a later stage, facilitate adoption and uptake.

9.2.1 Scenarios of use

The vaccine can be evaluated for different scenarios of use, including properties, target populations and immunisation delivery platform. Questions could be addressed such as:

- *Benefits;*
- *Associated costs;*
- *How strong the potential market is for each scenario?*
- *Would existing healthcare spending be re-allocated to purchase the vaccine?*
- *Can any identified obstacles to use be overcome?*

- *Are various pricing ranges deemed affordable?*
- *Likely time to introduction after WHO PQ;*
- *Will in-country studies be needed before the vaccine was used?*

People and stakeholders to be surveyed can include

- *Ministry of health officials (department heads, preventive medicine, planning or finance, and program managers of immunization program);*
- *Ministry of finance officials;*
- *Professional associations;*
- *Leading academics and researchers;*
- *National Immunization Technical Advisory Groups (NITAGs);*
- *International technical agency officials;*
- *Health officials from local governments.*

9.2.2 Settings for use

The settings most likely to license and use the vaccine, and to benefit from its use, need to be identified and summarized. This could be based on data on burden of disease.

9.2.3 Market-based efficacy thresholds and non-interference

Interviews with stakeholders can inform on the sensitivity of purchase intentions and vaccine uptake to different levels of vaccine efficacy.

9.2.4 Market penetration

Interviews with stakeholders can inform on the sensitivity of purchase intentions and vaccine uptake to different pricing levels. Estimates of sensitivity of uptake to price could be made and could consider when a WHO PQ vaccine might be available and recommended. The likelihood, and impact or a differential pricing approach could also be considered.

9.2.5 Hurdles in acceptability in key markets

Potential obstacles to introduction of the vaccine should be briefly summarized. These might include

- *Low awareness of the disease burden and low demand for prevention;*
- *The need for complex dosing;*
- *Perceived (or actual) low or unpredictable efficacy;*
- *Pricing that might not seem affordable or competitive;*
- *Side effects and safety issues;*
- *Difficulty delivering the vaccine to the target population.*

9.2.6 Forecast date of introduction

This is an estimate of the base year when a vaccine will be WHO PQ and available for public health use in LMICs, even though not all countries will immediately start to use the vaccine. Reasons for delayed introduction should be identified where possible, and might include

- *Lack of capacity to introduce the vaccine and also carry out surveillance;*
- *Competing priorities, such as civil unrest and economic instability;*
- *Preference to focus health budgets on other priorities.*

To predict rates of uptake, especially accelerated country introduction, a 'looks-like' analysis can be used, based on:

- *Historical uptake of similar vaccines;*
- *Disease burden data;*
- *Capacity in the relevant health service;*
- *Political will.*

Ideally, a base case and conservative case will be established, with the number of countries and whether they are HIC, UMIC, LMIC or LIC. Countries can be divided into:

- *Early introduction countries: perhaps in first five years after WHO PQ. For vaccines, early adopters drive the majority of revenues within the global market. Some will use the vaccine in sub-populations only, for example in healthcare workers (HCWs), or high-risk populations.*
- *Mid-introduction countries: additional numbers in years 6 to 10;*
- *Late-introduction countries: after 10 years (or not at all).*

Estimates for India and China are often determined and presented separately.

Summarize any other issues that might affect access and supply, for example the number and location of manufacturers.

9.3 Strategic vaccine demand forecast

The strategic demand forecast (number of doses per year, in what time frame) needs to determine whether it is possible to introduce an affordable vaccine with a sustainable supply. High initial demand can be challenging for manufacturers to meet, during scale up. Some demand forecasts estimate how many manufacturers, and working at what capacity, will be required to meet demand.

Report the assumptions used, which can include target population, introduction year, vaccine coverage rate, doses per course, wastage factor and countries' willingness and ability to adopt.

Table 15. Likely timescale for introduction of the vaccine

Country	Year of introduction	Assumptions

9.4 Key gaps in knowledge or research evidence

Table 16. Gap analysis and prioritization

Area	Gap in knowledge	Notes and prioritization

Area	Gap in knowledge	Notes and prioritization
	State the gap and comment on the impact on the development or use of the vaccine.	*Include references where possible.*

10 Impact of the vaccine on burden of disease and transmission

Where available, summarise the conclusions of modelling the impact of use of the vaccine on preventable burden of disease and other factors. Where no formal modelling has been performed, a list of factors (and possible ranges) that influence vaccine impact could be included. Cost effectiveness and economic aspects will be covered in Section 11.

Health impact of the vaccine can be reported as: deaths averted, cases and sequelae averted or DALYs averted, by the numbers vaccinated per year.

Include the factors included and assumptions made, which can include incidence rate, CFR, direct vaccine efficacy rate, herd effects, coverage rate, vaccine duration and frequency, target populations.

10.1 Measurement of vaccine benefits

The benefits of vaccines can be measured in several ways (see Section 11 for economic measurements): extended cost effective analysis (ECEA); incremental cost effectiveness ratio (ICER); multi-criteria decision-making processes; quality adjusted life years (QALY); social rates of return; social welfare function. (Gessner et al. 2017). Summarize the measures used and the data available (Table 17).

Table 17. Measures used to assess vaccine benefits

Measure	Data	Notes
Vaccine effectiveness (VE)		*The percentage of an outcome reduced by the vaccine. Can be used to calculate VPDI when multiplied by background disease incidence.*
Vaccine preventable disease incidence (VPDI)		*Also known as the vaccine attributable rate reduction or the incidence rate reduction.*
Number needed to vaccinate (NNV)		

10.2 Key gaps in knowledge or research evidence

Table 18. Gap analysis and prioritization

Area	Gap in knowledge	Notes and prioritization
	State the gap and comment on the impact on the development or use of the vaccine.	*Include references where possible.*

11 Economic analysis of the value of the vaccine

WHO is developing an Accounting Framework for Economic Evaluation, with an adaptation for vaccines and immunization programmes in preparation.[2] This can be used to guide the choice of methodology for economic analysis.

Types of analyses reviewed include

- *Budget impact analysis (BIA);*
- *Cost benefit analysis (CBA);*
- *Cost-effectiveness analysis (CEA);*
- *Cost of illness study (COI);*
- *Costing studies;*
- *Economic surplus analysis;*
- *Effectiveness studies;*
- *Extended cost-effectiveness analysis (ECEA);*
- *Fiscal impact modelling;*
- *Optimization modelling;*
- *Investment cases.*

The following questions should also be considered when assessing the public health value of vaccines: (1) what evaluations should be considered? (2) when should they be done pre- or post-licensure? and (3) who will see this as their responsibility? (Gessner et al. 2017)

11.1 Economic analysis: methodology

Summarize the methodologies used and the rationale for their selection.

11.2 Economic analysis: summary of findings

This section of the FVVA will summarise key conclusions, probably using a selection of figures; these should be understandable by a broad audience. The following section headings might be useful:

11.2.1 Disease burden costs

Can refer to the earlier section on health burden (Section 8). The costs can be direct or indirect.

11.2.2 Development costs

Summarize total R&D, manufacturing and marketing costs (Table 19). These include

- *The cost of discovery research;*
- *Clinical trials;*
- *Process development;*
- *Manufacturing;*

[2] Raymond Hutubessy, WHO IVB, personal communication.

- *Regulatory processes;*
- *Marketing and post-marketing activities.*

For vaccines, estimating development costs is very challenging; there is no known reliable method. Benchmarking to other, similar, vaccines might be useful.

Table 19. Estimated costs of **X vaccine development**

Stage	Cost (US$)	Notes
Discovery and pre-clinical		
Phase 1 (or 1 and 2a)		
Phase 2 (or 2b)		
Phase 3		
Process development		*Could include early process development as well as development and scale-up of the final process.*
Regulatory filings and approvals		
Post marketing		
Total		

Some estimations of development costs can include the total R&D expenditure of the organization, including development costs of candidates that fail. It should be clear what is included in the estimation.

Some economic evaluation methods will not include R&D costs, regarding them as 'sunk costs' and, therefore, not relevant to the calculation.

11.2.3 Delivery costs

This taken to mean the costs associated with getting a vaccine to the recipient. They can also be referred to as: deployment costs; health systems cost of delivering the vaccine, and operational cost. Typically, they include costs associated with:

- *Cold chain;*
- *Training and supervision;*
- *Vehicles and transport;*
- *Social mobilization and awareness raising;*
- *Surveillance;*
- *Monitoring and evaluation;*
- *Waste management;*
- *Overhead.*

Estimates can be derived from models such as Global Immunization Vision and Strategy (GIVS), which is based on target countries' financial sustainability plans or comprehensive multi-year plans (cMYPs).

11.2.4 Vaccine price

Pricing is a key driver for future revenue by developers of vaccines and also as part of the calculation of total procurement costs. The estimated prices can be derived from two sources:

- *A review of historical prices for similar vaccines launched in HICs, middle income countries (MICs), and low income countries (LICs). This can be used as an indicator of 'what the market will bear';*
- *Crude estimates of the vaccine's 'cost of goods' (COGs), based upon the technology and manufacturing processes used in its production.*

Alternatively, an estimate can be made for a solution space, defined as prices that represent a good investment case for donors and countries and at the same time are a good business case for suppliers.[3]

Prices can be summarised as price per schedule or per dose.

11.2.5 Strategic demand forecast

Summarize the number of vaccine doses demanded, with assumptions about the target population, vaccine coverage rate and the country's willingness to pay and ability to adopt the new vaccine. Demand can be summarised as doses per year by a specified date and stratified by target group.

11.2.6 Cost of goods estimates

Broad assumptions about manufacturing costs can be made. For example, manufacturing using cell culture can double the COGs compared with using recombinant technology in bacteria. (AERAS and Tuberculosis Vaccine Initiative 2012) It is still difficult, however, to make accurate estimates for COGs when the final commercial manufacturing process has not been defined; which is the case for vaccines at early stages of development. Factors to consider include

- *Fixed, variable and semi-variable costs;*
- *The utilization rate of the production plant;*
- *How long the plant is amortized (depreciation of valuation spread over time).*

11.3 Impact of investment

These can be health, economic and broader public health benefits (Table 20).

Table 20. Potential broader impacts of the infection/condition and vaccine use

Impact	Evidence	Notes
Anti-microbial resistance		
Consumer prices		

[3] http://www.preventpneumo.org

Impact	Evidence	Notes
Long-term/on-going disability		
Disease control cost		
Educational and cognitive outcomes		
Employment		
Expenditure equity		
Family integrity		
Financial protection		
Gross domestic product (GDP)		
Gross national income (GNI);		
Health care utilization		
Health equity		
Herd immunity		
Household integrity, disruption of		
Indirect effects on other infections or conditions		
Macroeconomic impact		
Outbreak control		
Political disruption		
Public sector budget impact		
Private consumption		
Sexual and reproductive health (SRH)		
Social disruption absenteeism		
Synergy with other health interventions		
Word loss		

11.3.1 Health gain

Direct and indirect, using dynamic models.

11.3.2 Health-systems strengthening

11.3.3 Healthcare costs averted

11.4 Estimation of cost effectiveness

11.4.1 Cost-benefit analysis

A cost-benefit analysis could be based on:

- *Developers' perspective: for example, costs incurred would be vaccine development costs, and the benefits would be health benefits based on vaccine impact estimate;*
- *Societal perspective: for vaccines, costs incurred are vaccine deployment costs. Benefits are health and economic, based on a vaccine impact estimate model. A decision could be made to exclude vaccine development costs.*

Costs could be presented as:

- *Cost per case averted;*
- *Cost per death averted;*
- *Cost per DALY averted.*

11.4.2 Vaccine cost-effectiveness

11.4.3 Multi-criteria decision-making processes

A tool such as the Strategic Multi-Attribute Ranking Tool (SMART), as used by the US Institute of Medicine for vaccine prioritization, could be applied. Vaccine attributes are divided into eight categories. Three core values are highlighted: (a) mortality and severity of the disease, (b) vaccine safety considerations, and (c) an economic evaluation that captures the full benefits of vaccination. (Barocchi, Black, and Rappuoli 2016)

11.4.4 Summary

Typically, economists aim to compute an incremental cost effectiveness ratio (ICER), against a benchmark or threshold, to allow comparisons across competing programs. (Gessner et al. 2017)

A Social Welfare Function (SWF) and Social Rates of Return (SRR) framework could replace the QALYs and ICERs framework (Gessner et al. 2017).

11.5 Key gaps in knowledge or research evidence

Table 21. Gap analysis and prioritization

Area	Gap in knowledge	Notes and prioritization
	State the gap and comment on the impact on the development or use of the vaccine.	*Include references where possible.*

12 Financing the development of the vaccine

Estimate, where possible, the total funding required globally for the development of the vaccine.

Describe possible sources of funding and the overall funding landscape, which might include the entities listed below and in Table 22:

- *Major funding institutions and agencies, from information in the public domain. These might include industry (big pharma and smaller biotech); government support; not for profit foundations:*
    - *Is there diversity?*
    - *How many are in based emerging markets, EU, India, China etc.?*
    - *What is the level of advocacy for the disease area?*
    - *Does the vaccine fit with poverty-related and neglected disease (PRND)?*
- *Multi-lateral initiatives, including with WHO and in product development partnerships (PDPs);*
- *Funding for capacity building for clinical trials, and manufacture of the vaccine. Is there funding available to support or promote commercial production in LMICs?*

Table 22. Global funding landscape

Funder (dates)	Basic science, discovery and preclinical development	Early-stage clinical development	Late-stage clinical development

12.1 Likely gaps in funding for development for use in LMICs

Provide a general description of whether current funding is sufficient to develop a vaccine with WHO PPCs and in a timely manner.

Funding might be available for the development of related vaccines with different indications, which could be adapted for use in LMICs.

Factors to consider include

- *Total commercial market for the vaccine: for example, expressed in US$ over 10 years. This can help attract the attention of financing partners;*
- *Blended capital: public (or philanthropic) funds can be targeted at the highest risk points in development, with private sector contributing more to the most expensive parts;*
- *Partnership approach to financing: including PDPs;*
- *Expansion of public-private partnerships (PPPs);*
- *Incentives to target developed economies;*
- *Rational portfolio management approach;*

- *Push mechanisms to phase I trials: grants, pharma-cost sharing, venture philanthropy, and prizes. For example, technology transfer to developing countries vaccine manufacturers (DCVMs);*
- *Valley of death of funding into phase III trials: grant cost-sharing (through portfolio manager), debt financing, late-stage equity (impact investors);*
- *Pull mechanisms into licensure: market-enhancing mechanisms such as pre-advanced market commitment (AMC), with pre-defined TPPs; debt finance; evidence-based health economic data;*
- *Other ways to minimize development costs for manufacturers.*

There might be insufficient data or opinion to describe (or publish in the public domain) the potential sources of financing the development of the vaccine. It might be necessary or useful to benchmark other similar vaccines.

12.2 Key gaps in knowledge or research evidence

Table 23. Gap analysis and prioritization

Area	Gap in knowledge	Notes and prioritization
	State the gap and comment on the impact on the development or use of the vaccine.	*Include references where possible.*

13 Conclusions and recommendations

This section could include

- *A summary of the estimated or perceive public health value of the vaccine;*
- *The commercial viability of the vaccine. Would the aim be to commercialize at least one vaccine?*
- *Need or desirability for a portfolio management approach, and who could do this?*
- *Likely portfolio development costs.*

Additional detail and recommendations could include

- *The potential for development and impact;*
- *A summary of work and data gathering in progress;*
- *Next steps for investors;*
- *Next steps for donors;*
- *Priority for development;*
- *Monitoring and data;*
- *Need for advocacy, especially the need for political commitment, good communication, and evidence-based decisions (e.g. technical aspects of vaccines, vaccine hesitancy and confidence); (Gessner et al. 2017)*
- *Need for more refined analysis.*

13.1 Next steps

Provide more detail (if needed) on the key areas from the list above. Possible example headings are:

13.1.1 Activities proposed or underway to provide data for the FVVA

This section should summarise known WHO projects, requests for proposals (RFPs) and also work by other groups and funders that will generate data relevant to the FVVA.

Table 24. Activities underway or in planning linked to the FVVA

Project area	Brief scope	Timescale to delivery
Epidemiology: burden of disease		
Modelling vaccine impact		

14 References

Include peer-reviewed publications, systematic reviews, meta-analyses, other data sources, etc.

AERAS, and Tuberculosis Vaccine Initiative. 2012. 'TB Vaccine Research & Development A Business Case for Investment. Draft Discussion Document'. http://www.aeras.org/pdf/TB_RD_Business_Case_Draft_3.pdf.

Anderson, Ian, Blerta Maliqi, Henrik Axelson, and Mikael Ostergren. 2016. 'How Can Health Ministries Present Persuasive Investment Plans for Women's, Children's and Adolescents' Health?' *Bulletin of the World Health Organization* 94 (6): 468–74. https://doi.org/10.2471/BLT.15.168419.

Barker, Lew, Luc Hessel, and Barry Walker. 2012. 'Rational Approach to Selection and Clinical Development of TB Vaccine Candidates'. *Tuberculosis (Edinburgh, Scotland)* 92 Suppl 1 (March): S25-29. https://doi.org/10.1016/S1472-9792(12)70009-4.

Barocchi, Michèle A., Steve Black, and Rino Rappuoli. 2016. 'Multicriteria Decision Analysis and Core Values for Enhancing Vaccine-Related Decision-Making'. *Science Translational Medicine* 8 (345): 345ps14. https://doi.org/10.1126/scitranslmed.aaf0756.

Biologicals, World Health Organization Dept of Vaccines and. 2002. 'Guidelines for Estimating Costs of Introducing New Vaccines into the National Immunization System'. http://www.who.int/iris/handle/10665/67342.

Brennan, Michael J., and Jelle Thole. 2012. 'Tuberculosis Vaccines: A Strategic Blueprint for the Next Decade'. *Tuberculosis* 92 (March): S6–13. https://doi.org/10.1016/S1472-9792(12)70005-7.

Gessner, Bradford D., David Kaslow, Jacques Louis, Kathleen Neuzil, Katherine L. O'Brien, Valentina Picot, Tikki Pang, Umesh D. Parashar, Mitra Saadatian-Elahi, and Christopher B. Nelson. 2017. 'Estimating the Full Public Health Value of Vaccination'. *Vaccine* 35 (46): 6255–63. https://doi.org/10.1016/j.vaccine.2017.09.048.

14.1 Further reading

Update and expand/reduce this list as appropriate:

WHO guidance on vaccine presentation, packaging, thermostability, formulation and disposal, addressed in the Generic Preferred Product Profile for Vaccines, developed by the Vaccine Presentation and Packaging Advisory Group (VPPAG): http://www.who.int/immunization/policy/committees/vppag/en/index2.html

Guidance about the WHO Prequalification (PQ) process and criteria by which vaccine quality, safety, efficacy and suitability for use in low and middle-income countries are assessed, in Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification: http://apps.who.int/iris/bitstream/10665/76537/1/WHO_IVB_12.10_eng.pdf

Guidance from WHO on regulatory expectations regarding clinical evaluation of vaccines can be found within Guidelines on clinical evaluation of vaccines: regulatory expectations: http://www.who.int/biologicals/expert_committee/WHO_TRS_1004_web_Annex_9.pdf?ua=1

Appendix 1. Abbreviations

To be completed.

Appendix 2. Glossary

Beneficiary

An individual, group of individuals, organisation or system who/that will benefit in any way from the vaccine being developed or used.

Business case

Similar to an investment case, a quantitative justification for investment in a fixed time period but with the justification targeted towards stakeholders with a profit interest in realizing the value. It focuses primarily on net revenues to establish its case and, secondarily, on the public health rationale. The pharmaceutical industry tends to focus on probability-weighted net present value, which will be very difficult or impossible for WHO to determine for vaccines at an early stage of development.

Disease burden

An indicator of health outcome. It can be expressed in many ways, such as the number of cases (e.g. incidence or prevalence), deaths, or disability-adjusted life years lost (DALYs) associated with a given condition.[4]
Preventable burden of disease: the proportion of the burden that the vaccine could prevent.

Integrated product development plan (IPDP)

Developed from the TPP, the IPDP summarizes all the multidisciplinary activities required to complete clinical and non-clinical development of the candidate product, as well as chemistry, manufacturing and controls (CMC) and regulatory activities. Definition of the targets and key claims of the product. The IPDP includes the estimated timelines and budgets for all activities. [5]

Investment case

There are many definitions and uses of investment case, from the very general to specific economic evaluation methodology. In brief, investment cases can communicate information that facilitate the understanding of relevant costs, benefits, risks and other various factors associated with the investment. As applied to immunization, they usually include a description of disease and economic burden; vaccine price and quantity demanded; cost of investment; impact of investment (health, economic and broad), and other considerations.[6]

Landscape analysis

Part of a business case. Typically, it uses literature searches and information obtained under confidential disclosure agreements (CDAs) between the authors/readers and the developers. Candidates are ranked using defined criteria, and there can be site visits and also financial or managerial due diligence. Pre-defined PPCs (or a TPP) are needed for ranking.

[4] http://www.who.int/immunization/monitoring_surveillance/burden/estimates/en/

[5] Adapted from http://resources.rhoworld.com/blog/bid/159899/How-to-Use-Your-Target-Product-Profile-to-Create-an-Integrated-Product-Development-Plan

[6] Literature review 2018. Raymond Hutubessy, personal communication

Outcome

A measurable event within a clinical trial or epidemiological study; this can be a direct effect of the vaccine or an indirect one.

Portfolio management

An approach for managing a portfolio of candidate vaccines for a given set of goals. It stretches from discovery to late-stage development of a vaccine. It is, preferably, independent of in-built biases towards particular approaches and candidates. Decisions are evidence-based and can expand, re-direct or terminate product development. Decisions are based on a comprehensive, strategic and well-defined approach. It can introduce new ideas, for example ways of testing and comparing candidates, and there can be overall R&D cost efficiencies. Agreeing a TPP is key to this approach and there can be priorities for development, including based on public health impact. Cost efficiencies can be based on milestone-based funding and 'Go/No go' criteria.

Public health

The science and art of preventing disease, prolonging life and promoting human health through organized efforts and informed choices of society, organizations, public and private, communities and individuals. Health takes into account physical, mental and social well-being; it is not merely the absence of disease or infirmity. In common usage, it tends to be used for population-level approaches to health improvement rather than at an individual level, especially those delivered by governments.

A public health paradigm in the context of value can consider the population impact of a vaccine and encompasses measures of community benefits against a range of outcomes. (Gessner et al. 2017)

Public welfare interest

Realization of non-monetary public benefits (such as improved quality of life).

Push and pull mechanisms

In vaccine R&D, refers to economic incentives that facilitate the development of vaccines perceived to be market failures or, where there is commercial viability, when the scientific risk and uncertainty are very high.

Push mechanisms for vaccine R&D can provide direct funding through grants that pay for research inputs; pull mechanisms that pay for research outputs increase the monetary rewards for the development of an effective vaccine.

Return on Investment (ROI)

A key part of a business or investment case. In R&D, it is the benefit (profits) to an investor resulting from an investment in R&D. A high ROI means the gains compare favourably to its cost. As a performance measure, ROI is used to evaluate the efficiency of an investment or to compare the efficiencies of several different investments.

Roadmap

Description of the process of development of a product or group of products.

Stage-specific gating strategy

Used in R&D management to review product development. At various gateway points (there can be more than one per development stage), candidates can be either selected for further development or terminated. Changes can also be made in resources and costs. The criteria are agreed in advance. The need for data and its quality tends to increase with stage of product development to reflect the increase in resources needed for later stages. For vaccines, characteristics can include production process; product characterisation and quality; safety; immunogenicity; protection and efficacy; clinical; regulatory and business. Each characteristic will have objectives and criteria to pass. (Barker, Hessel, and Walker 2012)

Standard care package

Part of the analysis of healthcare costs, it uses clinical guidelines and clinical norms to estimate maximum likely costs, even if individuals do not have full access to the care package or actually seek care.

Target product profile (TPP)

Definition of the targets and key claims of the product. The TPP provides a statement of the overall intent of the drug development program and gives information about the drug at a particular time in development. For vaccines, usually, the TPP is organized according to the key sections in the eventual vaccine label (FDA 2007).[7]

Technical feasibility

A process of validating the technology assumptions and design of a product or project.

Tiered pricing

The prices paid by different market segments typically vary. For vaccines, there is often a wide range of prices paid by different countries and in the public or private sector. There can also be different prices for the same product for infant and adult use. It can help low-resource countries to afford a vaccine.

Vaccine introduction costs

The total costs of implementing a vaccine in a health system. WHO has guidelines on how to calculate these, (Biologicals 2002) including using a costing tool such as WHO's OneHealth. Key data include the immunisation platform to be used, target coverage, and number of doses per person.

Vaccine pricing

The likely price of vaccines in development can be estimated using: knowledge of the cost of goods of vaccines using similar technology, pre-negotiated pricing scenarios (tiered pricing), or by benchmarking to vaccines with similar characteristics. The cost of goods is difficult to estimate for vaccines at an early-stage of development.

[7] Guidance for Industry and Review Staff Target Product Profile — A Strategic Development Process Tool https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm080593.pdf

Value

The monetary or other worth of a vaccine as perceived by an individual, group organisation or society. It can be measured in health outcomes per unit of currency spent, or the health gain, cost saving and/or benefit to society. Public health value can be measured by the extent to which a vaccine addresses an unmet public health need.

Value driver

A key factor that determines the value of a vaccine to a specified stakeholder. For vaccines, it could be the price, efficacy or indirect impact.

WHO preferred product characteristics (PPCs)

Definition of the desired characteristics of vaccines to address public health need, and usually with a LMIC focus. These characteristics include indications, target populations, implementation strategies, safety and efficacy requirements. PPCs don't aim to and capture or quantify, to the same extent as a WHO Full Value of Vaccines Assessment (FVVA) the likely economic or public-health value of the vaccines in question or the likely costs of development. For vaccines, one pathogen area might have more than one set of PPCs.

WHO Full Value of Vaccine Assessment

A value assessment can be defined as 'a promise of value to be delivered' or a review and analysis of costs and benefits to be delivered by a proposed investment, from a variety of perspectives: who, for whom and for what purpose. See Section 2 for a description. See also the definitions for: business case; investment case; and WHO preferred product characteristics (PPCs).

WHO public health value statement

A short description of the vaccine in question, with a summary of its indications, for what target group(s), what stage of development it is, key features and value to different beneficiaries and stakeholders. This can be based on the WHO PPCs for the vaccine.

Appendix 3. Overview of the product development process

The development of the vaccine can be divided into distinct phases (see Section 6):

- **Discovery and pre-clinical stage 1**: includes basic research and discovery, assay development, animal testing and early process development, leading to selection of the product candidate;
- **Pre-clinical development (stage 2)**: includes further assay development, Good Manufacturing Practice (GMP) pilot-scale manufacturing, Good Laboratory Practice (GLP) toxicology testing, and regulatory filing to conduct the first safety trial in humans;
- **Phase 1 and 2a clinical trials**: phase 1 includes the first testing in humans, starting with a small group of adult subjects to assess safety (and, for vaccines, immunogenicity). It can also, for vaccines, include age-de-escalation studies to reach the target age group. In Phase 2a, individuals can belong to groups at risk of acquiring the disease;
- **Phase 2b clinical trials**: these involve a much larger number (for example, low thousands) of healthy volunteers to assess safety. For vaccines, they also test for immunogenicity and preliminary data on efficacy. These studies are randomized and double blinded. Due to their size, they often include multiple sites in different disease-endemic countries;
- **Phase 3 clinical trials**: successful candidate(s) from Phase 2b trials enters even larger trials (for example tens of thousands) of people, to assess the safety and efficacy in a large group of people;
- **Pre-commerce**: involves the introduction of the vaccine to the market. Successful introduction is achieved by developing a comprehensive data package that makes a public health and economic case for adoption of the vaccine into national programs. Often a WHO recommendation is required as a prerequisite for adoption in LMICs. Comprehensive data packages include
    - Evidence for policy development, advocacy and communication at global and country levels;
    - Financing mechanisms to support comprehensive vaccination programs;
    - Health infrastructure required for delivery.
- **Commercialization**: further work on the value assessment of the added benefit of a new vaccine. Activities include
    - Ensuring logistical, regulatory, financing, and policy issues are in place;
    - Accurate supply chain forecasting;
    - Management of supply and demand to guarantee the vaccine is available when countries are ready;
    - Review of health infrastructure to support uptake;
    - Monitoring and surveillance systems.
- **WHO prequalification.**

Appendix 4. Draft target product profile (TPP)

For use in stakeholder interviews and for market analysis.

Table 25. Draft TPP for **X** vaccines

Parameter	Minimum acceptable target	Optimistic target
Indication		
Product/vaccine		
Strain/type coverage		
Target populations		
Efficacy		
Immunogenicity		
Safety, tolerability and reactogenicity		
Dosing schedule		
Route of administration		
Stability and shelf-life		
Presentation		
Protection threshold		
Cost of goods		
WHO PQ date		

Appendix 5. Authors, advisors and stakeholders interviewed

Authors

Scientific Advisory Group (SAG)

WHO Secretariat

Stakeholders interviewed

List stakeholder names with organisation, under headings.

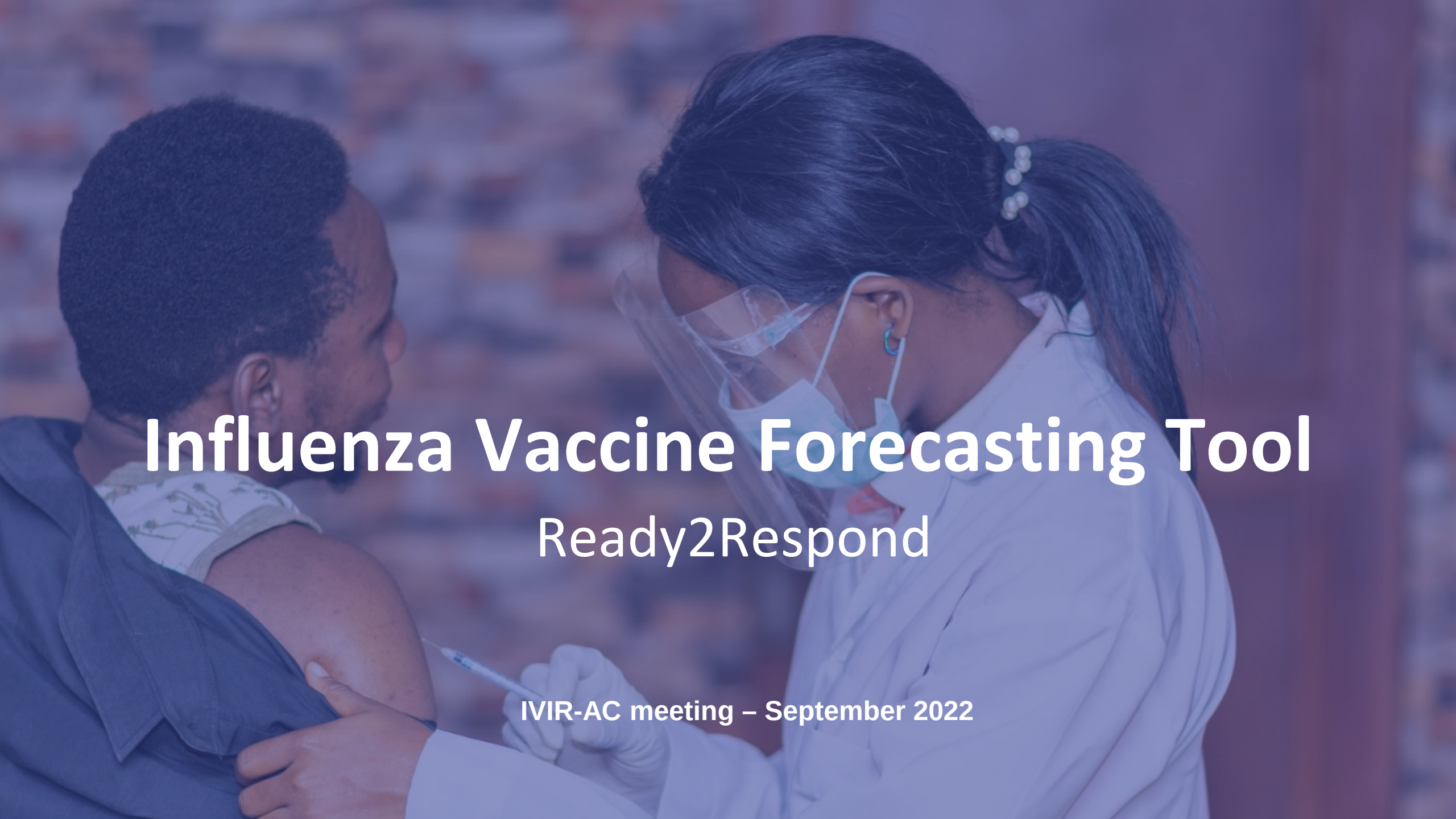
For example:

- *Vaccine developers: for a range of opinions it can be useful to interview people from large vaccine manufacturers, biotechnology companies, not-for-profit organisations, governmental and academic-based R&D, independent consultants and regulatory agencies;*
- *Global demand: it can useful to interview experts at BMGF, GAVI, PATH, UNICEF, WHO and World Bank;*
- *In-country demand: useful to interview people in Ministries of Health (or public health), academic settings and private practice in priority and large-population countries;*
- *Knowledge/opinion: supply: people who know about supply chain;*
- *Knowledge/opinion: epidemiology: useful to interview people working on modelling.*

World Health Organization

Session 3

Influenza Vaccine Global Demand Forecasting tool



Influenza Vaccine Forecasting Tool

Ready2Respond

IVIR-AC meeting – September 2022

Background

1. **WHO**: Influenza vaccines are underused in LMIC
   - Needed for BOD reduction
   - Needed for infrastructure and capacity building in preparation of an influenza pandemic

2. **UNICEF**: Seasonal Influenza Vaccine Supply Update note (September 2020)
   - "Inconsistent and sometime unreliable forecasts"

3. **IA2030**: Strategic Priority 6
   - Goal: "All countries have a reliable supply of appropriate and affordable vaccines of assured quality, and sustainable financing for immunization programs".
   - Key area of focus: "Vaccine forecasting, procurement and supply: improve national and global forecasting, planning and procurement capability to safeguard affordable, sustainable supplies, and strengthen relations with manufacturers to ensure that vaccine production and supply meet national needs in all countries".

Our forecasting tool addresses some of the most critical challenges encountered by MICs and LICs while planning seasonal influenza vaccination campaigns

Findings from Primary Research

Interviews with Experts from Vaccine Access EWG

- It is difficult to accurately forecast for seasonal influenza vaccines
- There is lack of evidence to make a case for vaccine funds
- Vaccine delivery is often delayed
- Supply of vaccines usually runs short
- Forecasting should be done for a long time horizon

Survey with Country Health Managers

- Planning for vaccination campaigns is limited in LMIC/LIC countries
- Delivery of vaccines is viewed as too slow and viewed as a key logistical challenge leading to waste
- Inaccurate and incomplete data limit planning and execution capabilities
- Data needs are abundant

The tool – which comes with a curriculum in 5 languages- will equip public health managers with the appropriate data and methodology to plan for seasonal influenza vaccination campaigns and influenza pandemic preparedness

Key benefits from intended use of VaxDemandTool

- Increase vaccination **demand planning expertise** and campaign **execution capability**
- Support **prioritization** and **resource allocation optimization** in the face of budget constraints
- Enable planning optimization to **reduce wastage with a calendar based vaccine rollout planning module**
- Enable timely **estimation and approval** of budget with templated budget output reports
- Provide **access to supporting data** needed for demand estimation in one place (population, target group size, etc.)
- Aid in **influenza pandemic preparedness** with a mechanism to estimate required resources in face of uncertainties

VaxDemandTool to be be hosted by a third party website and made accessible to end users through websites that are trusted by and familiar for them

Public Health Managers

Access forecasting tool through multiple web pages

VaxDemandTool Landing Pages with overviews of features, intended use

Training materials - recorded webinars and translated transcripts

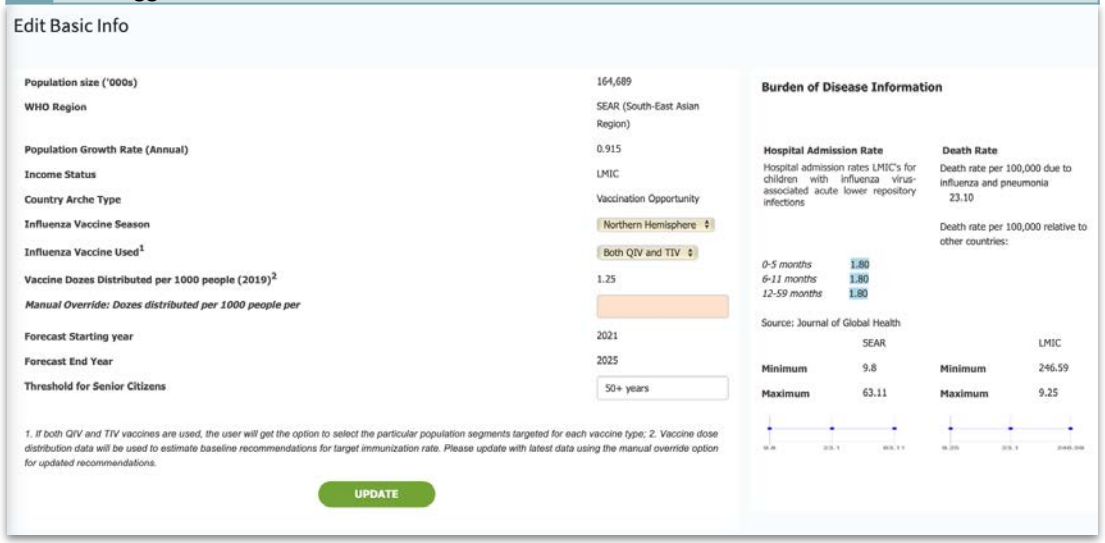
Cloud-based hosting of the tool

Forecast Inputs	**Vaccination Campaign Planning**	**Pandemic Scenario Planning**
Forecast Outputs		

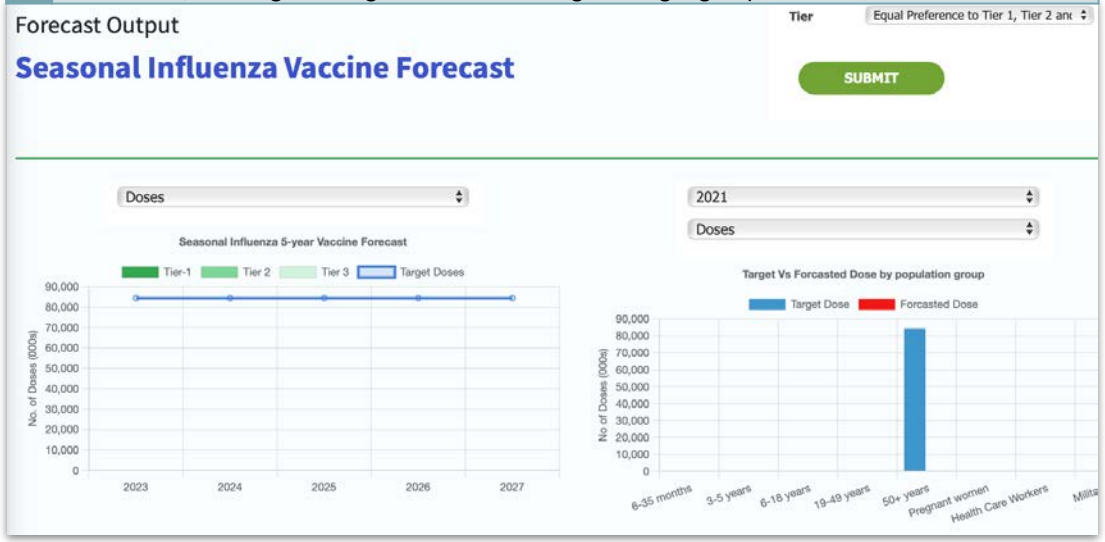
READY2RESPOND

The forecasting tool has been divided into 4 distinct components, each with robust data inputs, automated logics, and guided navigation

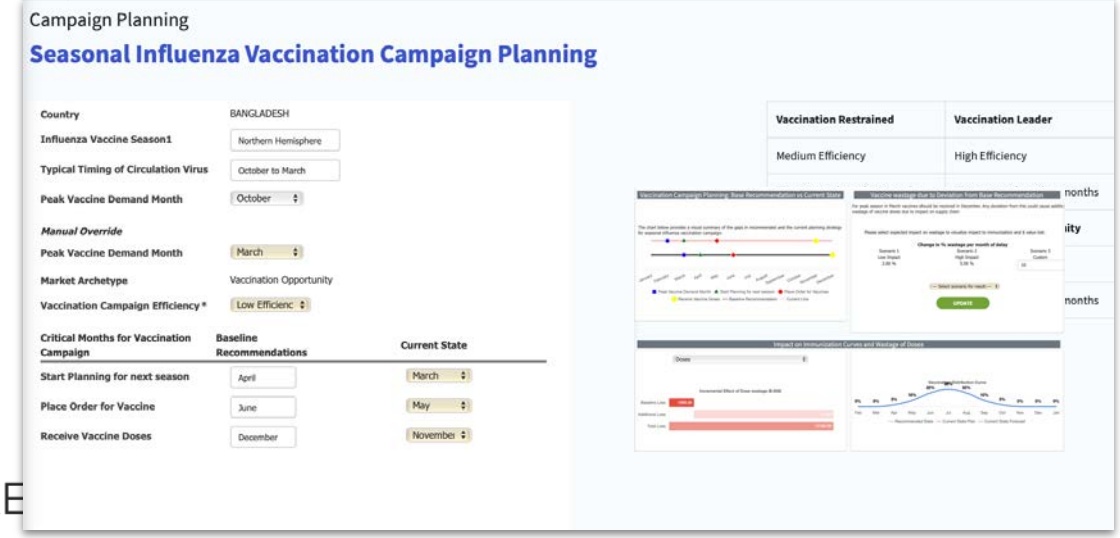
1 **Forecast Inputs**: User-driven inputs for the seasonal influenza vaccines forecast, with prefilled data suggestions which can be overridden



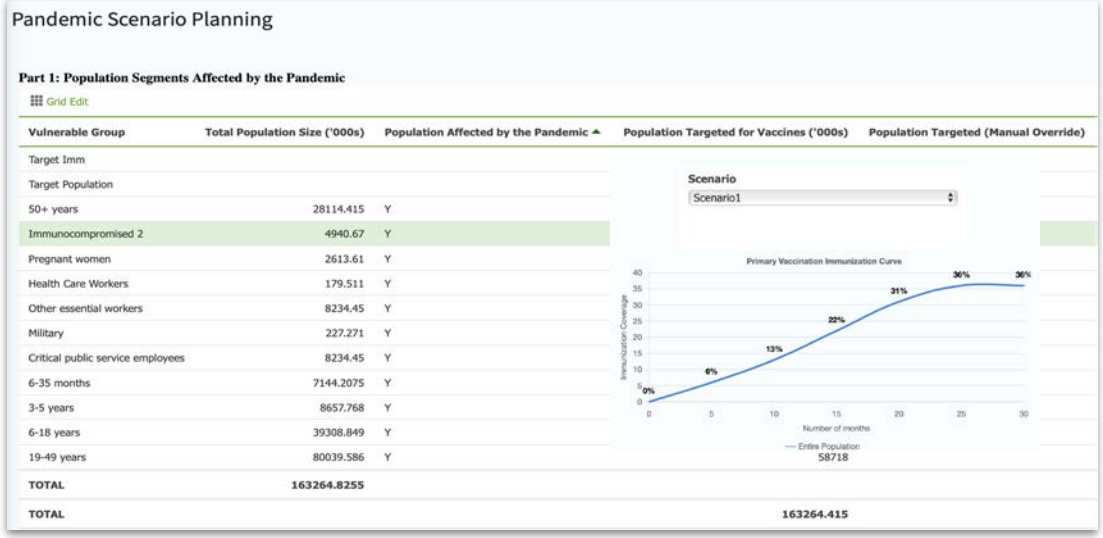
2 **Forecast Outputs**: Results of the seasonal influenza forecast in the form of visual charts and tabular data, allowing for budget allocation among the target groups



3 **Vaccination Campaign Planning:** Comparison of campaign planning current and recommended states, and estimation of impact of delay



4 **Pandemic Scenario Planning:** Vaccine demand forecast during an influenza pandemic-like situation, along with ability to simulate different scenarios



Questions to IVIR-AC

1. How can **access** to the current tool be **enhanced** ?
2. How can **use** by public health managers be **strengthened**?
3. An extension of the tool is in preparation to forecast next generation (improved) influenza vaccine demand. What is IVIR-AC's advice on assumptions to be considered for this new functionality, including the "improved" vaccine **features** to be considered?

Vaccine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Vaccine complacency and dose distribution inequities limit the benefits of seasonal influenza vaccination, despite a positive trend in use

Abraham Palache [a,*], Steven Rockman [b,c], Beverly Taylor [d], Meral Akcay [e], John K Billington [f], Paula Barbosa [g], on behalf of the IFPMA Influenza Vaccine Supply (IFPMA IVS) task force

[a] Consultant at Abbott, C.J. van Houtenlaan 36, 1381 CP Weesp, the Netherlands
[b] Seqirus Ltd, 63 Poplar Road, Parkville, Victoria 3052, Australia
[c] Department of Immunology and Microbiology, the University of Melbourne, Parkville, Victoria, Australia
[d] Seqirus Vaccines, Renaissance Way, Speke, Liverpool L24 9JW, UK
[e] Sanofi Pasteur, 2 Ave Pont Pasteur, Lyon 69007, France
[f] GSK Vaccines, Av. Fleming 20, 1300 Wavre, Belgium
[g] International Federation of Pharmaceutical Manufacturers and Associations, Ch. des Mines 9, P.O. Box 195, 1211 Geneva 20, Switzerland

ARTICLE INFO

Article history:
Received 11 June 2021
Received in revised form 26 August 2021
Accepted 27 August 2021
Available online xxxx

Keywords:
Seasonal influenza
Vaccination policy
Vaccination coverage rates
Pandemic preparedness
Vaccine recommendations
Monitoring and evaluation

ABSTRACT

Sustainable demand for seasonal influenza vaccines is a component of national security strategies for pandemic preparedness. However, the ongoing COVID-19 pandemic has revealed many weaknesses in the capacity of countries to design and execute sustainable vaccination programs. An influenza pandemic remains a global threat and yet there is no global monitoring system for assessing progress towards influenza vaccination coverage targets. The International Federation of Pharmaceutical Manufacturers and Associations' (IFPMA) Influenza Vaccine Supply International Task Force (IVS) developed a survey method in 2008 to estimate seasonal influenza vaccination coverage rates, which in turn serves as a crude estimate of pandemic preparedness. It provides evidence to guide expanded efforts for pandemic preparedness, specifically for increasing COVID-19 vaccine immunization levels. Furthermore, the results presented herein serve as a proxy for assessing the state of pandemic preparedness at a global and regional level. This paper adds data from 2018 and 2019 to the previous analyses. The current data show an upward or stable global trend in seasonal influenza vaccine dose distributed per 1,000 population with a 7% increase between 2017 and 2018 and 6% increase between 2018 and 2019. However, considerable regional inequities in access to vaccine persist. Three regions, Africa, the Middle-east, and Southeast Asia together account for 50% of the global population but only 6% of distributed seasonal influenza vaccine doses. This is an important finding in the context of the ongoing COVID-19 pandemic, as distribution of influenza vaccine doses in many ways reflects access to COVID-19 vaccines. Moreover, improving seasonal vaccine uptake rates is critical for optimizing the annual benefits by reducing the huge annual influenza-associated societal burdens and by providing protection to vulnerable individuals against serious complications from seasonal influenza infections.
© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

The World Health Organization's (WHO) Global Action Plan for Influenza Vaccines (GAP) was established in 2006 to increase the production capacity for influenza vaccines, one of several critical actions needed to better prepare for an influenza pandemic [1]. When it ended in November 2016, the GAP had increased seasonal influenza vaccine use and quadrupled the potential production capacity for pandemic influenza vaccine, including through the establishment of local production in low- and middle-income countries (LMICs). Despite improving capacity and accessibility, the report of the third consultation on the GAP concluded that the world was still not ready to adequately respond to an influenza pandemic and that the initial approaches used were unlikely to achieve further progress. Making up for a shortfall of 3.6 billion doses in production capacity would depend on sustainable demand

* Corresponding author.
E-mail addresses: bram.palache@ziggo.nl (A. Palache), Steven.Rockman@Seqirus.com (S. Rockman), Beverly.Taylor@Seqirus.com (B. Taylor), Meral.Akcay@sanofi.com (M. Akcay), john.k.billington@gsk.com (J.K Billington), p.barbosa@ifpma.org (P. Barbosa).

https://doi.org/10.1016/j.vaccine.2021.08.097
0264-410X/© 2021 The Authors. Published by Elsevier Ltd.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Please cite this article as: A. Palache, S. Rockman, B. Taylor et al., Vaccine complacency and dose distribution inequities limit the benefits of seasonal influenza vaccination, despite a positive trend in use, Vaccine, https://doi.org/10.1016/j.vaccine.2021.08.097

for seasonal vaccines as part of health security strategies in countries.

To help better prepare for an influenza pandemic, in 2019 the WHO launched its 2019-2030 Global Influenza Strategy [2]. Amongst the 4 objectives of the strategy are the specific actions for countries to "design and implement evidence-based immunization policies and programmes to reduce transmission and disease severity" and for stakeholders to "strengthen national, regional and global planning to enable timely and effective pandemic readiness". The Pandemic Influenza Risk Management (PIRM) guidance, which includes pandemic vaccine production (revised in 2017 [3]), advocates for advanced planning and preparedness to mitigate the impacts of an influenza pandemic. In 2020, the WHO embarked on the development of the Pandemic Influenza Vaccine Response Operational Plan (PIVR OP) [4], based on the outputs of the WHO Pandemic Switch meetings held from 2015 to 2017 [5,6,7] to review the influenza vaccine response during the start of a pandemic. The PIVR-OP is intended to convey how the WHO will operationalize the response to an influenza pandemic. However, as the recent ongoing COVID-19 pandemic has revealed, many weaknesses remain in the capacity of countries to design and execute sustainable vaccination programs. In this regard, Ready2Respond [8], a collaboration between public and private and non-profit sectors, is committed to help low- and middle-income countries use seasonal influenza vaccination programs as a foundation for using vaccines in the event of an emergency such as COVID-19.

The COVID-19 pandemic highlights the consequences of lack of pandemic preparedness, and unfortunately the world remains unprepared for the next influenza pandemic. For example, there is no global monitoring system for influenza vaccination coverage. This is problematic given that ensuring high seasonal influenza vaccination coverage is also an important step towards pandemic preparedness. The International Federation of Pharmaceutical Manufacturers and Associations' (IFPMA) Influenza Vaccine Supply International Task Force (IVS) developed a survey method in 2008 to assess the global distribution of influenza vaccine doses as a proxy for vaccination coverage rates [9], which serves as a crude estimate of this important aspect of pandemic preparedness.

Three regions, Africa (AF), the Middle East (EM), and Southeast Asia (SEA), which account for about 50% of the global population, have consistently only accounted for about 5% of the share of distributed doses. This is an important finding in the context of the ongoing COVID-19 pandemic as distribution of influenza vaccine doses may be a useful proxy for access to COVID-19 vaccines.

This paper adds data from 2018 and 2019 to the previous analyses of seasonal influenza vaccine distribution. These data help to monitor progress toward vaccination coverage and pandemic preparedness goals and provide evidence to guide expanded efforts for pandemic preparedness, specifically for increasing COVID-19 vaccine immunization levels, and to identify weaknesses in current strategies and tactics. Furthermore, the results presented herein serve as a proxy for assessing the state of pandemic preparedness at a global and regional level. They show that much remains to be done to achieve timely and effective pandemic readiness, underscoring the urgency and importance of WHO's and other global efforts underway to better prepare the world for the next pandemic.

2. Methods

The survey methodology was previously described by Palache [9]. Member companies of the IFPMA IVS (Abbott Biologicals, Adimmune Corporation, Biken, Denka Seiken, GC Pharma, GlaxoSmithKline, Hualan Biological, Institute of Ultrapure Biologicals, Kitasato Daiichi Sankyo Vaccine, Saint-Petersburg Scientific Research Institute of Vaccines and Sera, Sanofi Pasteur, Seqirus, Sinovac, and Takeda), who agreed to provide information on the doses of seasonal influenza vaccine supplied to all WHO Member States during 2018 and 2019. The survey results were confidentially collected and aggregated by the IFPMA Secretariat, in compliance with anti-trust regulations. The resulting anonymized database was then combined with the results of the previous IFPMA IVS surveys (2004–2017). Data were available from a total of 195 countries over the 2004–2019 period.

The manufacturers covered by the survey are based in 13 countries and represent approximately 90% of all influenza vaccine manufacturers globally [10]. Although there has been an increase in the total number of companies producing influenza vaccines in the last decade, the proportion of vaccines covered by the survey has remained relatively constant, declining by only about 5% (from 95% to 90%) since 2013 [11].

In order to assess changes in the distribution of seasonal influenza vaccines we used the following parameters, in each year, for all countries, and then categorized data into WHO regions:

- the numbers of countries in which any seasonal influenza vaccine doses were distributed;
- the absolute number of seasonal influenza vaccine doses distributed;
- the number of doses distributed to each country per 1,000 persons
- the annual number of countries globally and in each WHO region with doses distributed $\geq$ 15.9% of the population (the **"hurdle rate**" - defined in a previous survey [9] based on the proportion of the elderly proportion in 2008 [12]).

To adjust for the population size of each country, we used population data from the World Bank [13]. For each of the above parameters, we conducted the following critical analyses over the entire survey period, and over 5-year intervals (2005 – 2009, 2010 – 2014, and 2015 – 2019):

- the compound annual growth rate (CAGR), using Microsoft Excel 365, where:
  CAGR = [(rate per 1,000 in 2019 − rate per 1,000 in 2004)$^{1/16}$ − 1] × 100;

As in previous IFPMA IVS surveys [9], we also assessed:

- the correlation between the natural log numbers of doses distributed per 1,000 population and natural log of the country Gross National Income (GNI), for countries with any distributed doses globally and in each WHO region, using the regression function in the data analysis add-in for Microsoft Excel 365.

3. Results

Numbers of countries in which any seasonal influenza vaccine doses were distributed – Globally, the number of countries where any doses of seasonal influenza vaccine were distributed increased from 108 in 2004 to 134 in 2019. Note that the total number of countries in the current survey (195) is lower than in the previous survey (200) because of reclassification of Hong Kong, and Macao into a single reporting country (China) and the combination of reports from New Caledonia, French Polynesia, and Wallis and Fatuna with France. The 1.5 % CAGR in the number of countries distributing any doses between 2004 and 2019 remains unchanged from the previous survey (2004–2017). In 2019, 135 countries had some level of dose distribution. The number of countries distributing any doses has remained fairly constant since 2012, except in 2018 when the number of countries dropped by 20 to 115. The

peak year for number of countries distributing any doses was 2011 (140 countries), the year after the 2009–2010 pandemic.

Absolute number of seasonal influenza vaccine doses distributed – The total number of doses distributed in 2004 was approximately 262 million and this had risen to about 531 million in 2019, an overall 103% increase (Supplemental Fig. 1). However, compared to the peak number of doses distributed in 2014 of 534 million doses, the 2019 total represents a 0.3% decline. The overall growth in the number of doses distributed has largely been driven by the increase in absolute number of doses distributed in the Americas (AM) (a 154 million dose difference between 2004 and 2019).

The share of doses distributed to AM has increased from about 41% in 2004 to 49% in 2019, whereas the share for European region (EU) has declined from 34% in 2004 to 27% in 2019. The share from the Western Pacific (WP) has oscillated between an all-time high of 24% in 2004 to a low of 18% in 2019. In 2019, three regions, AF, EM, and SEA, together accounted to 50% of the total population, but only 6% of the share of distributed doses.

Numbers of countries with distributed doses ≥ "hurdle rate" – Globally, the number of countries that achieved the hurdle rate doubled between 2004 and 2019 (from 16 to 31 countries) but the growth in number of countries was not steady, with a year-to-year variation of between 1 and 10. No countries in AF, EM or SEA achieved the hurdle rate in 2019, compared to 18 countries in EU, 9 in AM and 4 in WP.

Numbers of doses distributed in each country per 1,000 persons – The AM and EU regions have consistently had higher distribution rates of seasonal influenza vaccine per 1,000 population than the global rate of 70 doses per 1,000 population (Fig. 1). In 2019, the rate in AM was 259 per 1,000 population, an overall CAGR of 5% between 2004 and 2019. However, the 2019 rate is 20% lower than the peak rate of 322 in 2014. In EU, the 2019 rate of 153 doses per 1,000 population was the highest it has been since the peak of 167 in 2009 (or 8% lower than in the peak year). While the rate in EU is the highest it has been in a decade, it is still 41% lower than the rate in AM, and the EU rate is still marginally below the hurdle threshold. The AM region has consistently surpassed the hurdle rate since 2005 whereas the EU region has only twice exceeded the hurdle rate (in 2008 and 2009). In WP, the rate of 51 per 1,000 population is higher than in recent years, but still below the global rate of 70 per 1,000.

However, the overall regional growth rates in dose distribution mask inequities of distribution within each region. The intra-regional ranges are shown in Supplemental Fig. 2. The greatest inequities in distribution can be observed in AF, where a majority of countries (66%) have no distribution, and in WP where 54% have none, and in SEA where the median dose distribution rate is only 2 doses per 1,000 population.

Five-year average numbers of doses distributed –There was little change in the 5-year average number of doses distributed for the last two periods. The 5-year average declined slightly in WP and AM (two regions with high use) and globally (Fig. 2). All three regions where vaccine usage is the lowest (EM, SEA, AF) showed steady increase from period to period, but the averages are very small relative to the other regions.

Percentage of vaccines per population – Fig. 3 shows the percentage of vaccines distributed per population, by WHO region, for

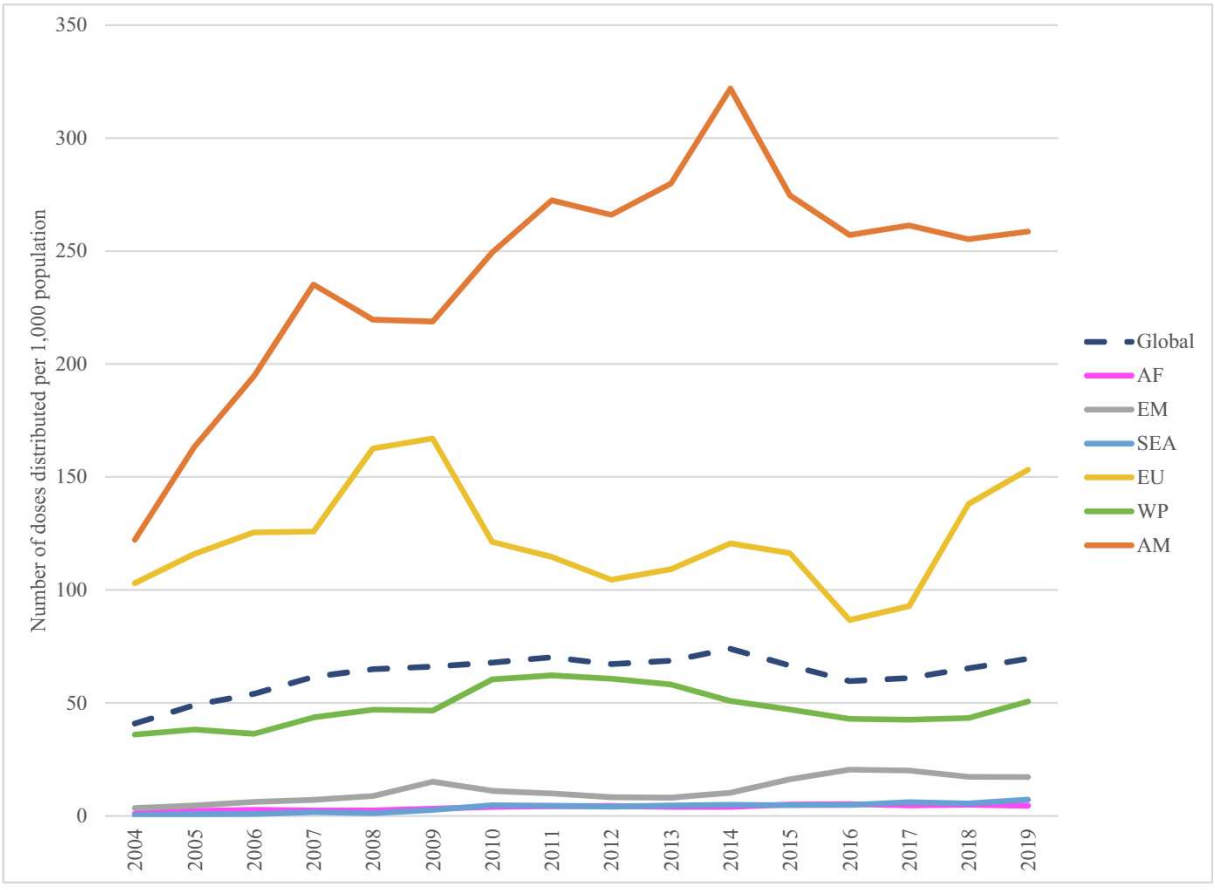


Fig. 1. Number of doses of seasonal influenza vaccine distributed per 1,000 persons by year and WHO region.

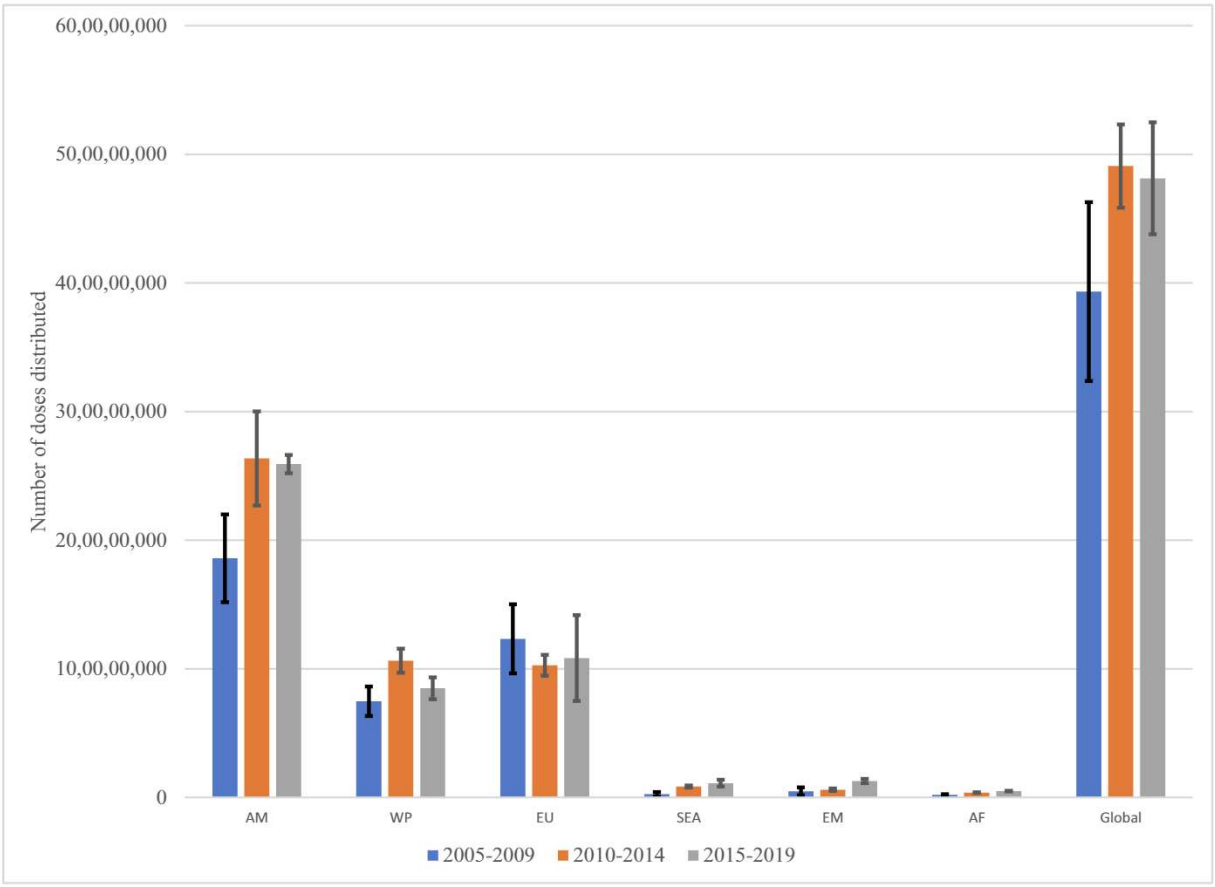


Fig. 2. Five-year average number of doses of seasonal influenza vaccine distributed by WHO region.

the latest year for which there is data (2019). As noted above, the AM region is the only region that exceeds the "hurdle rate" of 15.9%.

Correlation between doses distributed per 1,000 persons and Gross National Income (GNI) – As in the previous IFPMA IVS surveys, we assessed the correlation between doses per 1,000 population and country GNI for 2018 and 2019 (Table 1). Globally the correlation in 2018 and 2019 was weak ($r^2 = 0.46$, $r^2 = 0.52$ respectively), but in some regions, like WP, the correlation was moderate ($r^2 = 0.64$, $r^2 = 0.69$) and achieved significance. The correlation was not significant in AM and SEA and very weak in AM at $r^2 = 0.01$, and $r^2 = 0.16$ in 2018 and 2019 respectively. Just as for the number of doses distributed in each region, gross variations in GNI exist within a region. The intra-regional ranges are shown in Supplemental Fig. 3. The smallest range can be observed in AF and SAE where the highest GNI is considerably lower than in other regions. Nevertheless, even in regions with the greatest variation in GNI, there was little or no association between GNI and dose distribution levels, suggesting that there are other factors that are more critical to vaccine uptake in all regions.

4. Discussion

The IFPMA IVS dose distribution survey is a valuable tool for monitoring year-to-year progress in the utilisation of seasonal influenza vaccine doses and may be a useful proxy for assessing pandemic preparedness. Globally, over the last 16 years, there has been steady but modest progress in global distribution of influenza vaccine doses, rising from 41 per 1,000 population in 2004 to 70 per 1,000 population in 2019. Most of the growth has been driven by AM region and to a lesser extent EU region. In both regions, distribution peaked several years ago (in 2014 in AM and in 2009 in EU), although dose distribution in EU has been trending upwards since 2016. Furthermore, only AM has consistently surpassed the hurdle rate of 15.9% of the population. All WHO regions except AF saw positive trends in vaccine distribution for the 2018–2019 period.

The most notable increase in vaccine dose distribution occurred in the EU region, where distributed doses rose by a remarkable 49% between 2017 and 2018 and then again by another 11% between 2018 and 2019. A positive trend in the 5-year averages is also noted for the EU region, where there was a 5% increase in the 5-year average for the latest period (2014–2019) over the previous period (2010–2014). We also note substantive increases in the 5-year averages over the previous period for SEA, EM and AF: 31%, 113%, and 34% respectively. The 5-year average remained virtually constant for AM (just a 2% decline from 2010 to 2014 to 2015–2019) but dropped by 20% for the WP region where year-to-year distribution has been more variable. However, WP did see a 17% increase in doses distributed per 1,000 population between 2018 and 2019. These findings suggest that for the most recent years there is an upward or stable trend in vaccine dose distribution with a 7% increase between 2017 and 2018 and 6% increase in doses distributer per 1,000 population between 2018 and 2019 globally.

As noted in Fig. 3, there continue to be considerable inequities in the percentage of population that has access to a dose of vaccine across WHO regions. The highest percentage of doses per population are available in AM (26%) and EU (15%) whereas regions like SEA and AF have less than 1%, and WP is in between with 5%. This is an important finding in the context of the ongoing COVID-19

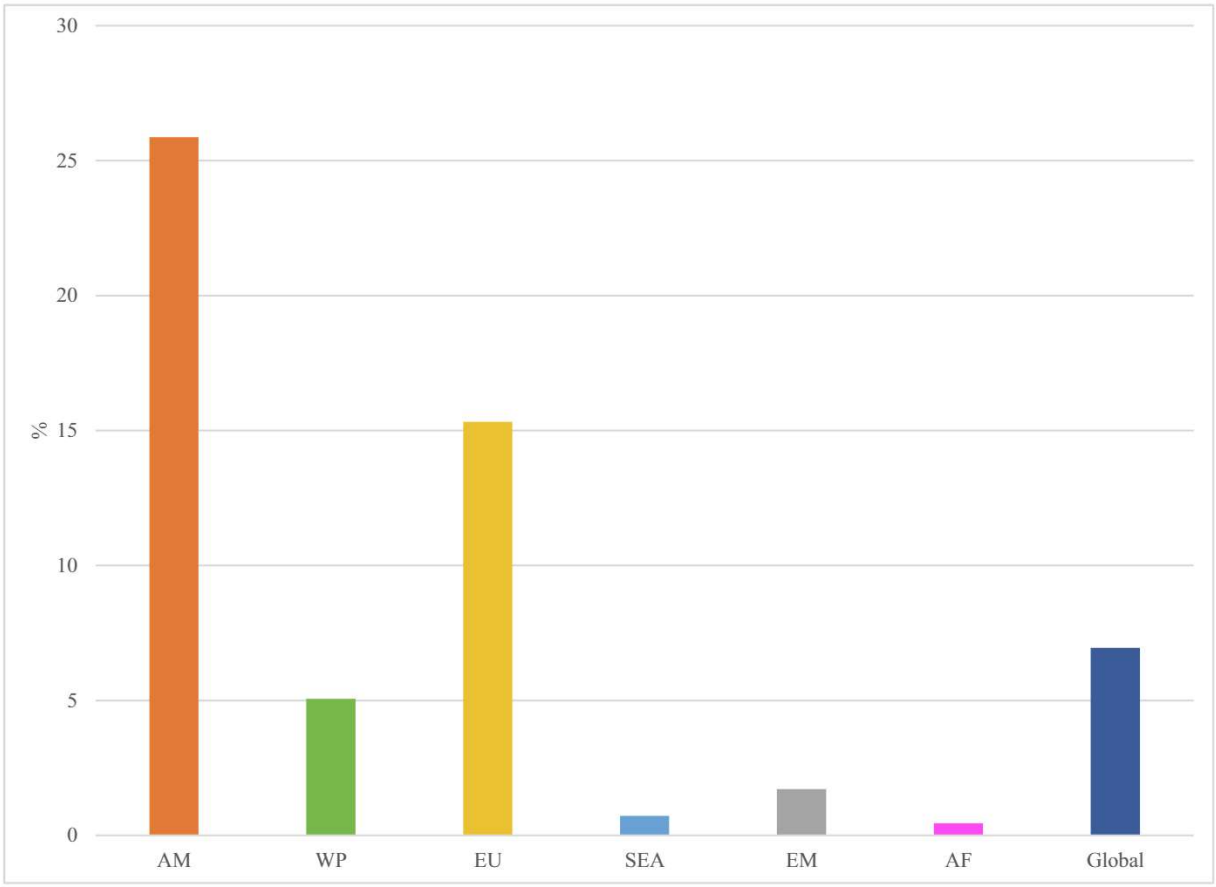


Fig. 3. Percentage vaccine distribution per population in WHO regions in 2019.

Table 1
Correlation between numbers of doses distributed per 1,000 population and GNI for 2018 and 2019, using regression in Microsoft Excel 365.

	2018			2019		
	n	r^2	significance	n	r^2	significance
Global	114	0.46	p = 0.000	133	0.52	p = 0.000
AM	28	0.01	p = 0.550	33	0.16	p = 0.023
WP	11	0.64	p = 0.003	13	0.69	p = 0.000
EU	46	0.65	p = 0.000	48	0.57	p = 0.000
SEA	7	0.55	p = 0.064	8	0.27	p = 0.184
EM	14	0.64	p = 0.000	17	0.65	p = 0.000
AF	8	0.63	p = 0.018	14	0.70	p = 0.000

pandemic and concerns surrounding equitable access to vaccination, as distribution of influenza vaccine doses in many ways reflects access to COVID-19 vaccines and suggests that regions with better access to influenza vaccines also have better access to pandemic vaccines. As of March 2021, 380 million doses of COVID-19 vaccine have been administered with 29% in the US, 13% European Union, 7% United Kingdom and <6% South America [14].

The COVID-19 pandemic may also pose an additional concern regarding uptake of influenza vaccination. While vaccination coverage for the 2020–2021 influenza season has increased in many countries [15,16], the record low number of influenza cases reported in many regions [17,18,19] may lead to complacency in the coming season (2021 southern hemisphere seasons and 2021–2022 northern hemisphere season). Vaccine complacency is a recurring impediment to seasonal vaccination coverage [20,21]. Of particular concern is that the low rate of transmission over the last season may leave the public particularly vulnerable to influenza in the coming season due to waning immunity from lack of exposure and the potential for new strains to arise [22]. One strain change (H1N1 for the 2021 – 2022 northern hemisphere campaign) has already occurred during the COVID-19 pandemic [23]. Thus, influenza viruses still evolve effectively and new emerging strains will likely cause severe seasons, possibly coinciding with the end of the COVID-19 pandemic. An influenza – SARS-CoV-2 syndemic would have devastating public health consequences, hence the importance of optimizing pandemic response capabilities with seasonal influenza vaccination.. Influenza vaccination has a important role to play in mitigating the impacts of COVID-19 by facilitating the management of respiratory outbreaks

by reducing the epidemiological noise of influenza and by securing the infrastructure to deliver other routine immunizations during the pandemic [24].

Further confounding the situation are national efforts to rollout COVID-19 vaccines during the influenza season, which may impede influenza vaccination uptake either because of the heightened priority of COVID-19 over influenza vaccination or because the earlier recommended 14 day interval between COVID-19 and influenza vaccinations [25,26,27] may limit influenza vaccine uptake in countries where this interval is maintained. Influenza remains a global healthcare challenge, and a syndemic of COVID-19 and influenza would create significant issues with respect to clinical management, diagnosis, and strain upon global health resources. Stowe et al [28] found that coinfection of influenza and SARS-CoV-2 increased the risk of death 6-fold compared to those without either infection, and doubled the risk of ventilation or admission to ICU, and therefore may have a significant impact on demand for health services.

The annual burden of influenza-associated disease, hospitalizations and deaths is well recognised and documented [29,30,31,32], and influenza is known to contribute to social and healthcare costs from NCDs [33,34,35,36,37]. The WHO position paper on the use of influenza vaccination is clear and soundly supported by evidence [29]. Even when vaccine effectiveness is low, large numbers of cases can be prevented [38]. Low vaccination coverage can result from poor appreciation of disease burden by the public, and lack of prioritization within national budgets [38]. However, estimates of the impact of influenza vaccination on disease reduction and broader societal health systems are very compelling in favour of the value of vaccination [39,40,41]. In the US, Kostova et al [40] estimated that between 1 and 5 million influenza cases were averted each season by vaccination. In Europe, Preaud et al [41] estimated that vaccination prevents between 1.6 million and 2.1 million cases of influenza each year and 45,300 to 65,600 hospitalizations and 25,200 to 37,200 deaths. Furthermore, this report and the previous IFPMA IVS survey reports [9,42,43,44] indicate that GNI is not a strong determinant of dose distribution. Influenza therefore remains "a preventable disease not being prevented" [45] and considerable economic and healthcare burden continues to occur because of seasonal influenza [41].

Globally, COVID-19 vaccination strategies have opened the door to new vaccine technologies with the potential to increase vaccine effectiveness through improved T cell mediated responses and these vaccines will most likely be applied to influenza. Much research and development effort continues to be expended on the development of novel 'universal' influenza vaccines that would impart lasting immunity and not require annual revaccination [46,47]. Ultimately, these efforts may inspire further improvement of future influenza immunization programs. At the same time, current seasonal vaccine production capacity is only at 50% [1], so better use of existing vaccines is possible and required from a public health perspective. Making better use of the existing vaccines is critical so that when the next generation of vaccines arrives, the necessary infrastructure and programs are in place to best ensure uptake and impact on public health.

The primary limitation of this study is the exclusion of data from non-IFPMA manufacturers from the survey, however we note that 90% of all influenza vaccine manufacturers globally are covered [10]. In addition, the survey does not consider the impact of vaccination policies and practices on the uptake of vaccines. Since vaccination policies apply to target groups other than persons over 65 years of age, our method underestimates the true coverage gaps in country programs. Nevertheless, this survey provides some of the most comprehensive data on global influenza prevention and can serve as an important proxy parameter for pandemic preparedness.

5. Conclusion

The current IFPMA IVS survey shows a positive tendency in the uptake of influenza vaccines in the last two years (2018 and 2019). The survey also provides an important proxy for country pandemic readiness as influenza vaccination infrastructure is ideally suited for a viral respiratory disease pandemic response. However, while the benefits of seasonal influenza vaccination are clear and well documented by the WHO, vaccine complacency continues to reduce the potential benefits of influenza vaccination at a population level. Fifty percent of the global population has access to only a 6% share of distributed doses. The COVID-19 pandemic provides an opportunity for countries to build or improve existing immunization systems and at the same time enhance their pandemic readiness. The WHO's 2019–2030 strategy and tactics and the efforts of the Ready2Respond collaboration are available to support countries in optimizing the use of existing influenza vaccines. Improving seasonal vaccine uptake rates is not only an important driver for pandemic preparedness, but also for optimizing the annual benefits in the at-risk individuals for whom vaccination is recommended. Increased vaccine uptake can substantially reduce the huge annual influenza-associated societal burden as well as protect vulnerable persons against serious complications from influenza infections.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Abraham Palache reports a relationship with Abbott that includes: consulting or advisory. Abraham Palache, Steven Rockman, Beverly Taylor, Meral Akcay, John K Billington are full-time or contract employees of member companies of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Influenza Vaccine Supply International Task Force (IVS). The IFPMA IVS member companies develop, manufacture and supply the majority of the world's influenza vaccines. Representatives of IFPMA IVS member companies may have other financial interests in those companies. Paula Barbosa is a full-time employee of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

Acknowledgements

The study was commissioned and funded by the IFPMA IVS. The IFPMA IVS provided input into the study design, data collection, analysis, manuscript writing, and decision to submit the manuscript for publication. Consequently, the resultant manuscript is submitted on behalf of IFPMA IVS. The authors gratefully acknowledge the writing services of Shawn Gilchrist, president of S Gilchrist Consulting Services Inc.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.08.097.

References

[1] World Health Organization. Report of the Third WHO Consultation on the Global Action Plan for Influenza Vaccines. Geneva, Switzerland, 15–16 November 2016. Available at: http://apps.who.int/iris/bitstream/handle/10665/259727/WHO-HIS-TTi-17.6-eng.pdf;jsessionid=8226CB8099F043948B-45AB5E283D95EA?sequence=1. Accessed April 22, 2021.

[2] World Health Organization. Global influenza strategy 2019-2030. World Health Organization; 2019. Available at: http://www.who.int/iris/handle/10665/311184. Accessed Aug 2, 2019.

[3] World Health Organization. Pandemic Influenza Risk Management: A WHO guide to inform and harmonize national and international pandemic preparedness and response. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. Available at: http://apps.who.int/iris/bitstream/handle/10665/259893/WHO-WHE-IHM-GIP-2017.1-eng.pdf;jsessionid=C57DD85154E5CB99358377BA5219ACE5?sequence=1. Accessed April 28, 2021.
[4] World Health Organization. WHO Pandemic Influenza Vaccine Response Operational Plan Draft Annotated Outline 1 December 2020. Available at : https://extranet.who.int/dataformv3/upload/surveys/776836/files/Draft%20WHO%20Pandemic%20Influenza%20Vaccine%20Response%20Operational%20Plan%20Annotated%20Outline_1%20December%202020.pdf. Accessed April 28, 2021.
[5] World Health Organization. Influenza Vaccine Response during the Start of a Pandemic. Report of a WHO Informal Consultation held in Geneva, Switzerland, 29 June - 1 July 2015. Available at: https://apps.who.int/iris/bitstream/handle/10665/207751/WHO_OHE_PED_GIP_2016.1_eng.pdf;sequence=1. Accessed July 29, 2021.
[6] World Health Organization. Influenza Vaccine Response during the Start of a Pandemic. Report of the Second WHO Informal Consultation held in Geneva, Switzerland 21 -22 July 2016. Available at: https://apps.who.int/iris/handle/10665/254743. Accessed July 29, 2021.
[7] World Health Organization. Influenza Vaccine Response During the Start of a Pandemic. Report of the Third WHO informal consultation, 7-9 June 2017, Geneva, Switzerland. Available at: https://apps.who.int/iris/handle/10665/325973. Accessed July 29, 2021.
[8] Ready2Respond. Available at: https://ready2respond.org/. Accessed April 28, 2021.
[9] Palache A. Seasonal influenza vaccine provision in 157 countries (2004–2009) and the potential influence of national public health policies. Vaccine 2011;29(51):9459–66. https://doi.org/10.1016/j.vaccine.2011.10.030. Epub 2011 Oct 21.
[10] International Federation of Pharmaceutical Manufacturers and Associations. Influenza vaccine supply (IVS) international task force. Available at: https://www.ifpma.org/subtopics/influenza-vaccine/. Accessed April 22, 2021.
[11] International Federation of Pharmaceutical Manufacturers and Associations. Improving pandemic preparedness. Seasonal influenza vaccination series: Paper 5. 2013. Available at: https://www.ifpma.org/wp-content/uploads/2016/01/IFPMA-IVS-Eng-FactSheet5-01.13.pdf
[12] United Nations Department of Economic and Social Affairs / Population Division. World Population Prospects 2019. Available at: https://population.un.org/wpp/Download/Standard/Population/
[13] World Bank. Population, total. Available at: https://data.worldbank.org/indicator/SP.POP.TOTL. Accessed April 28, 2021.
[14] OECD. Access to COVID-19 vaccines: Global approaches in a global crisis. March 18, 2021. Available at: https://www.oecd.org/coronavirus/policy-responses/access-to-COVID-19-vaccines-global-approaches-in-a-global-crisis-c6a18370/. Accessed May 21, 2021.
[15] Bachtiger P, Adamson A, Chow JJ, Sisodia R, Quint JK, Peters NS. The impact of the COVID-19 pandemic on the uptake of influenza vaccine: UK-wide observational study. JMIR Public Health Surveill 2021;7(4):. https://doi.org/10.2196/26734e26734.
[16] Centers for Disease Control and Prevention. Influenza (flu). Weekly National Flu Vaccination Dashboard. Available at: https://www.cdc.gov/flu/fluvaxview/dashboard/vaccination-dashboard.html. Accessed April 29, 2021.
[17] Olsen SJ, Azziz-Baumgartner E, Budd AP et al. Decreased influenza activity during the COVID-19 pandemic — United States, Australia, Chile, and South AFica, 2020. MMWR Morb Mortal Wkly Rep 2020; 69:1305–1309. DOI: http://dx.doi.org/10.15585/mmwr.mm6937a6external icon.
[18] Centers for Disease Control and Prevention. Weekly U.S. Influenza Surveillance Report. Available at: https://www.cdc.gov/flu/weekly/index.htm. Accessed April 29, 2021.
[19] World Health Organization. Influenza update – 390. 29 March 2021, based on data up to 14 March 2021. Available at: https://www.who.int/publications/m/item/influenza-update-n-390. Accessed July 29, 2021.
[20] González-Block MA, Gutiérrez-Calderón E, Pelcastre-Villafuerte BE, et al. Influenza vaccination hesitancy in five countries of South America. Confidence, complacency and convenience as determinants of immunization rates. PLoS ONE 2020;15(12):. https://doi.org/10.1371/journal.pone.0243833e0243833.
[21] Schmid P, Rauber D, Betsch C, Lidolt G, Denker ML. Barriers of influenza vaccination intention and behavior – a systematic review of influenza vaccine hesitancy, 2005–2016. PLoS ONE 2017;12(1):e0170550.
[22] Laurie KL, Rockman S. Which influenza viruses will emerge following the SARS-CoV-2 pandemic? Influenza Other Respi Viruses. 2021;00:1–4. https://doi.org/10.1111/irv.12866.
[23] World Health Organization. Recommended composition of influenza virus vaccines for use in the 2021-2022 northern hemisphere influenza season. 26 February, 2021. Available at: https://www.who.int/publications/i/item/recommended-composition-of-influenza-virus-vaccines-for-use-in-the-2021-2022-northern-hemisphere-influenza-season. Accessed July 29, 2021.
[24] Maltezou HC, Theodoridou K, Poland G. Influenza immunization and COVID-19. Vaccine. 2020;38(39):6078–9. https://doi.org/10.1016/j.vaccine.2020.07.058.
[25] Centers for Disease Control and Prevention. Vaccines and immunization. interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States. Available at: https://www.cdc.gov/vaccines/COVID-19/info-by-product/clinical-considerations.html#Administration. Accessed April 29, 2021.
[26] World Health Organization. Interim recommendations for use of the ChAdOx1-S [recombinant] vaccine against COVID-19 (AstraZeneca COVID-19 vaccine AZD1222, SII Covishield, SK Bioscience). Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-2021.1
[27] Australian Technical Advisory Group on Immunization (ATAGI). Advice on the relative timing of administering influenza and COVID-19 vaccines in 2021 Version 2.0. Available at: https://www.health.gov.au/sites/default/files/documents/2021/03/COVID-19-vaccination-atagi-advice-on-influenza-and-COVID-19-vaccines.docx. Accessed April 29, 2021.
[28] Stowe J, Tessier E, Zhao H, et al. Interactions between SARS-CoV-2 and influenza, and the impact of coinfection on disease severity: a test-negative design. Int J Epidemiol 2021:dyab081. https://doi.org/10.1093/ije/dyab081.
[29] World Health Organization. Vaccines against influenza - WHO position paper – November 2012. Wkly Epidemiol Rec 2012 Nov 23;87(47):461–76.
[30] Gasparini R, Amicizia D, Lai PL, Panatto D. Clinical and socioeconomic impact of seasonal and pandemic influenza in adults and the elderly. Hum Vaccin Immunother 2012;8(1):21–8. https://doi.org/10.4161/hv.8.1.17622. Epub 2012 Jan 1.
[31] Heikkinen T, Tsolia M, Finn A. Vaccination of healthy children against seasonal influenza: a European perspective. Pediatr Infect Dis J 2013;32(8):881–8. https://doi.org/10.1097/INF.0b013e3182918168.
[32] Iuliano AD, Roguski KM, Bresee JS, for the Global Seasonal Influenza-associated Mortality Collaborator Network. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet 2018; 391 (10127): 1285-1300. doi: 10.1016/S0140-6736(17)33293-2. Epub 2017 Dec 14.
[33] Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. New Engl J Med 2004;351:2611–8. https://doi.org/10.1056/NEJMoa041747.
[34] US Centers for Disease Control and Prevention. Flu and people with diabetes. Available at: https://www.cdc.gov/flu/highrisk/diabetes.htm. Accessed Aug 2, 2019.
[35] UK Health Protection Agency. Surveillance of Influenza and other Respiratory Viruses in the UK 2010/2011. London, UK; 2011. Available at: https://webarchive.nationalarchives.gov.uk/20140629102627/http:/hpa.org.uk/webc/HPAwebFile/HPAweb_C/1296687414154. accessed Aug 2, 2019.
[36] Madjid M, Miller CC, Zarubaev VV, Marinich IG, Kiselev OI, Lobzin YV, et al. 3rd influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34,892 subjects. EU Heart J 2007;28(10):1205–10. https://doi.org/10.1093/EUheartj/ehm035. Epub 2007 Apr 17.
[37] Plans-Rubio P. Prevention and control of Influenza in persons with Chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2007;2(1):41–53.
[38] Palache A. Global seasonal influenza disease and vaccination: a paradox with substantial public health implications. Int Med Rev 2018;4(11):1–22. https://doi.org/10.18103/imr.v4i12.775.
[39] Reed C, Chaves SS, Daily Kirley P, Emerson R, Aragon D, Hancock EB, et al. Estimating influenza disease burden from population-based surveillance data in the United States. PLoS ONE 2015;10(3):. https://doi.org/10.1371/journal.pone.0118369e0118369.
[40] Kostova D, Reed C, Finelli L, Cheng P-Y, Gargiullo PM, Shay DK, et al. Influenza Illness and Hospitalizations Averted by Influenza Vaccination in the United States, 2005–2011. PLoS ONE 2013;8(6):. https://doi.org/10.1371/journal.pone.0066312e66312.
[41] Preaud E, Macabeo B, Markas N, et al. Annual public health and economic benefits of seasonal influenza vaccination: a European estimate. BMC Public Health. 2014 Aug;7(14):813. https://doi.org/10.1186/1471-2458-14-813.
[42] Palache A, Oriol-Mathieu V, Fino M, Xydia-Charmanta M. Seasonal influenza vaccine dose distribution in 195 countries (2004–2013): little progress in estimated global vaccination coverage. Vaccine 2015;33(42):5598–605. https://doi.org/10.1016/j.vaccine.2015.08.082.
[43] Palache A, Oriol-Mathieu V, Abelin A, Music T. Seasonal influenza vaccine dose distribution in 157 countries (2004–2011). Vaccine 2014;32(48):6369–76. https://doi.org/10.1016/j.vaccine.2014.07.012. Epub 2014 Nov 1.
[44] Palache A, Tsai T, Vasiliev Y, et al. Global influenza vaccine distribution survey demonstrates urgency of implementation of objective 3 of WHO influenza strategy 2019-2030. Internal Medicine Review 2020; 6 (2). Available at: https://internalmedicinereview.org/index.php/imr/article/viewFile/850/pdf. Accessed April 29, 2021.
[45] Mostow SR. Influenza–a preventable disease not being prevented. Am Rev Respir Dis 1986;134(1):1. https://doi.org/10.1164/arrd.1986.134.1.1.
[46] Wong T, Ross TM. Steps toward a universal influenza vaccine: research models and comparison of current approaches. In Steps Forwards in Diagnosing and Controlling Influenza. IntechOpen. Ed Manal Mohammad Baddour. 2016. https://doi.org/10.5772/64369.
[47] National Institutes of Allergy and Disease. Universal influenza vaccine research. Available at: https://www.niaid.nih.gov/diseases-conditions/universal-influenza-vaccine-research. Accessed April 29, 2021.

World Health Organization

Session 4
Pneumococcal Conjugate Vaccine use in humanitarian crises

Pneumococcal conjugate vaccine use in humanitarian crises

Jenny A. Walldorf, MD, MSc

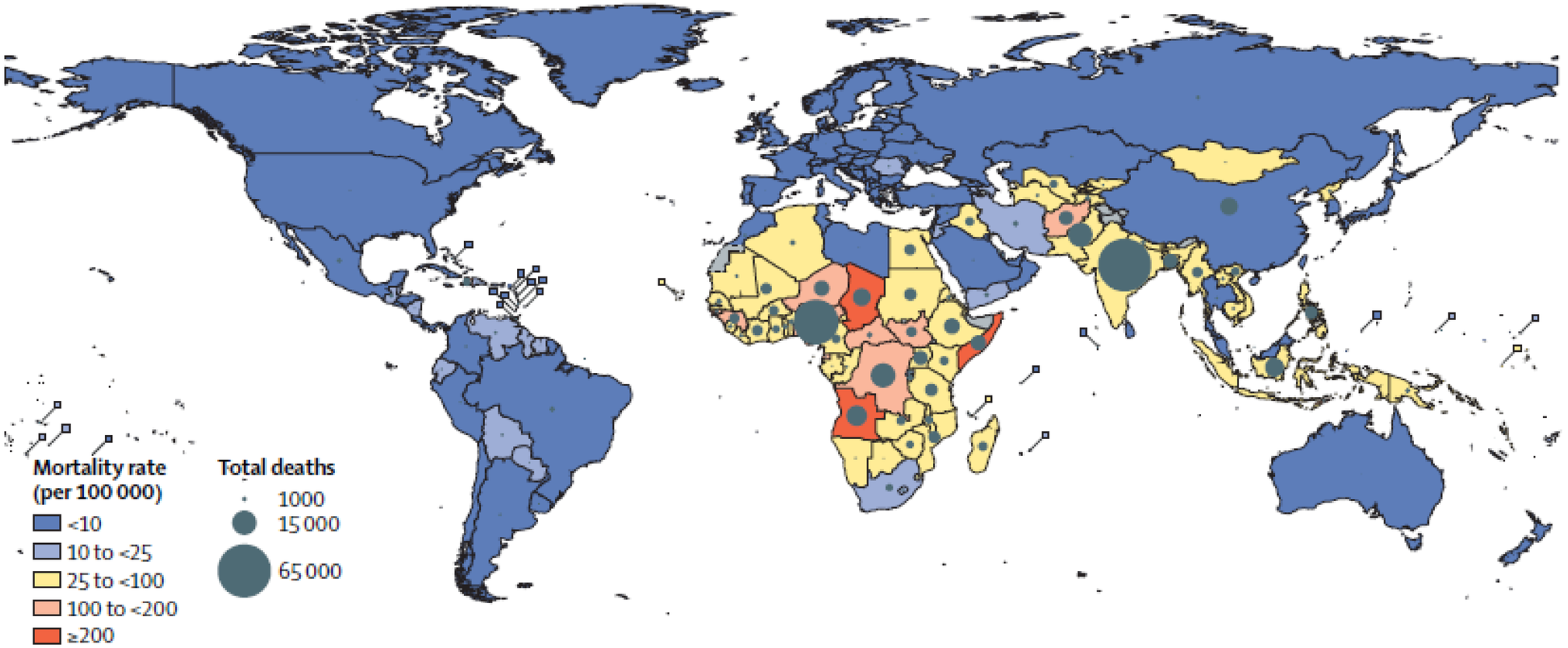
New Vaccines Officer
Lifecourse Integration Team, EPI Unit, IVB, WHO

IVIR-AC

September 13, 2022

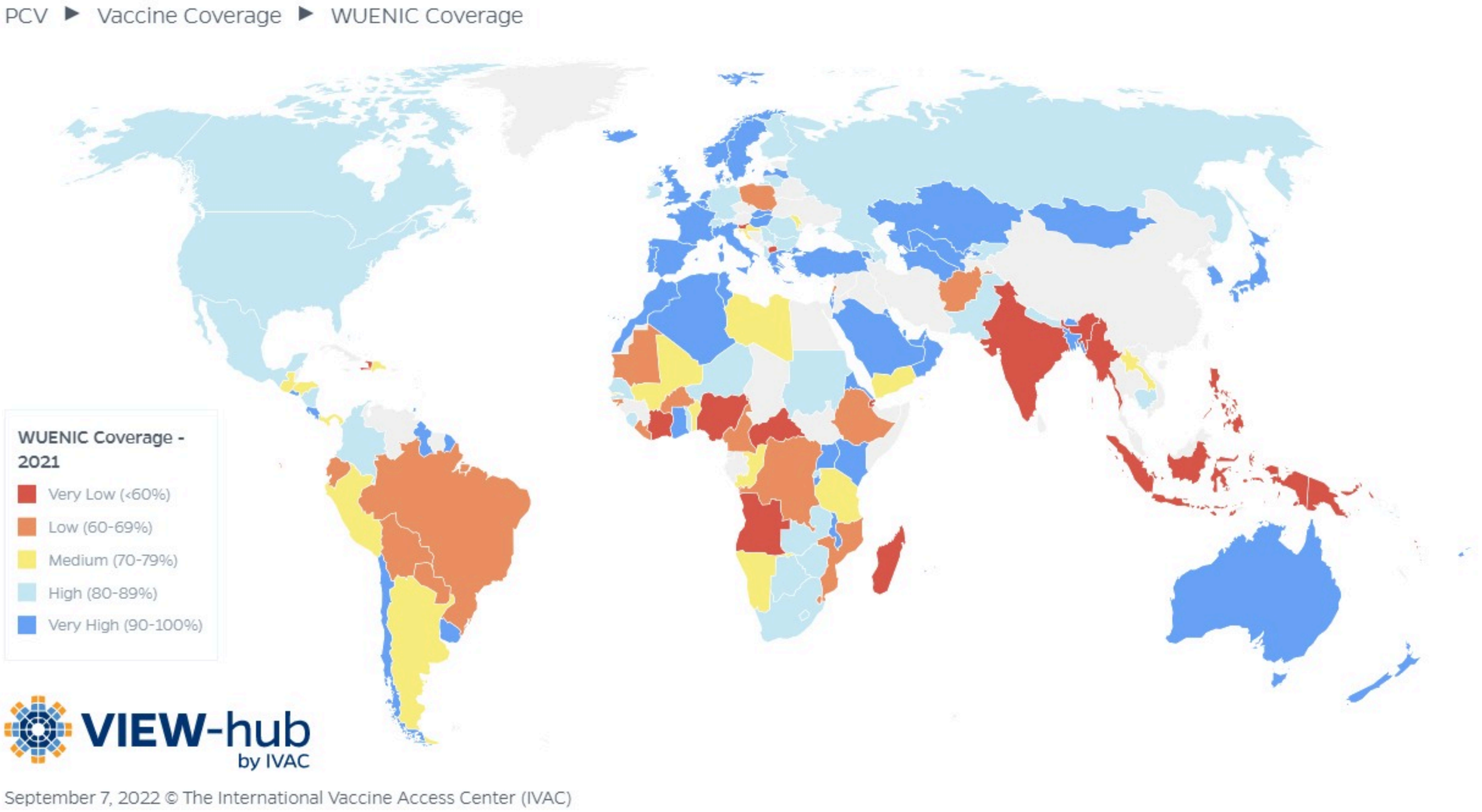
Global pneumococcal disease burden

Streptococcus pneumoniae **is the most common cause of bacterial pneumonia and one of the most common causes of meningitis in children under 5 years**



Country-specific mortality rates and deaths attributable to pneumococcus, children 1 to 59 months, 2015. *Adapted from Wahl et al. Lancet Glob Health 2018*

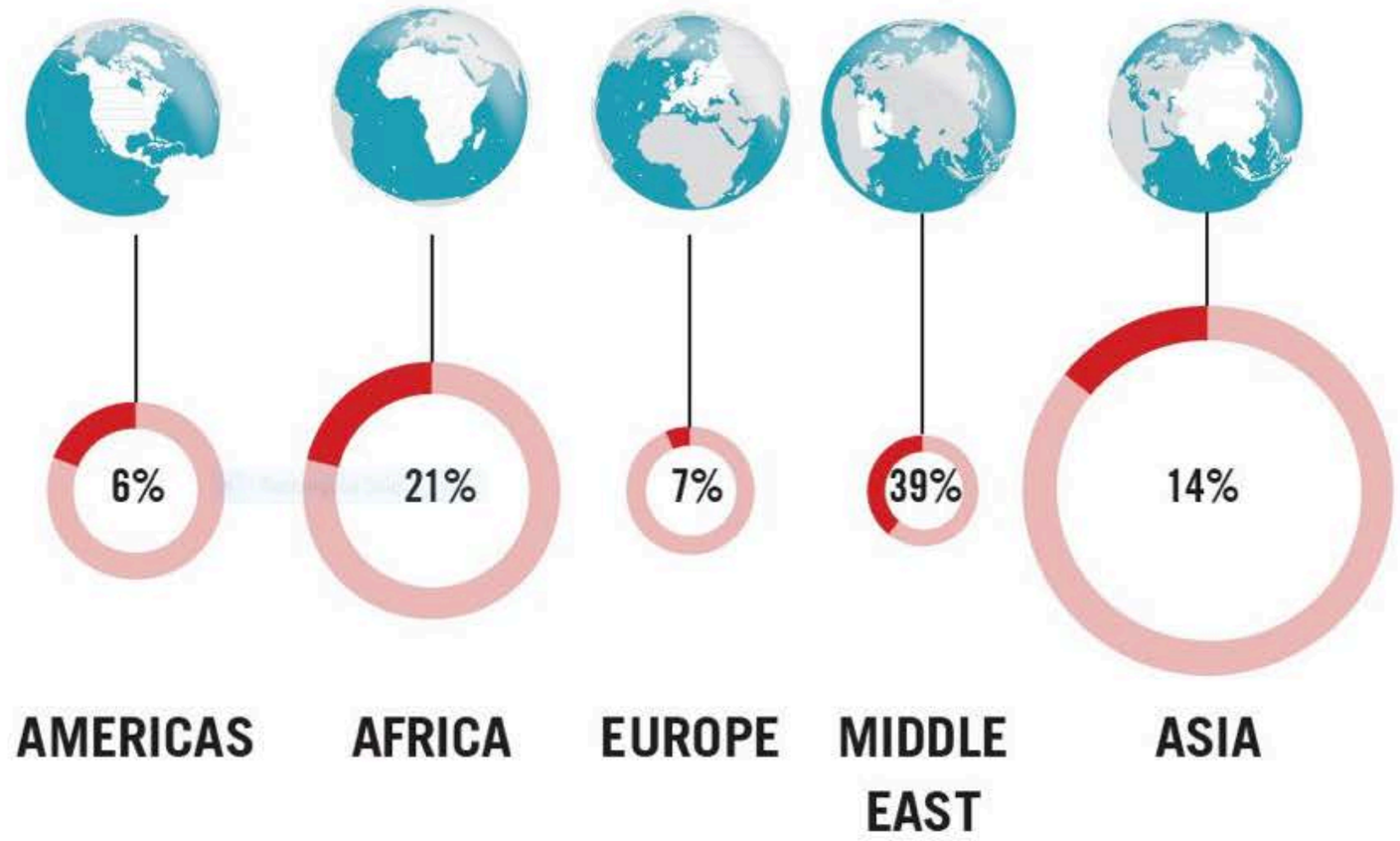
WUENIC PCV coverage estimates, 2021:
Need to recover & enhance PCV coverage to optimize protection

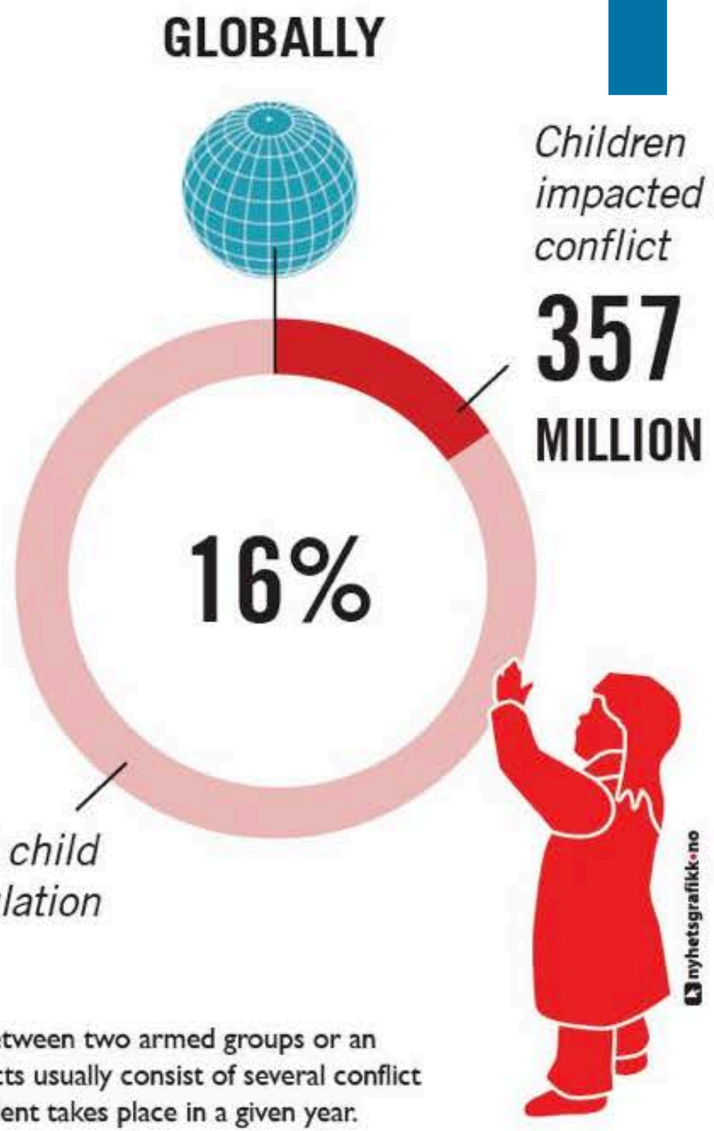


Children affected by conflict

452Mn (2020)

1 in 6 children were living in conflict areas in 2016





PRIO Save the Children

A conflict event is defined as a lethal incident, either a violent clash between two armed groups or an attack on civilians by a group/groups, at a given time and place. Conflicts usually consist of several conflict events. Conflict area: an area 50km or less from where a conflict incident takes place in a given year.

Data source: PRIO/UCDP. For more information: www.savethehildren.net/waronchildren

An estimated 50 million children are displaced or refugees worldwide, and growing in number

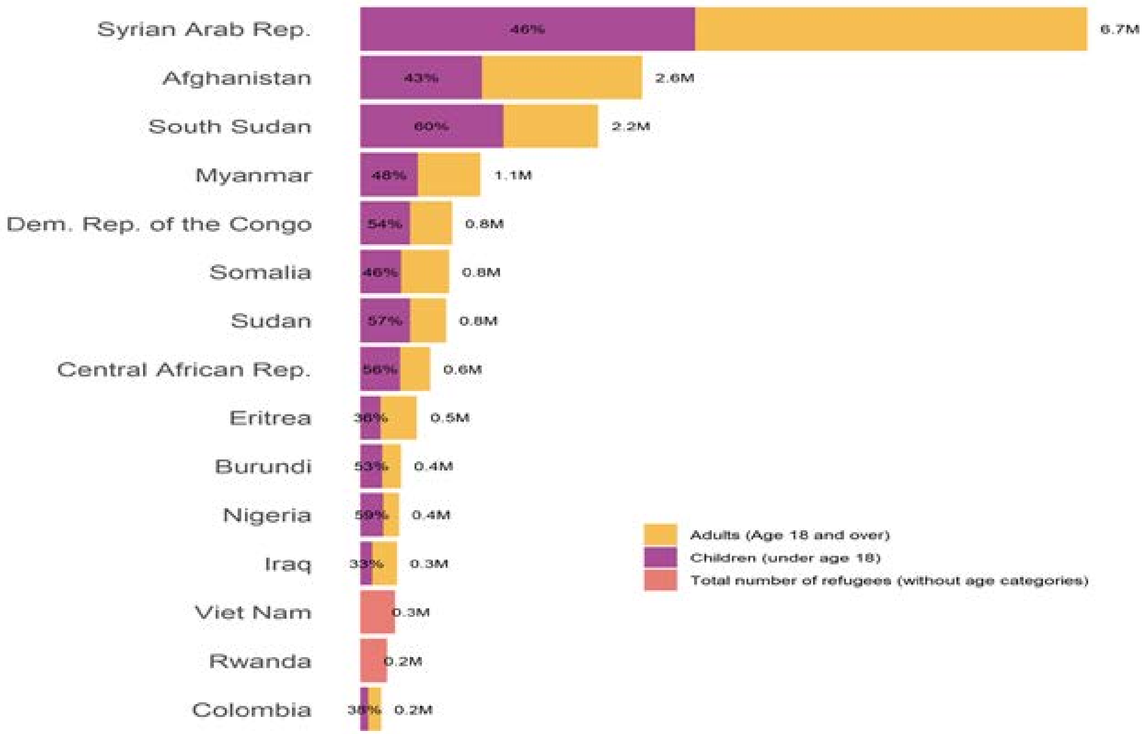
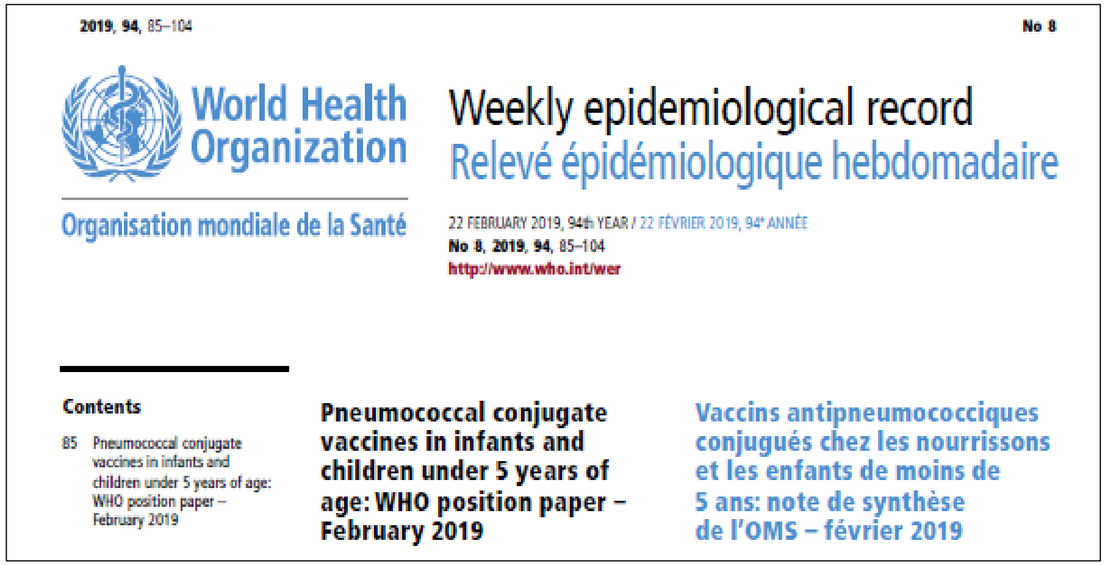


Photo courtesy of UNICEF

Figure 1. Number of refugees by age and country of origin, 2020 (in millions), Source: https://data.unicef.org/topic/child-migration-and-displacement/displacement/#_ftn1

WHO Position, 2019

- WHO recommends the inclusion of PCVs in childhood immunization programmes worldwide … **3-dose schedule** administered either as 2p+1 or as 3p+0, starting as early as 6 weeks of age.
- **In humanitarian or other emergency situations**, age-appropriate schedules of PCV vaccination should be used for children <1 year of age and considered for children ≤5 years of age, as indicated by the situation



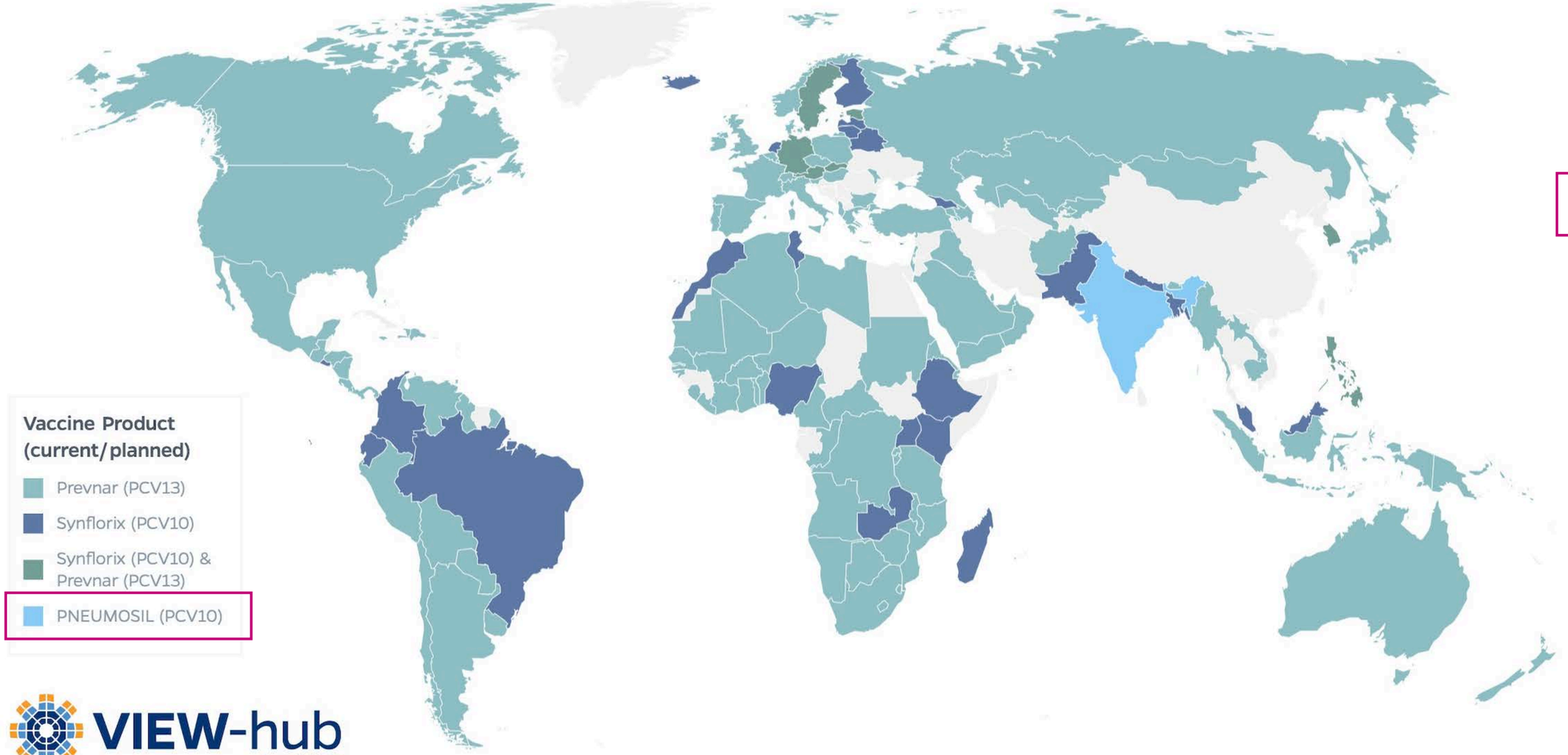
- Wherever possible, **catch-up vaccination** at the time of introduction of PCV should be used to accelerate its impact on disease in children aged 1–5 years, particularly in settings with a high disease burden and mortality.
- **Catch-up vaccination** may also be an important means to prevent outbreaks … but experience is currently lacking.

PCV use in humanitarian settings

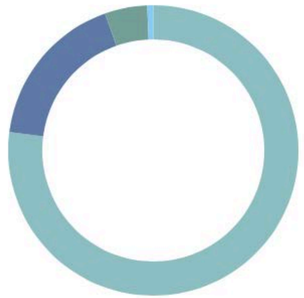
- Risk factors for pneumococcal and other respiratory pathogen transmission are high in humanitarian settings
- Yet, PCV use is not common
- Reaching children with the 3 dose PCV schedule may be very challenging in crisis settings → low coverage, high-drop out
- Lack of evidence to support recommendations for alternate implementation strategies to achieve impact in these populations

Four WHO prequalified PCV products in use

PCV Vaccine Introduction Vaccine Product (current/planned)



	Global	Gavi
Prevnar (PCV13)	**114**	50
Synflorix (PCV10)	**26**	10
Synflorix (PCV10) & Prevnar (PCV13)	**7**	0
PNEUMOSIL (PCV10)	**1**	1



VIEW-hub by IVAC

June 20, 2022 © The International Vaccine Access Center (IVAC)

Conclusion

- Studies are needed to fill the evidence gap:
  - Effectiveness and programmatic feasibility of reduced dosing schedules and catch-up or single dose campaigns in children under 5 years of age
  - Effectiveness of using newer lower cost vaccine products (i.e. PNEUMOSIL®)
- To inform guidance on the optimal use of PCV in humanitarian crises

World Health Organization | IVB

Thank you

Pneumococcal vaccination strategies in humanitarian crises

IVIR-AC meeting September 2022

K van Zandvoort, on behalf of ESPICC and EEPICC study team

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Questions for IVIR-AC

We are looking to guidance from IVIR-AC on the strength of evidence generated so far and on opportunities to enhance planned studies in order to increase its impact

1. What is IVIR-ACs **opinion on the quality of evidence generated thus far?**

2. A **follow-up study** will commence in October 2022, with cross-sectional surveys planned after 6, 12, and 24 months, and routine surveillance data collection between these periods.
   Does IVIR-AC have **any recommendations for this study**, e.g. regarding the planned data that will be collected, that may be useful for IVIR-AC recommendations?

3. A substantial amount of generated evidence will come from mathematical modelling. Are there **any suggestions to explore additional scenarios or outcomes** that are not yet unexplored, but would be useful to inform IVIR-AC recommendations?

Humanitarian crises

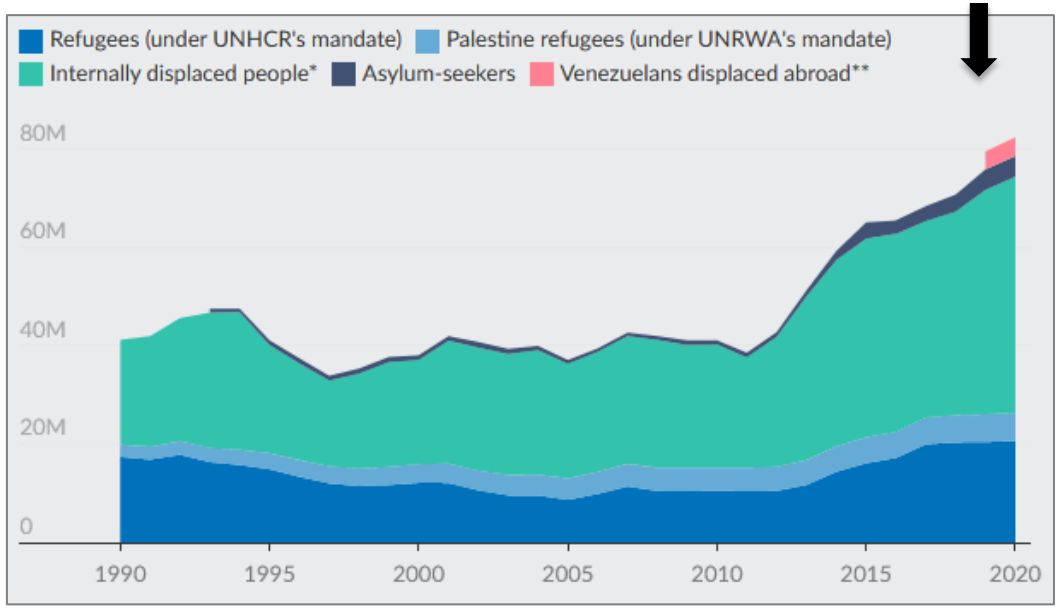
Any event that threatens the health, safety or wellbeing of a large group of people.

Crises can be caused by war, natural disasters, famine, and disease outbreaks.

Recent crises

Acute phase	Protracted phase
War in Ukraine	Conflict in North-East Nigeria
Hunger crisis in East Africa	Instability and conflict in DRC
Civil war in Yemen	Hyperinflation and malnutrition in Venezuela

>80M people (!)



UNHCR (2021)

Pneumococcal burden in humanitarian crises

- Largely unknown
- Increased disease and mortality rates
    - All-cause mortality is frequently ≥2 times pre-crisis baseline
    - Respiratory infections leading cause of mortality in <5y
    - Presence of risk factors relevant for pneumococcal spread

Risk factor	Carriage	Disease	Death
Acute malnutrition	++	+++	+++
Measles outbreaks and other viral RTIs	++	++	++
Overcrowding and altered social contact patterns	+++		
Disrupted routine PCV use	+	+++	
Low access to curative care	+	+	+++
Smoke inhalation		+	
Inadequate water and sanitation	++	+	

Bellos et al (2010); Van Zandvoort et al (2019)

Intervention

- Pneumococcal Conjugate Vaccines (PCV)
  - Safe and effective
  - Introduced in most EPI programmes
  - Expensive, but mitigated by Humanitarian Mechanism (+Pneumosil)
  - **Rarely used in crisis settings**

- Little guidance on the use of PCVs in humanitarian settings
  - WHO recommendation on PCV in crises
    - Use in children <1 year
    - Consider in children <5 years
  - Routine immunization often not feasible

ESPICC study

- Aim: to identify optimal vaccination strategies for populations affected by humanitarian crises

- cRCT would be ideal study design, but not feasible
- Alternative study design
    1. **Primary data collection of key model parameters**
        - Contact and carriage patterns
        - Conducted a cross-sectional survey in Somaliland IDP camp in 2019

    2. **Mathematical modelling of different vaccination strategies**

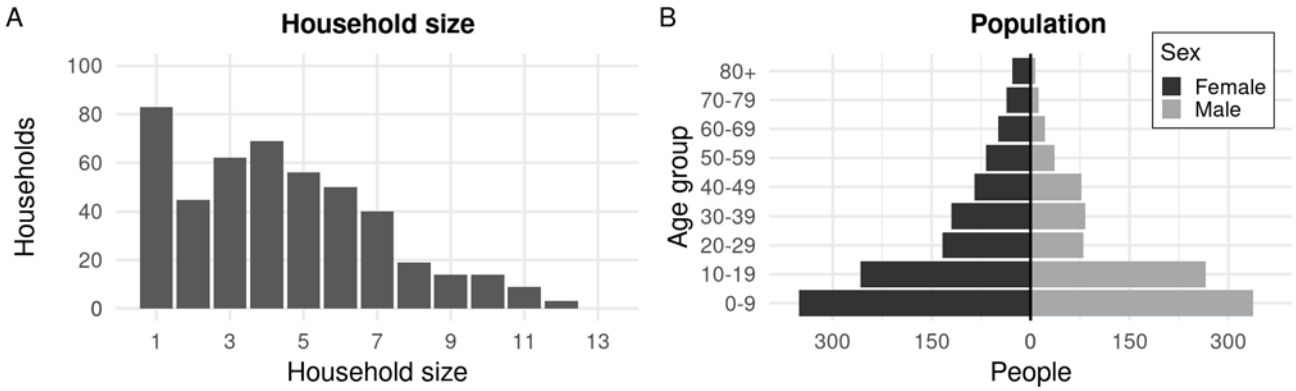
    3. **Follow-up intervention study (EEPICC)**

Primary data collection

- Digaale IDP camp, Hargeisa, Somaliland
- Save the Children and Somaliland Ministry of Health Development

Digaale characteristics

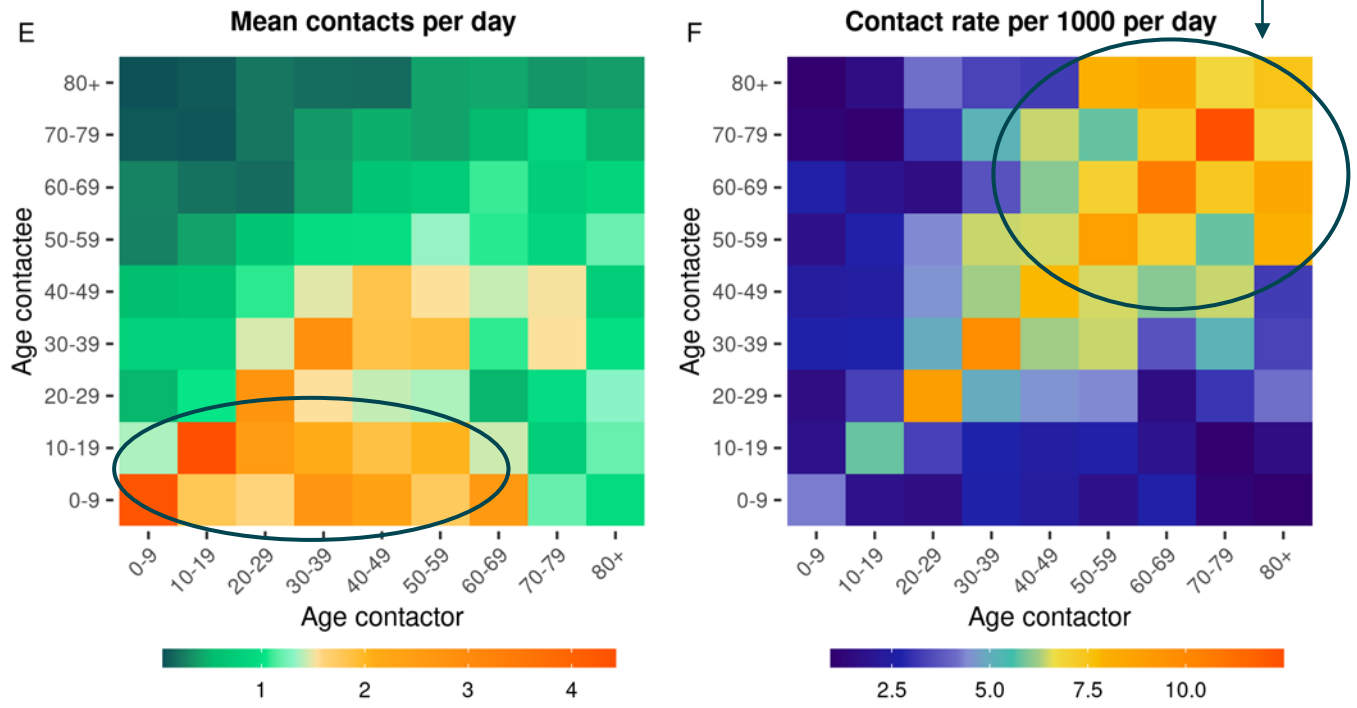
- ~715 inhabited shelters (~3000 people)
- Overcrowding
- Young population
- High crude death rates
- High migration rates
- Malnutrition



Digaale, contact patterns

- 78% of contacts physical
- Most contacts at home
- Very few contacts at school or work
- Very few contacts outside IDP camp

High levels of intergenerational mixing



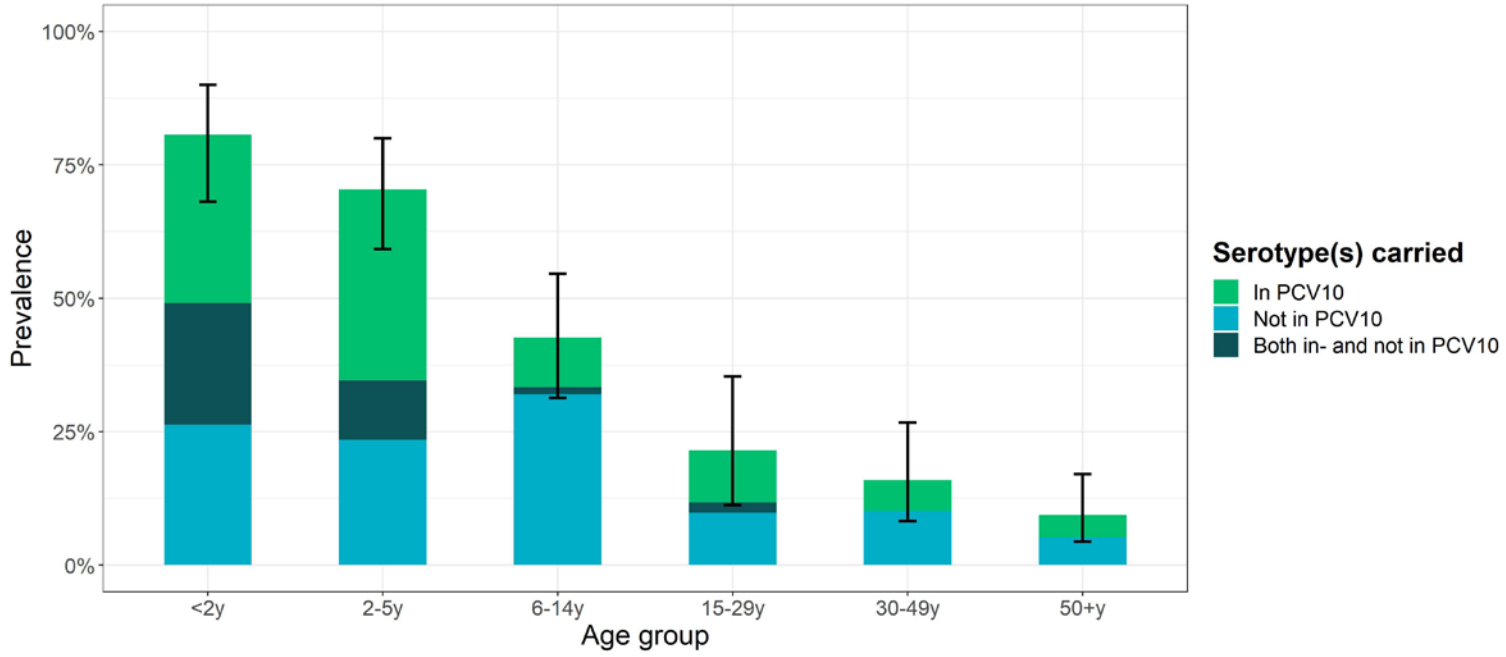
Most contacts made by/with children

Digaale, pneumococcal carriage prevalence

- N_{swabs} = 454

- 45%, tested positive for pneumococcus
- 75% in children <5 years
- ~50% are VT serotypes

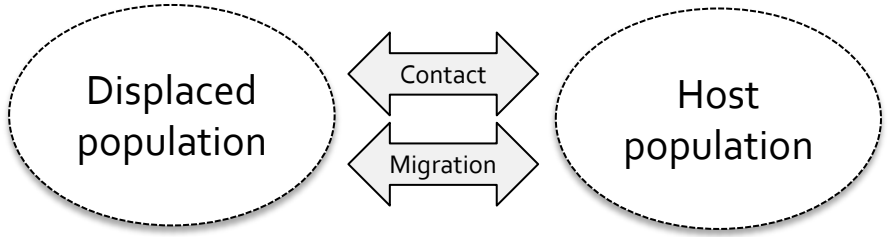
- Lower than the Gambia
- Similar to Kenya, Uganda, Malawi



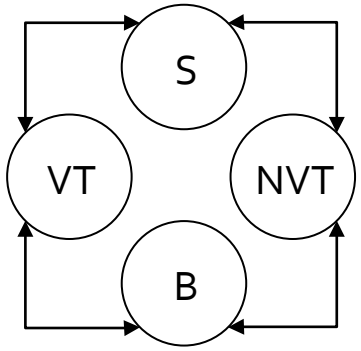
PCV transmission model (Digaale)

Transmission model

1. Populations



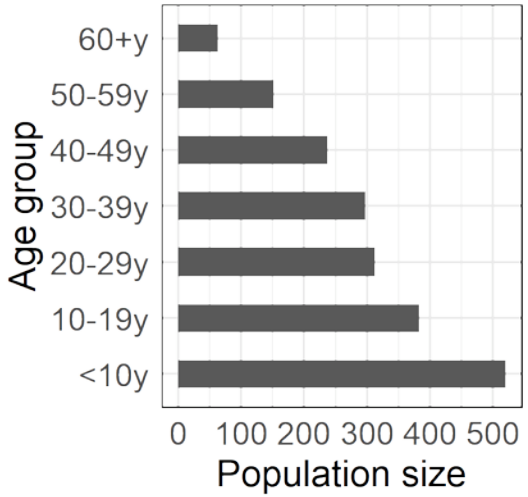
2. Epidemiological states

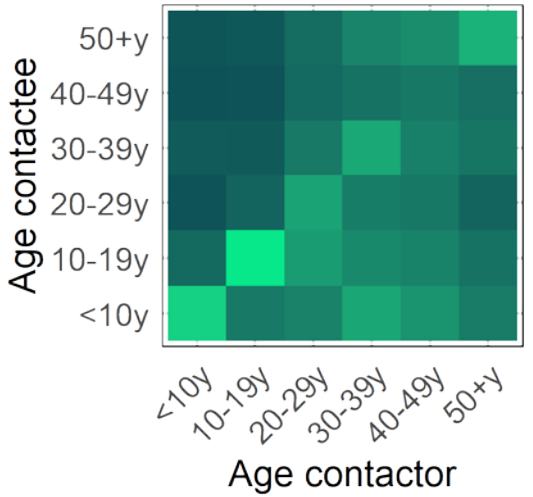


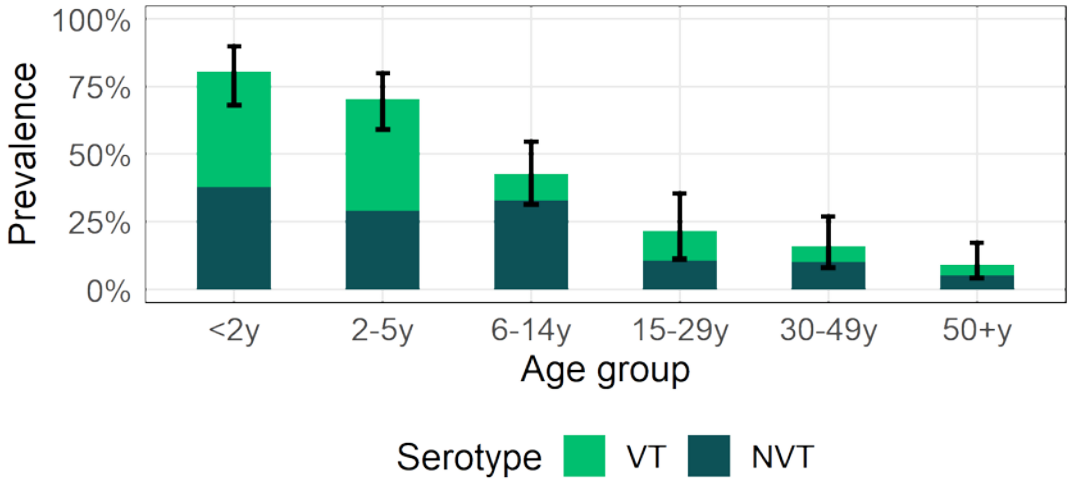
3. Stratified by

- Age
- Vaccination status
- Nutritional status

Parameters







Van Zandvoort et al (2021)

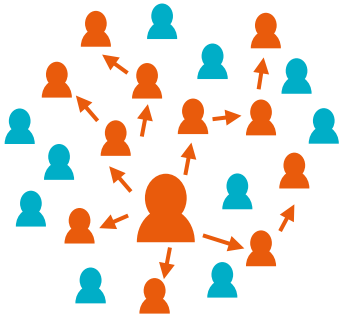
Modelling PCV strategies

- Transmission model simulates pneumococcal transmission
- Simulate a single PCV campaign, **without routine immunization**
- Aim to achieve high level of herd-immunity (against VT strains)

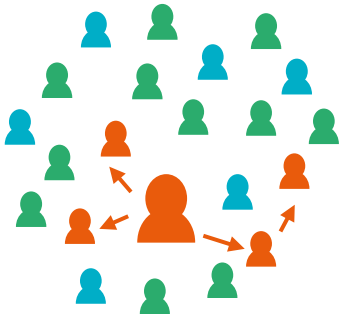
- High vaccine coverage (assume 85%)
  - Modelled PNEUMOSIL
  - Direct protection to those vaccinated
  - Indirect protection to those unvaccinated: herd immunity

- Compare a single PCV campaign targeting children:
  - <1 y
  - <2 y
  - <5 y
  - <10 y
  - <15 y

1. Without herd immunity



2. With herd immunity



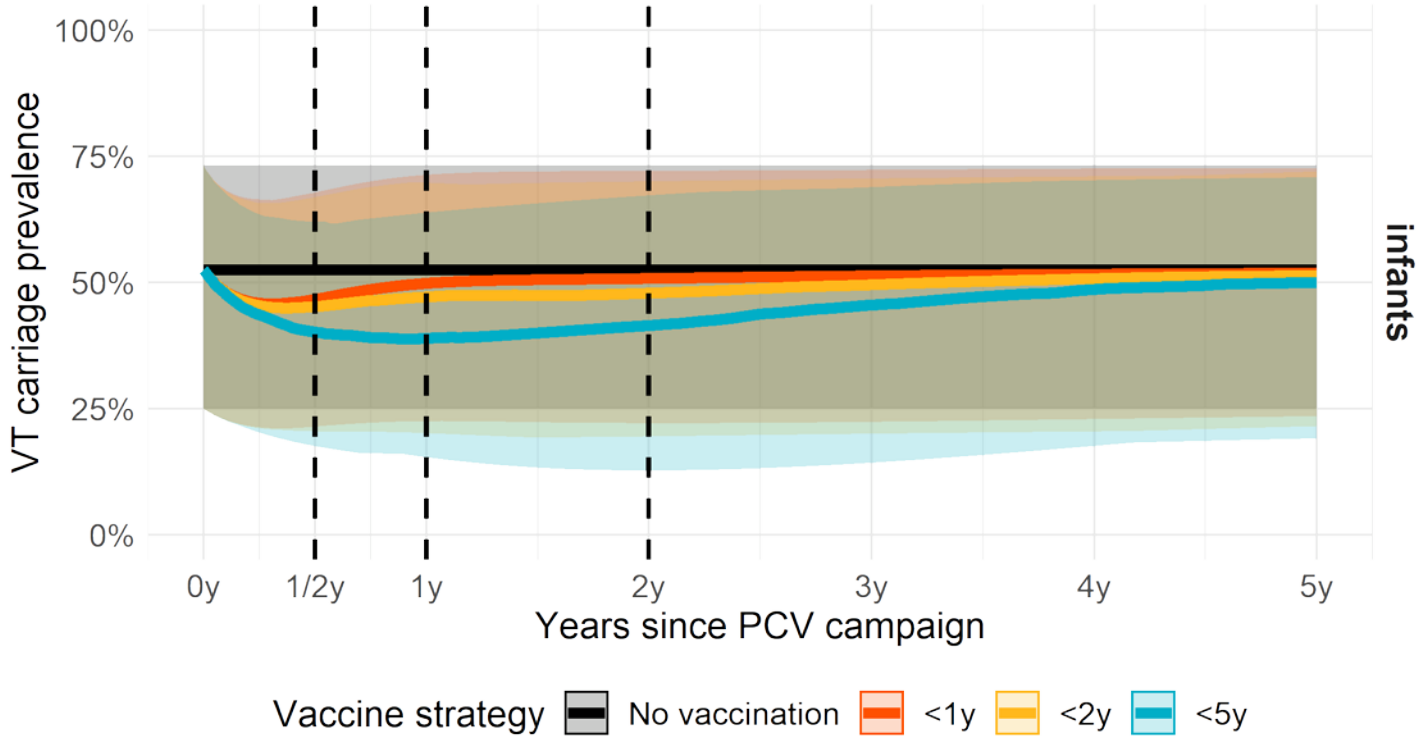
State

- Susceptible
- VT carrier
- (Partially) immune

Carriage prevalence in infants

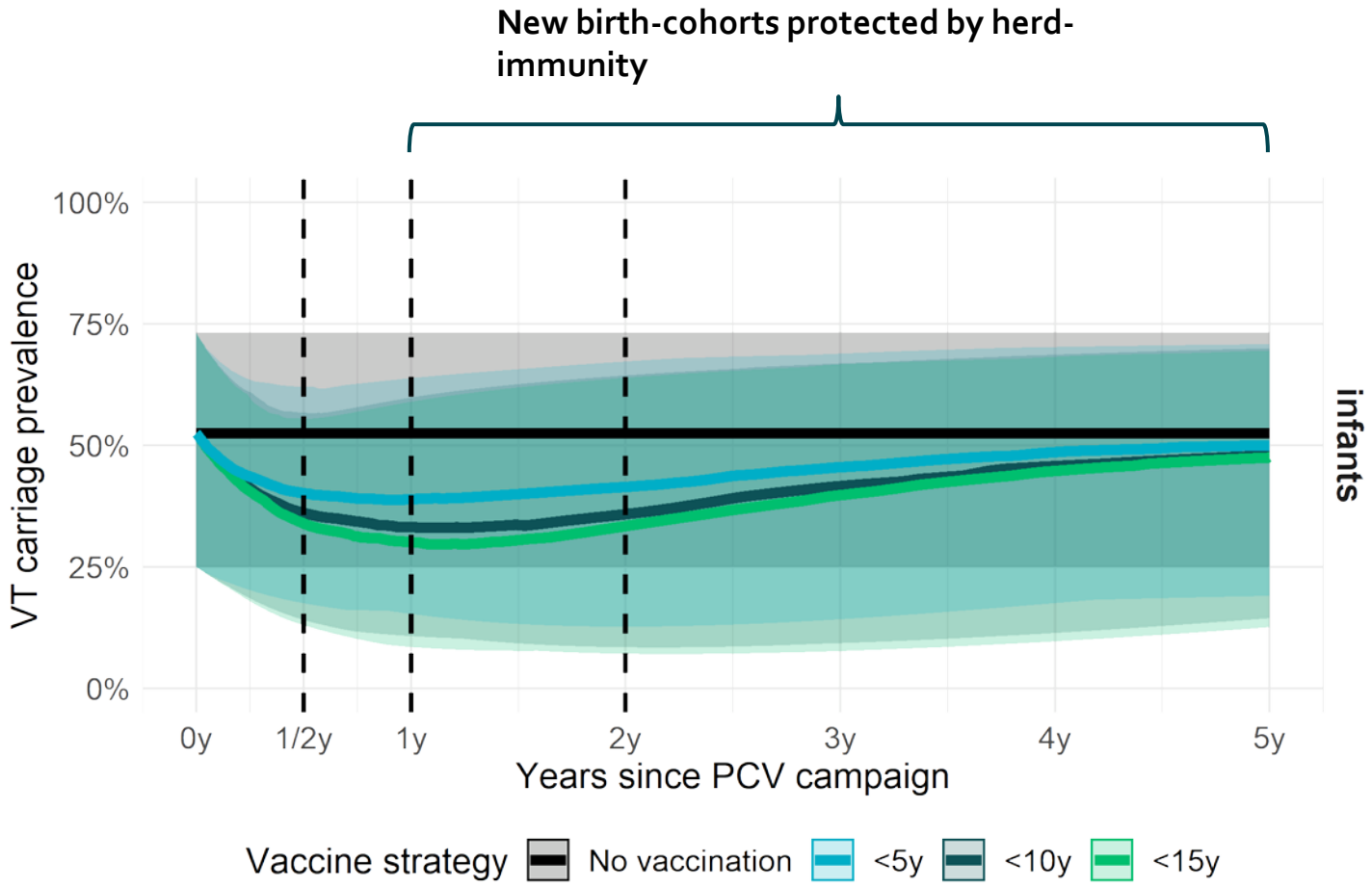
Current recommendations

- <1y and <2y campaigns do not result in substantial impact
- Wider age targeting does result in higher and longer impact
- First six months in infants primarily direct impact

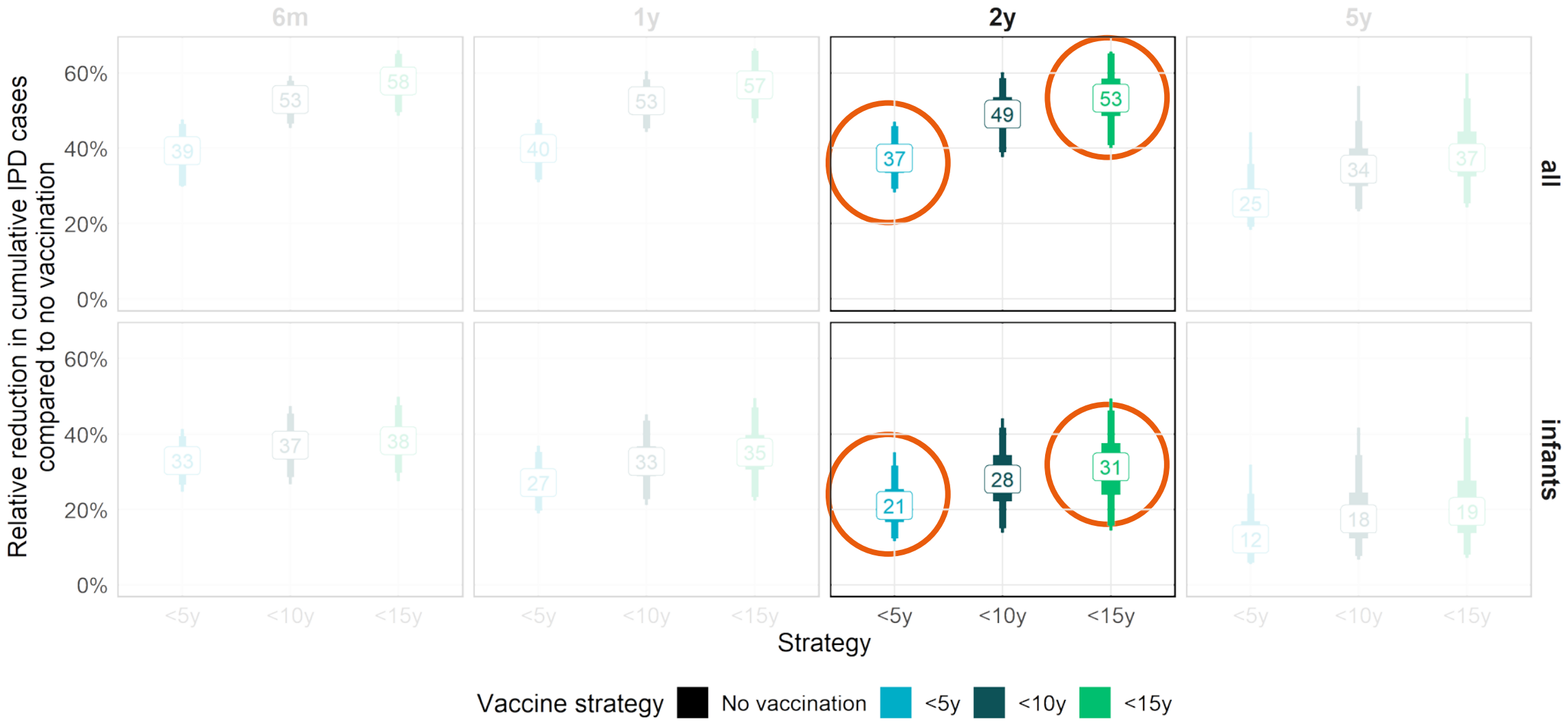


Carriage prevalence in infants

- Able to establish partial herd immunity
- Peak impact at ~1 year after campaign
- Larger impact with wider age targeting
- Faster waning with <5y campaign
- Will return to baseline in absence of additional vaccination

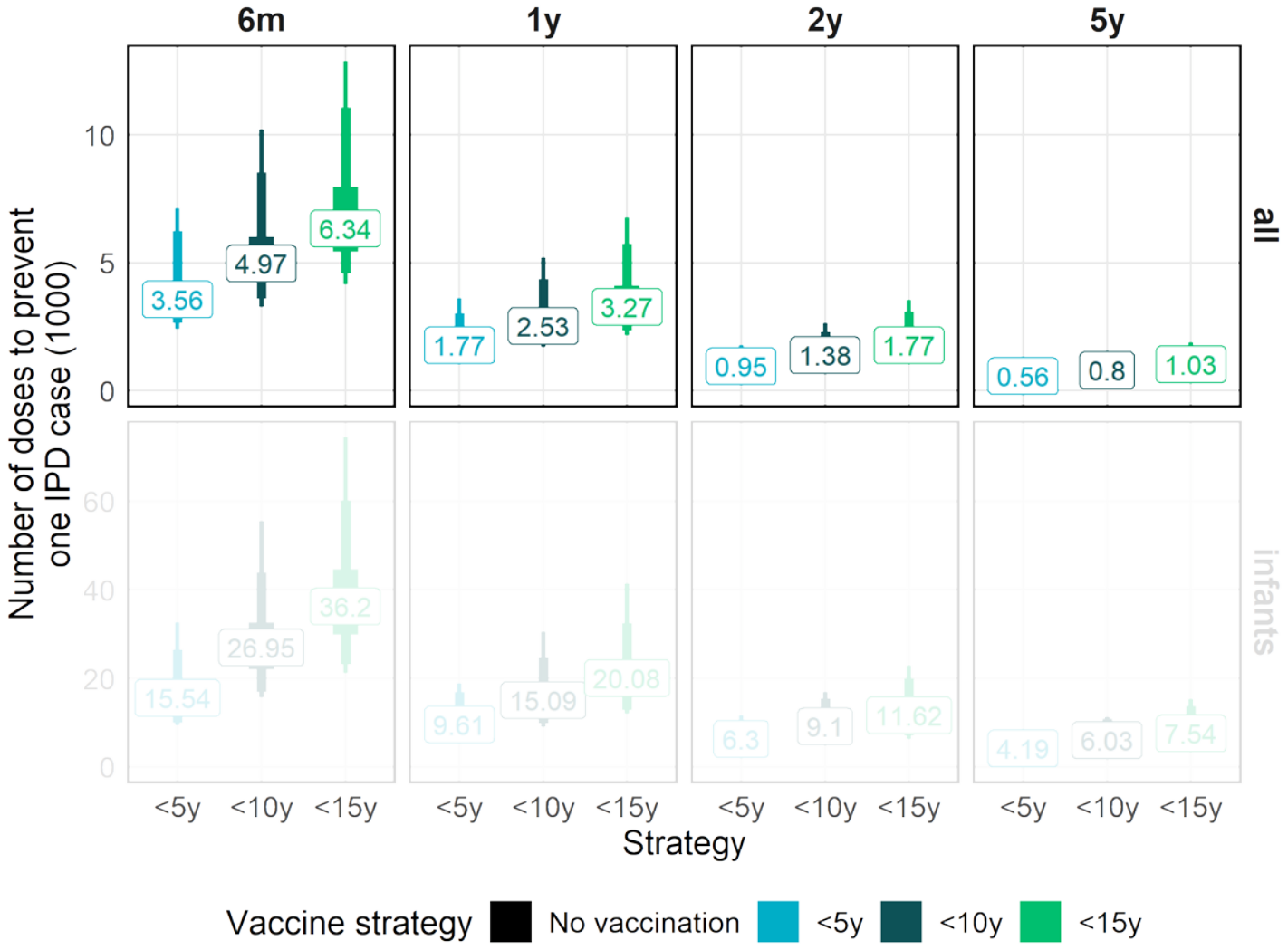


Cumulative impact on IPD cases



Efficiency of campaigns

- Wider age targeting less efficient
  - Diminishing returns
  - More doses needed to prevent additional cases
  - Overall efficiency improves over time
  - Better or similar efficiency (after 5y) than PCV doses in routine EPI programme in Kenya



Main assumptions affecting PCV impact

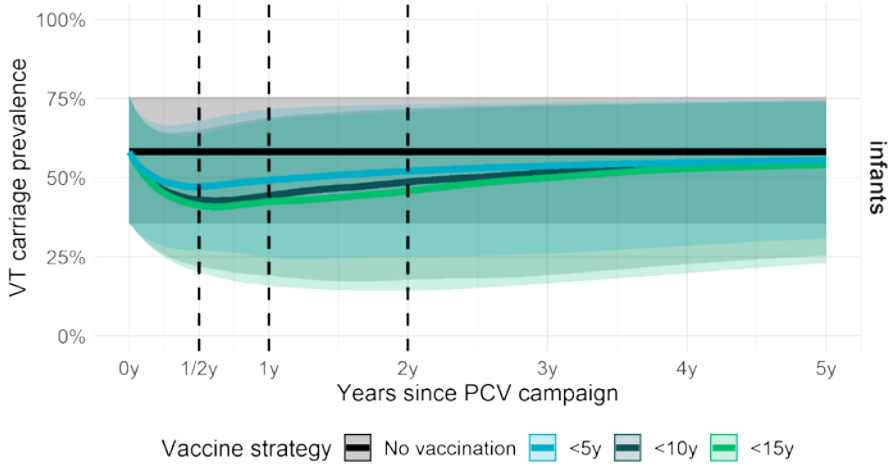
Parameter	Value	Source
Vaccine coverage	85%	Assumption
Vaccine efficacy	~50% VT carriage and additional ~50% VT disease	le Polain de Waroux et al (2015) Flasche et al (2017)
Duration of vaccine protection	~6 years	le Polain de Waroux et al (2015)
Age-specific contact patterns	Setting-specific - Digaale: estimated - Elsewhere: adjusted from Digaale - Host populations: synthetic contact matrices	v Zandvoort et al (2022) Prem et al (2021)
Birth and migration rates	Setting-specific - Estimated in all settings	v Zandvoort et al (2022) Adogaye (2019) Patil (2019) Concern (2015)
Contact between IDP and (unvaccinated) host-population	Setting-specific - Digaale: estimated - Elsewhere: extrapolated from Digaale or assumed from population sizes	v Zandvoort et al (2022)

Modelling PCV campaigns (other settings)

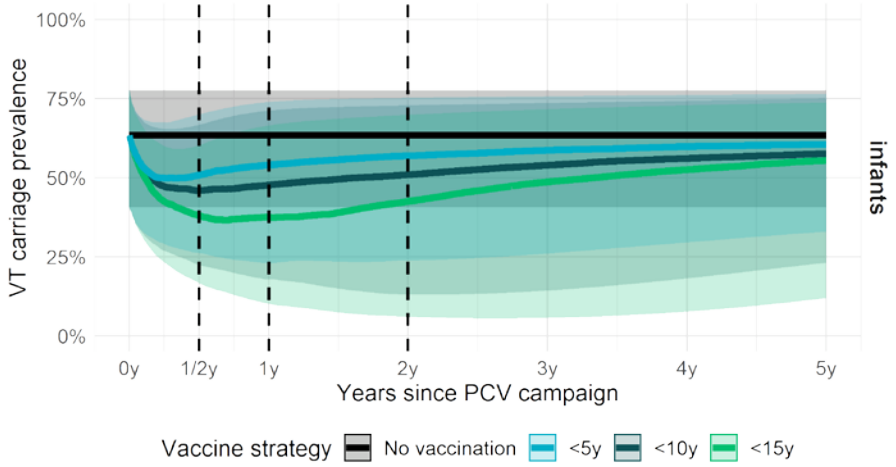
Population	Phase	Population type	Mixing with host population	Migration	Malnutrition (GAM)
Digaale, Somaliland, 2019	Protracted	IDP camp	Low	Moderate	Moderate
Bentiu PoC, South Sudan, 2015	Acute	IDP camp	Low	High	High
Bambari, Central African Republic, 2019	Protracted	Rural host pop	N/A	N/A	High
Maiduguri, Nigeria, 2016	Acute	Urban mix IDP and Host	High	High	High
Maiduguri, Nigeria, 2019	Protracted	Urban mix IDP and Host	High	Moderate	Moderate

Modelling PCV campaigns (other settings)

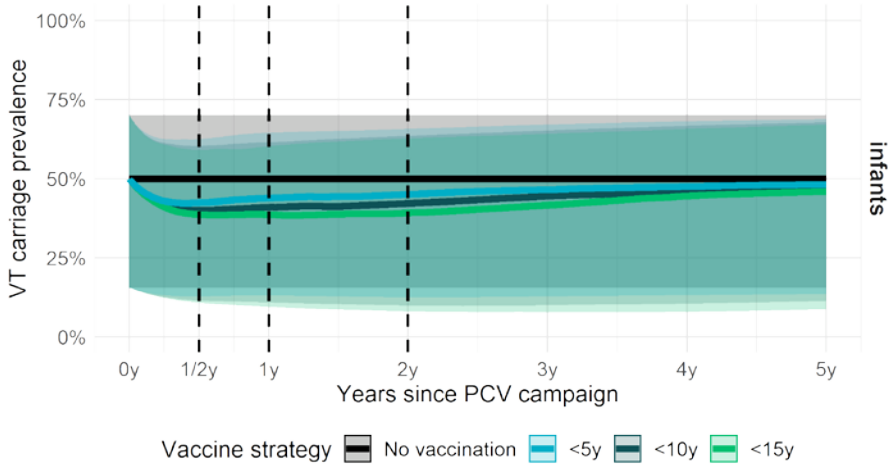
Bentiu, PoC (2015 - acute)



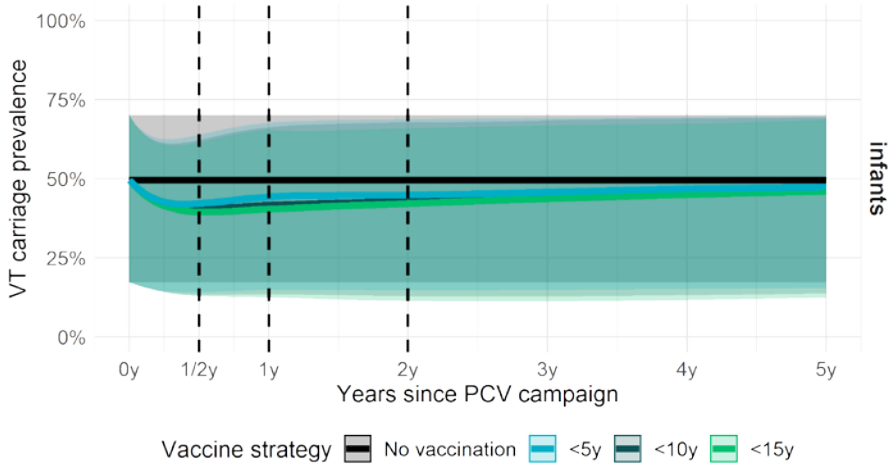
Bambari (2019 - protracted)



Maiduguri (2016 - acute)



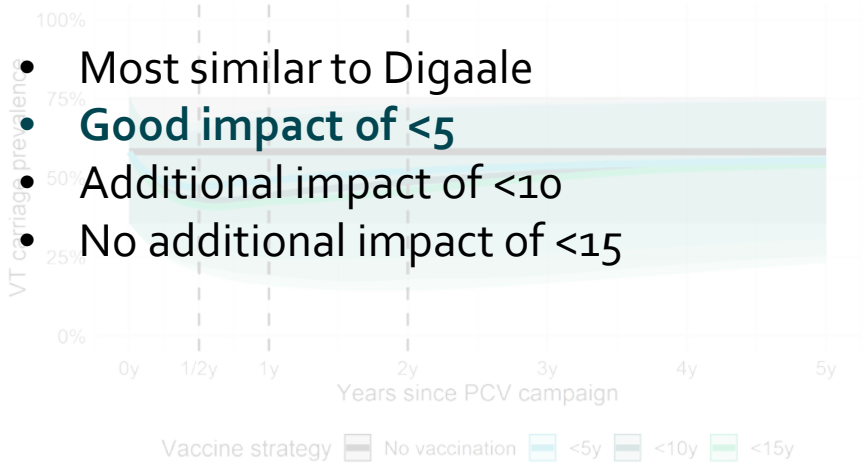
Maiduguri (2019 - protracted)



Modelling PCV campaigns (other settings)

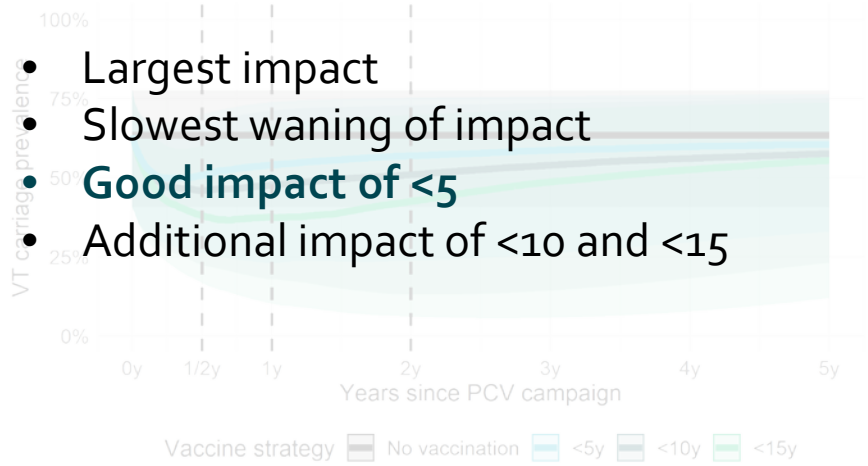
LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Bentiu, PoC (2015 - acute)



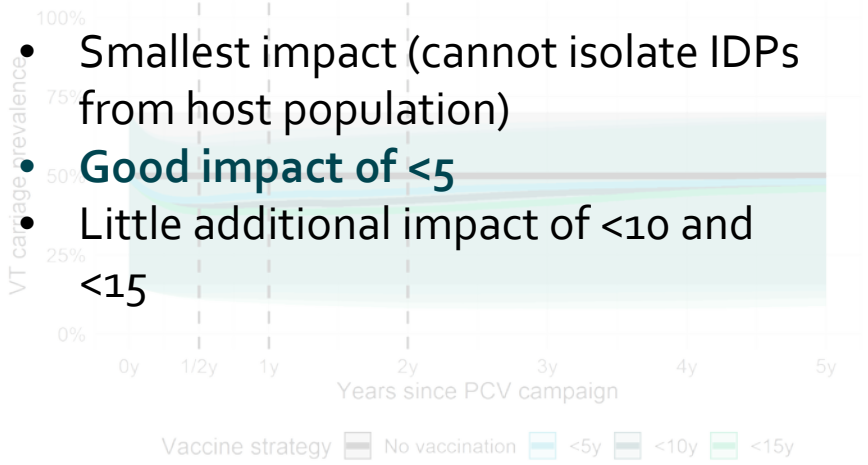
- Most similar to Digaale
- **Good impact of <5**
- Additional impact of <10
- No additional impact of <15

Bambari (2019 - protracted)



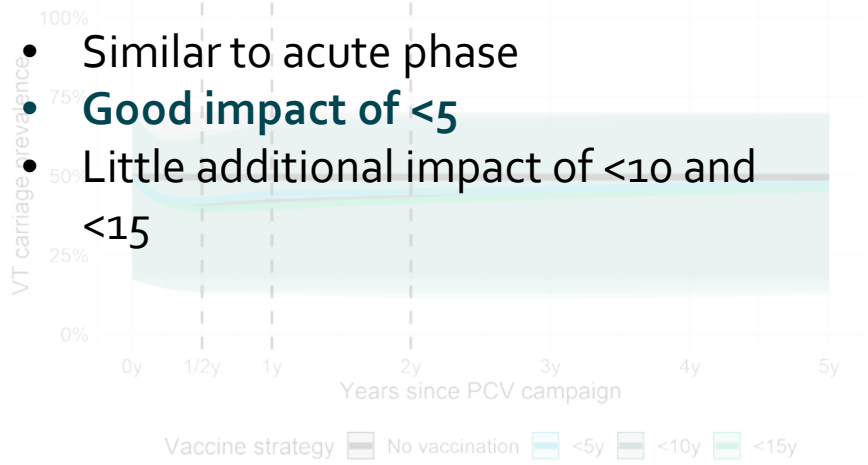
- Largest impact
- Slowest waning of impact
- **Good impact of <5**
- Additional impact of <10 and <15

Maiduguri (2016 - acute)



- Smallest impact (cannot isolate IDPs from host population)
- **Good impact of <5**
- Little additional impact of <10 and <15

Maiduguri (2019 - protracted)



- Similar to acute phase
- **Good impact of <5**
- Little additional impact of <10 and <15

Impact PCV campaigns (other settings)

Population	Impact IPD (infants; 2y post campaign) – higher is better		Impact IPD (all ages; 2y post campaign) – higher is better		Efficiency (all ages; 2y post campaign) – lower is better	
	<5 campaign	<15 campaign (ratio)	<5 campaign	<15 campaign (ratio)	<5 campaign	<15 campaign (ratio)
Digaale, Somaliland, 2019	18%	28% (1.6)	34%	51% (1.5)	950	1,768 (1.8)
Bentiu PoC, South Sudan, 2015	15%	22% (1.5)	29%	44% (1.5)	1,067	1,682 (1.6)
Bambari, Central African Republic, 2019	15%	30% (2.0)	32%	52% (1.6)	827	1,213 (1.5)
Maiduguri, Nigeria, 2016	14%	20% (1.4)	26%	39% (1.5)	1,404	2,320 (1.7)
Maiduguri, Nigeria, 2019	12%	16% (1.3)	27%	40% (1.5)	1,402	2,273 (1.6)
Overall	**~15%**	**~15 to 30%**	**~30%**	**~40 to 50%**	**~900 to 1,400**	**~1,200 to 2,400**

Preliminary conclusions

- PCV campaigns can be effective to prevent pneumococcal disease in populations affected by humanitarian crises in the short- to mid-term (where routine immunization is not feasible)
- Unvaccinated birth cohorts can be partially protected by high vaccine coverage in older children
- Campaigns in U5 achieve good impact in all scenarios
- Wider age-targeting may be beneficial in some settings
- PCV campaigns in crises are efficient use of PCV, if routine use is impossible

EEPICC study

- Aim: Evaluating impact of an <5y PNEUMOSIL campaign on pneumococcal carriage in a Somaliland IDP camp (Digaale)

- Builds on ESPICC study, strategy informed by model

EEPICC study – primary objectives

- Estimate effectiveness of PCV campaign against vaccine-type (VT) **pneumococcal carriage in children <24mo†**
- Document safety of PNEUMOSIL (reason: off-label use in children aged 24-59mo)

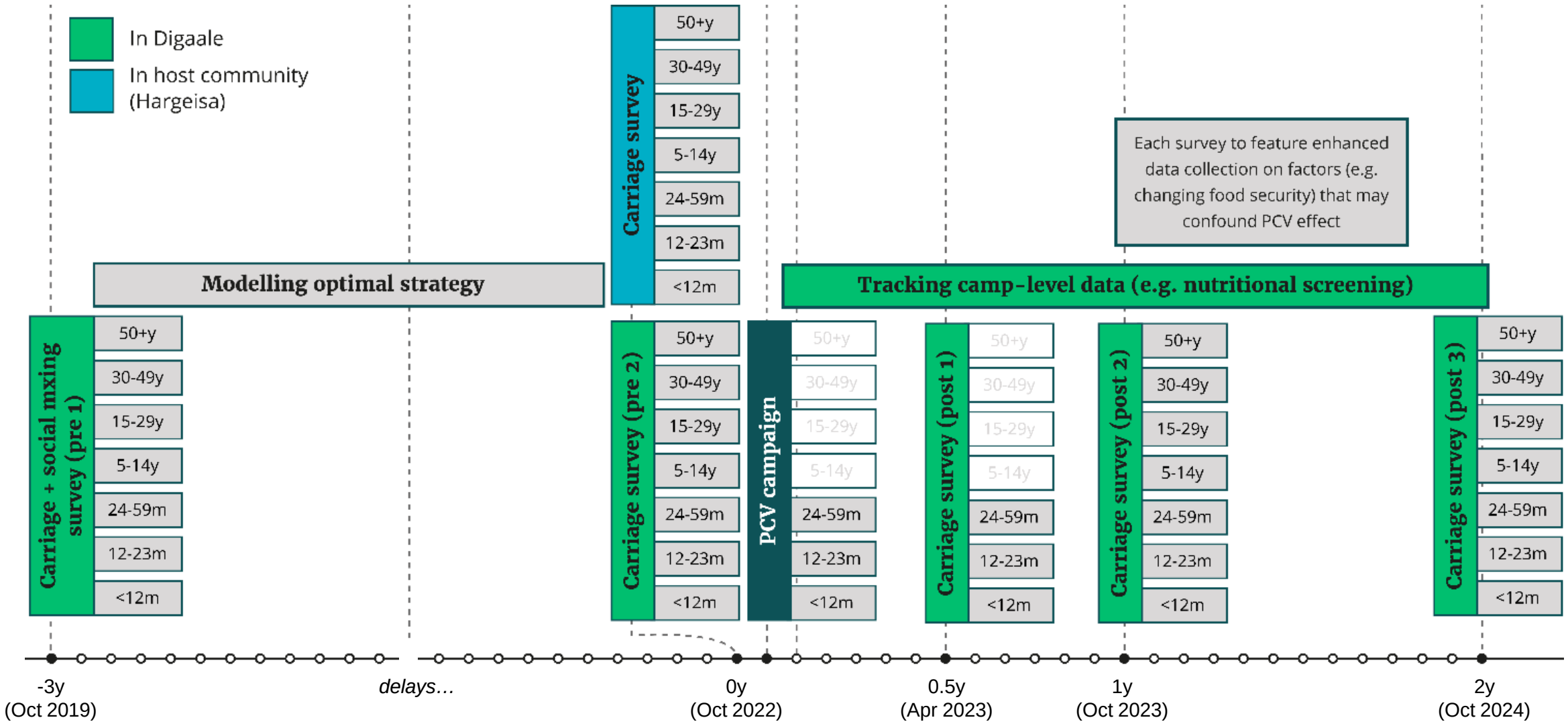
† *at 6, 12 and 24mths post-campaign, compared to 'baseline'*

EEPICC study – secondary objectives

- Estimate effectiveness against carriage among other age groups, and for non-vaccine-type (NVT) serotypes†
- Estimate effectiveness against incidence of Acute Lower Respiratory Infections (ALRI) and antibiotic prescriptions†
- Compare carriage prevalence in IDPs versus in the host population
- Use mathematical models informed by the study results to evaluate PCV introduction and 'maintenance' strategies
- Quantify campaign cost and compute cost-effectiveness of different strategies

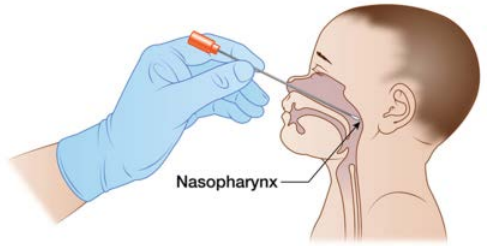
† *at 6, 12 and 24mths post-campaign, compared to 'baseline'*

EEPICC study - timeline



Measurement of carriage effects

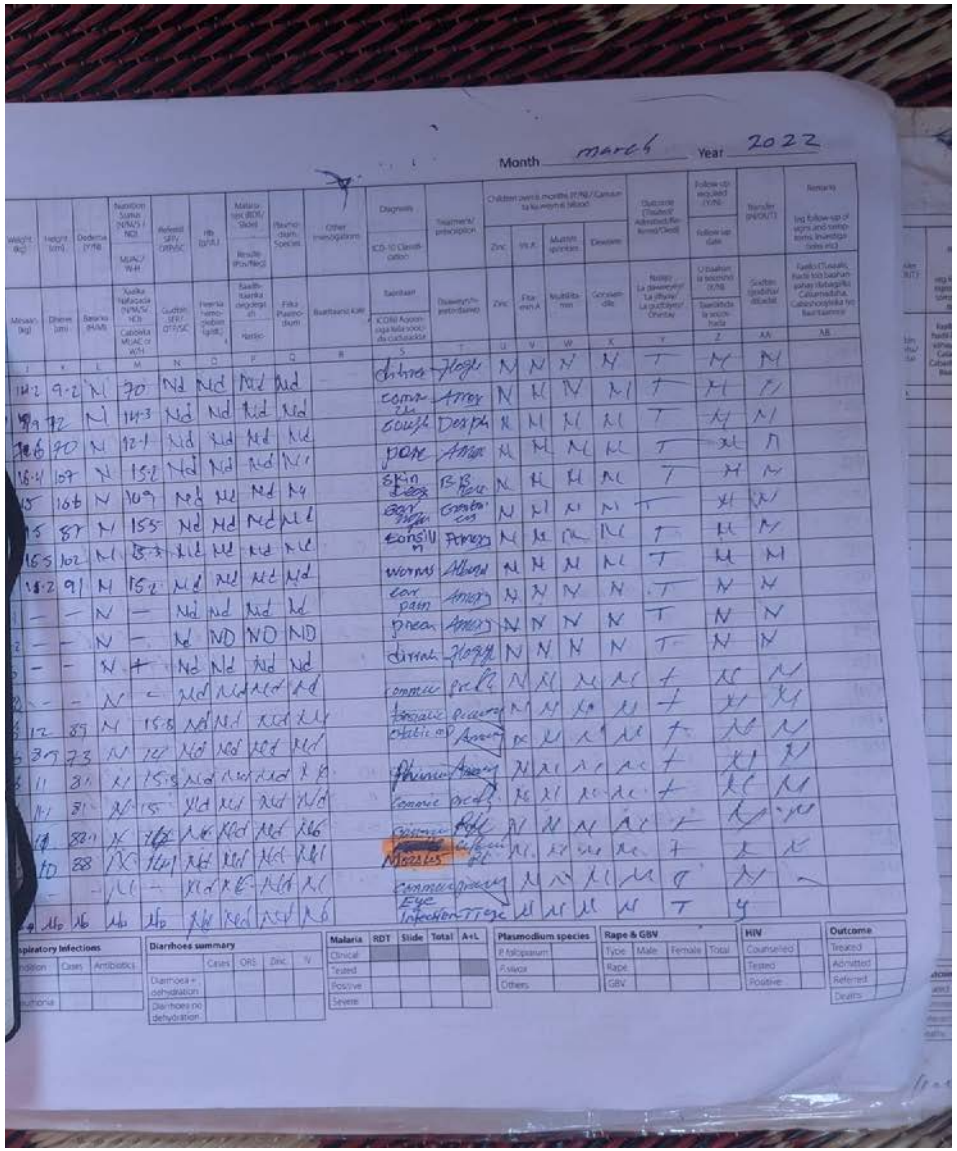
Age group	Target sample size
<12mo	100
12-23mo	100
24-59mo	100
5-14yo	100
15-29yo	100
30-49yo	100
≥ 50yo	100
Total	**700**



- **Nasopharyngeal swabs in Digaale and Hargeisa**
- **Additional data collection on potential confounders:**
  - Malnutrition
  - Health service utilisation
  - WASH and shelter conditions

Measurement of other (secondary) outcomes

- Outcomes
  - Hospitalisations for ALRI/pneumonia/invasive disease among children <24mo
  - Outpatient antibiotic prescriptions among children <59mo
- Both collected based on existing health facility records
  - Retrospectively for 24mths prior to vaccination campaign
  - Updated at 6, 12 and 24mths
- Before vs. after comparison
- Note: don't expect to have sufficient study power to detect an effect



Study team

LSHTM

Stefan Flasche

Francesco Checchi

Kevin van Zandvoort

Catherine R McGowan

Abdihamid Warsame

Olivier le Polain

Rosalind M Eggo

Anna Carnegie

SCI Somaliland

Mohamed Bobe

Mohamed Abdi

Saed Ibrahim

Mohamed Egeh Binyam Gebru

Mohamed Magan

Mohamed Saed

Mohamed Kahow

MoHD Somaliland

Abdirahman I Buqul

Mohamed A Hergeeye

Saeed M Soleman

Mohamed Y Warsame

SC UK

Rachael Cummings

Emma Diggle

Olimpia de la Rosa

MCRI

Catherine Satzke

Casey Pell

Kim Mulholland

MSF

Bhargavi Rao

Ruby Siddiqui

Kartini Gadroen

Questions for IVIR-AC

We are looking to guidance from IVIR-AC on the strength of evidence generated so far and on opportunities to enhance planned studies in order to increase its impact

1. What is IVIR-ACs **opinion on the quality of evidence generated thus far?**

2. A **follow-up study** will commence in October 2022, with cross-sectional surveys planned after 6, 12, and 24 months, and routine surveillance data collection between these periods.
   Does IVIR-AC have **any recommendations for this study**, e.g. regarding the planned data that will be collected, that may be useful for IVIR-AC recommendations?

3. A substantial amount of generated evidence will come from mathematical modelling. Are there **any suggestions to explore additional scenarios or outcomes** that are not yet unexplored, but would be useful to inform IVIR-AC recommendations?

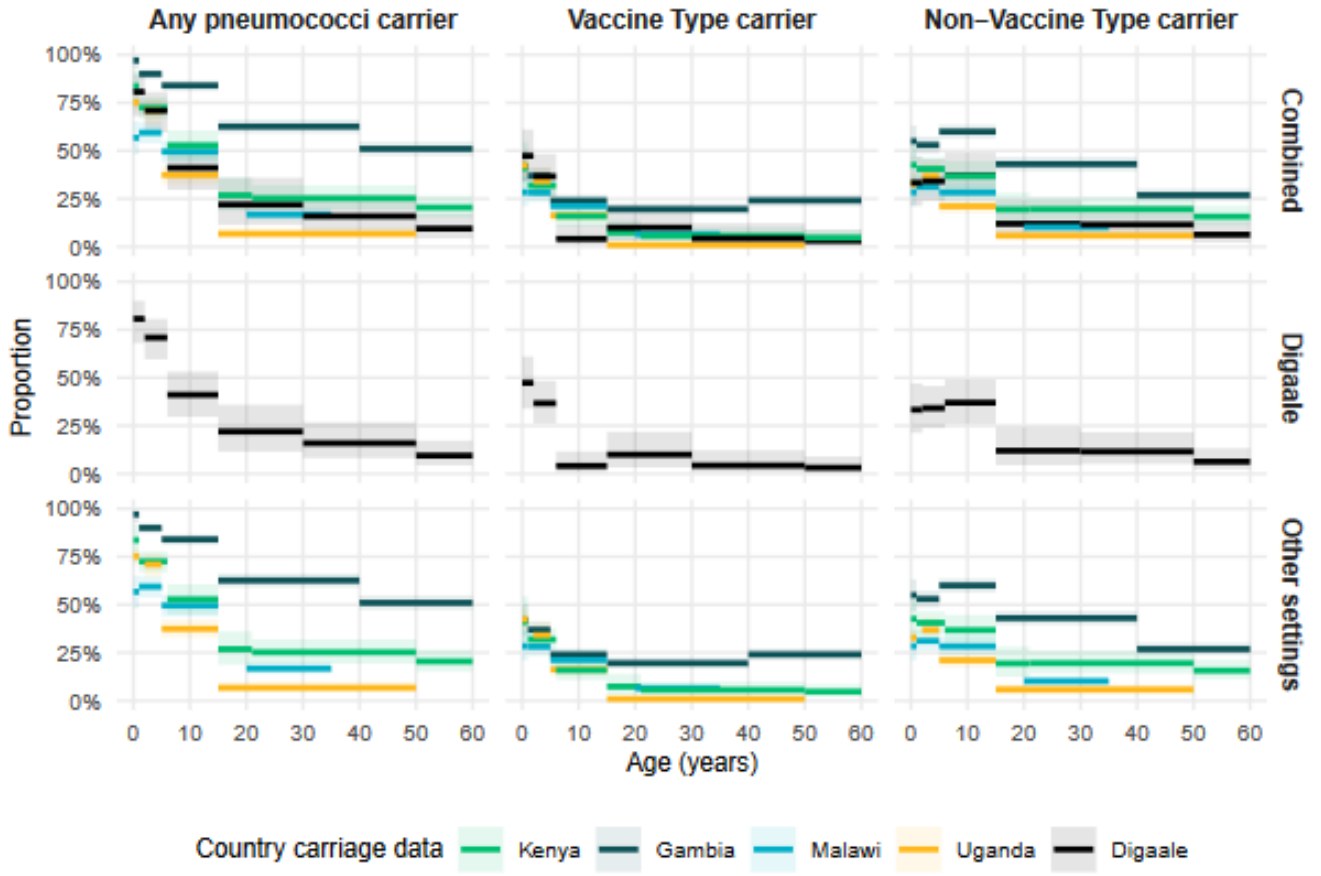
References

- United Nations High Commissioner for Refugees. Figures at a Glance. https://www.unhcr.org/figures-at-a-glance.html
- Bellos A, Mulholland K, O'Brien KL, Qazi SA, Gayer M, Checchi F. The burden of acute respiratory infections in crisis-affected populations: a systematic review. *Conflict and Health*. 2010;4(1):3. doi:10.1186/1752-1505-4-3
- Van Zandvoort K, Checchi F, Diggle E, et al. Pneumococcal conjugate vaccine use during humanitarian crises. *Vaccine*. 2019;37(45):6787-6792. doi:10.1016/j.vaccine.2019.09.038
- World Health Organization, 2019. Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper–February 2019. *Wkly Epidemiol Rec*, 94(8), pp.85-104
- van Zandvoort, K., Bobe, M.O., Hassan, A.I., Abdi, M.I., Ahmed, M.S., Soleman, S.M., Warsame, M.Y., Wais, M.A., Diggle, E., McGowan, C.R. and Satzke, C., 2022. Social contacts and other risk factors for respiratory infections among internally displaced people in Somaliland. *Epidemics*, p.100625.
- De Waroux, O.L.P., Flasche, S., Prieto-Merino, D., Goldblatt, D. and Edmunds, W.J., 2015. The efficacy and duration of protection of pneumococcal conjugate vaccines against nasopharyngeal carriage: a meta-regression model. *The Pediatric infectious disease journal*, *34*(8), pp.858-864.
- Flasche, S., Ojal, J., Le Polain de Waroux, O., Otiende, M., O'Brien, K.L., Kiti, M., Nokes, D.J., Edmunds, W.J. and Scott, J.A.G., 2017. Assessing the efficiency of catch-up campaigns for the introduction of pneumococcal conjugate vaccine: a modelling study based on data from PCV10 introduction in Kilifi, Kenya. *BMC medicine*, *15*(1), pp.1-10.
- Prem, K., Zandvoort, K.V., Klepac, P., Eggo, R.M., Davies, N.G., Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group, Cook, A.R. and Jit, M., 2021. Projecting contact matrices in 177 geographical regions: an update and comparison with empirical data for the COVID-19 era. *PLoS computational biology*, *17*(7), p.e1009098.
- Adogaye, B., 2019. Nutrition Survey using SMART Methodology and Mortality in Pulka MSF OCBA project, Borno State / Nigeria. Survey Report
- Patil, N., 2019. TECHNICAL REPORT ON ASSESSING NUTRITION STATUS, MORBIDITY AND MORTALITY OF CHILDREN, MAIDUGURI METROPOLITIAN COUNCIL LGA, BORNO STATE, NIGERIA
- Concern, 2016. Nutrition Anthropometry & Retrospective Mortality Survey Report Bentiu PoCs, Rubkona County, South Sudan

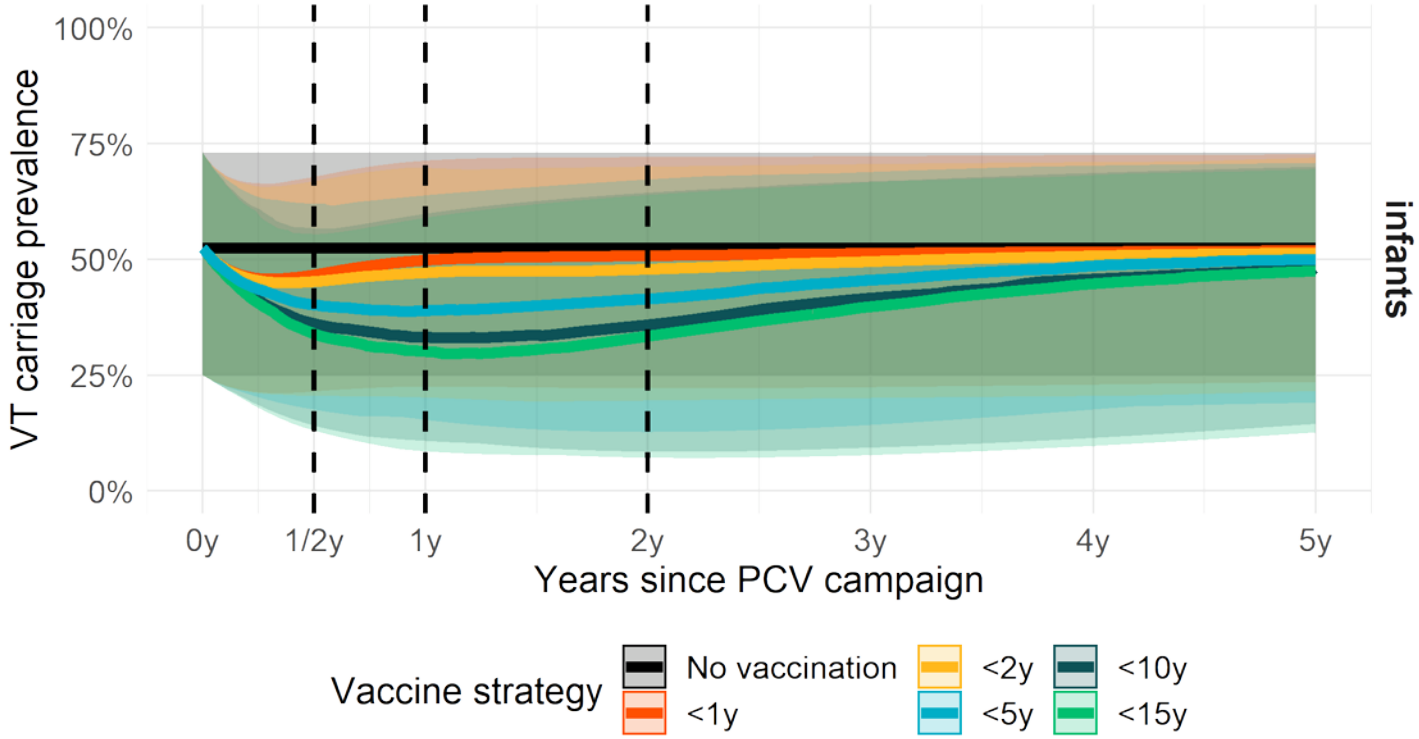
Additional slides

Pneumococcal carriage prevalence

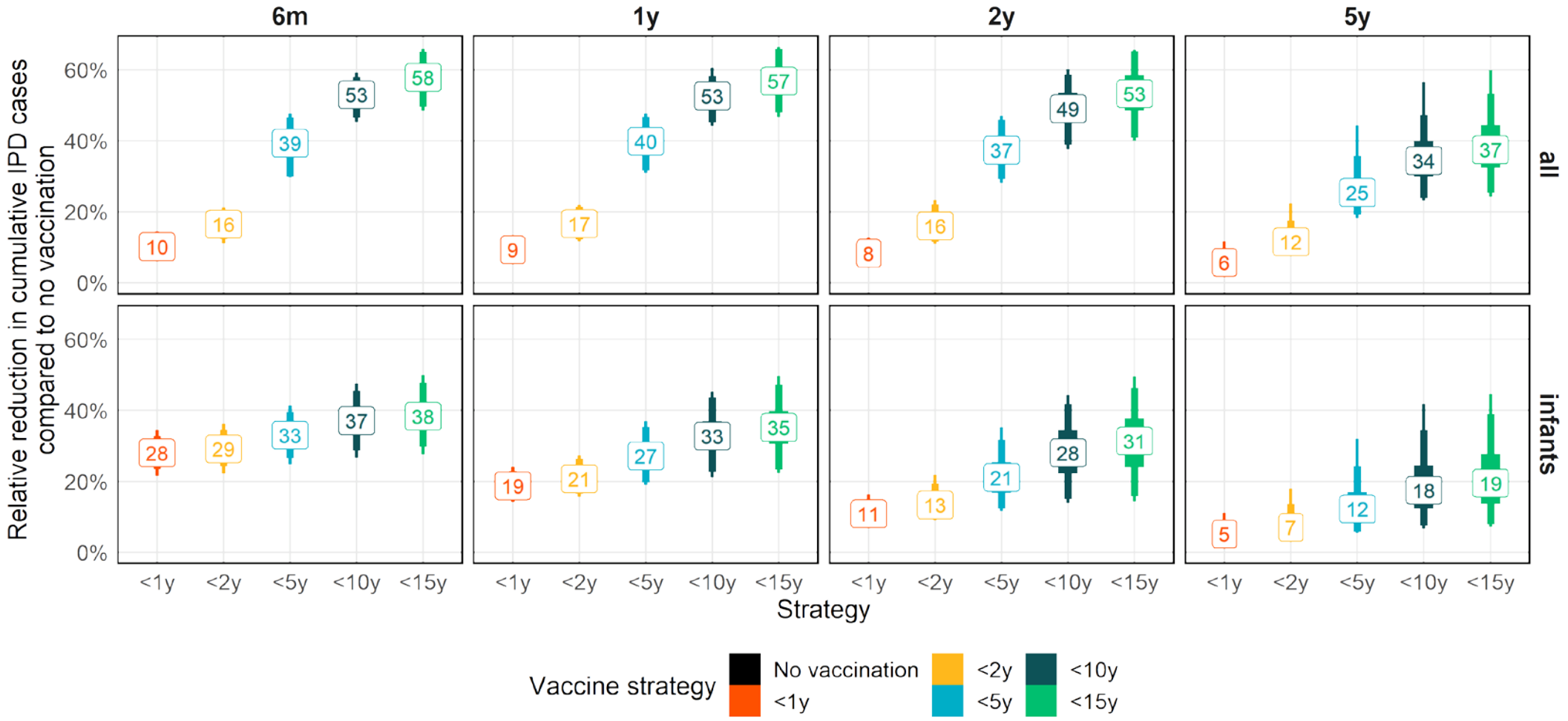
- Similar to Kenya, Uganda, Malawi
- Lower than the Gambia



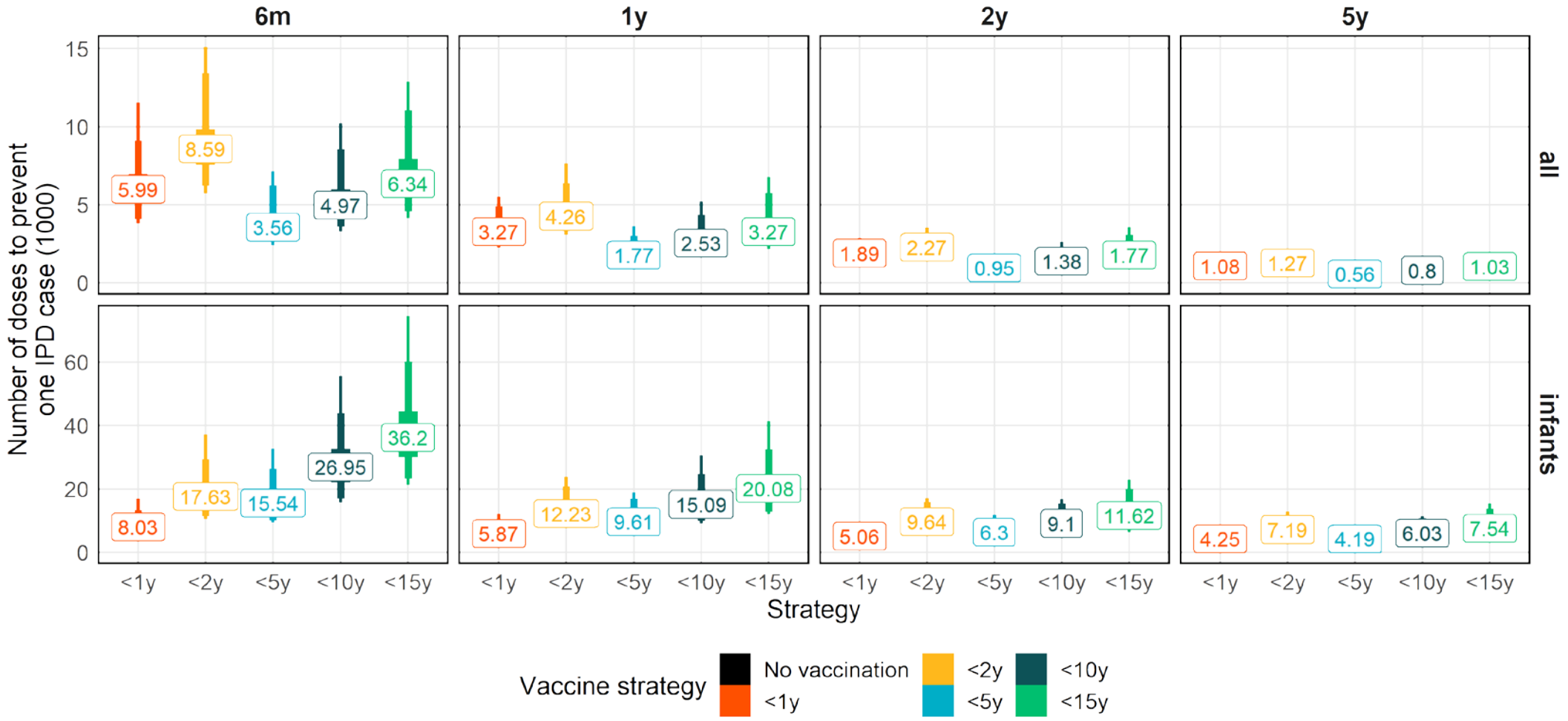
Digaale, all campaigns



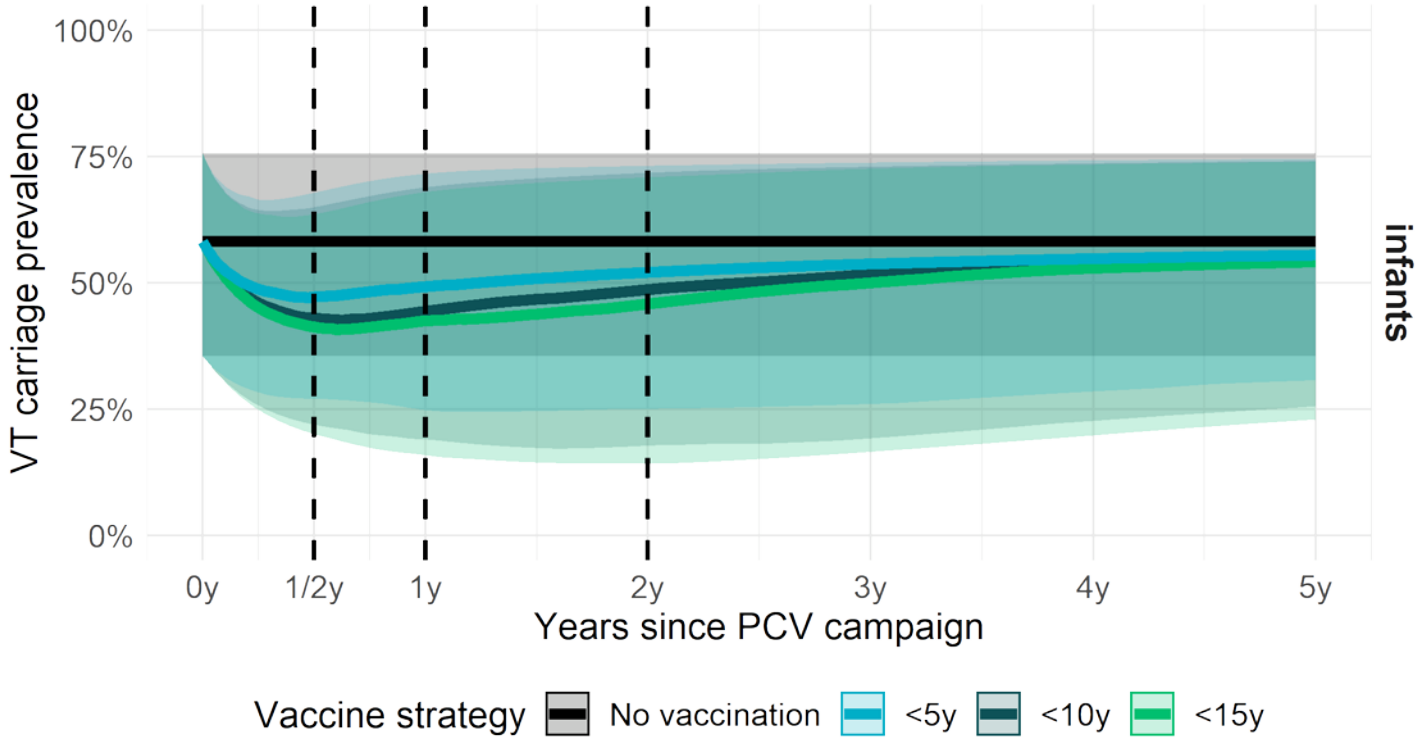
Digaale, all campaigns



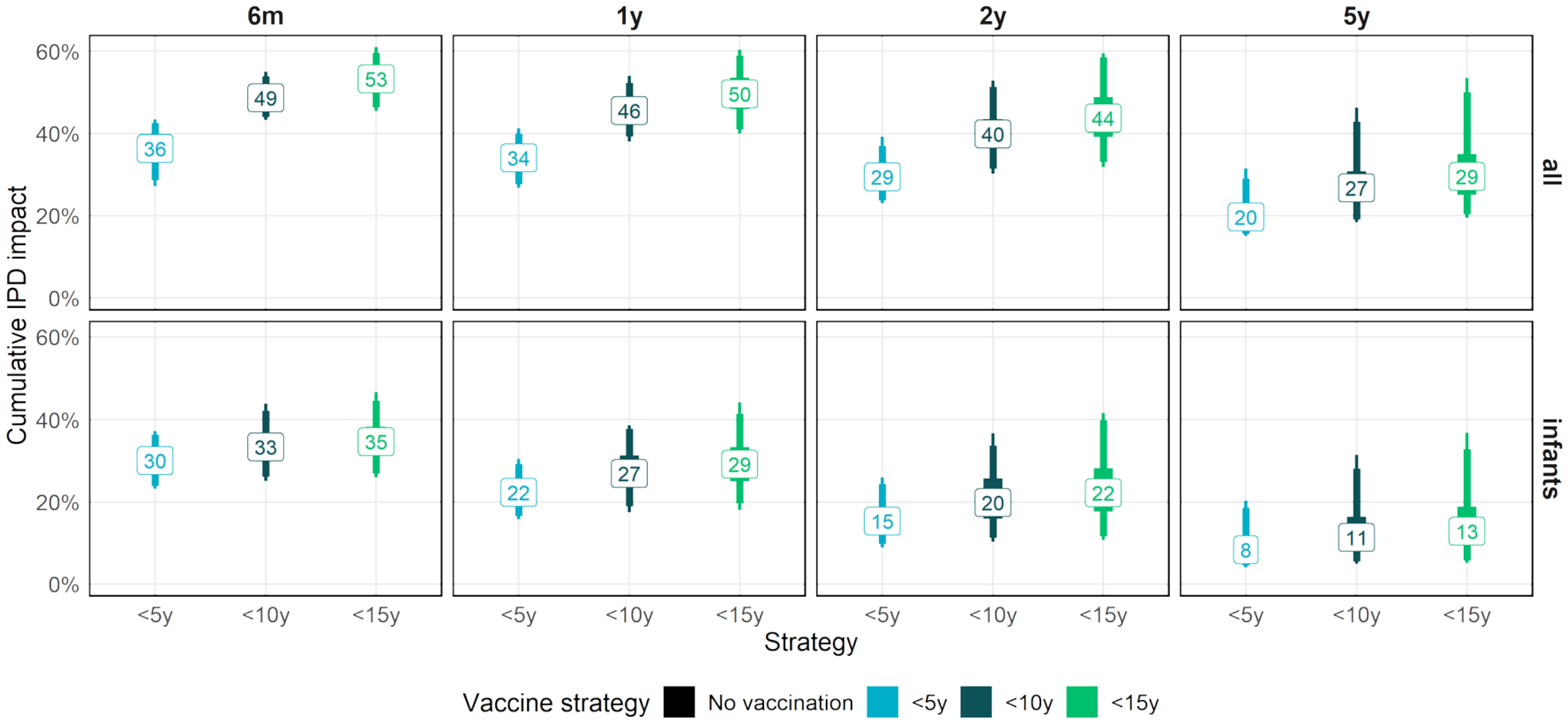
Digaale, all campaigns



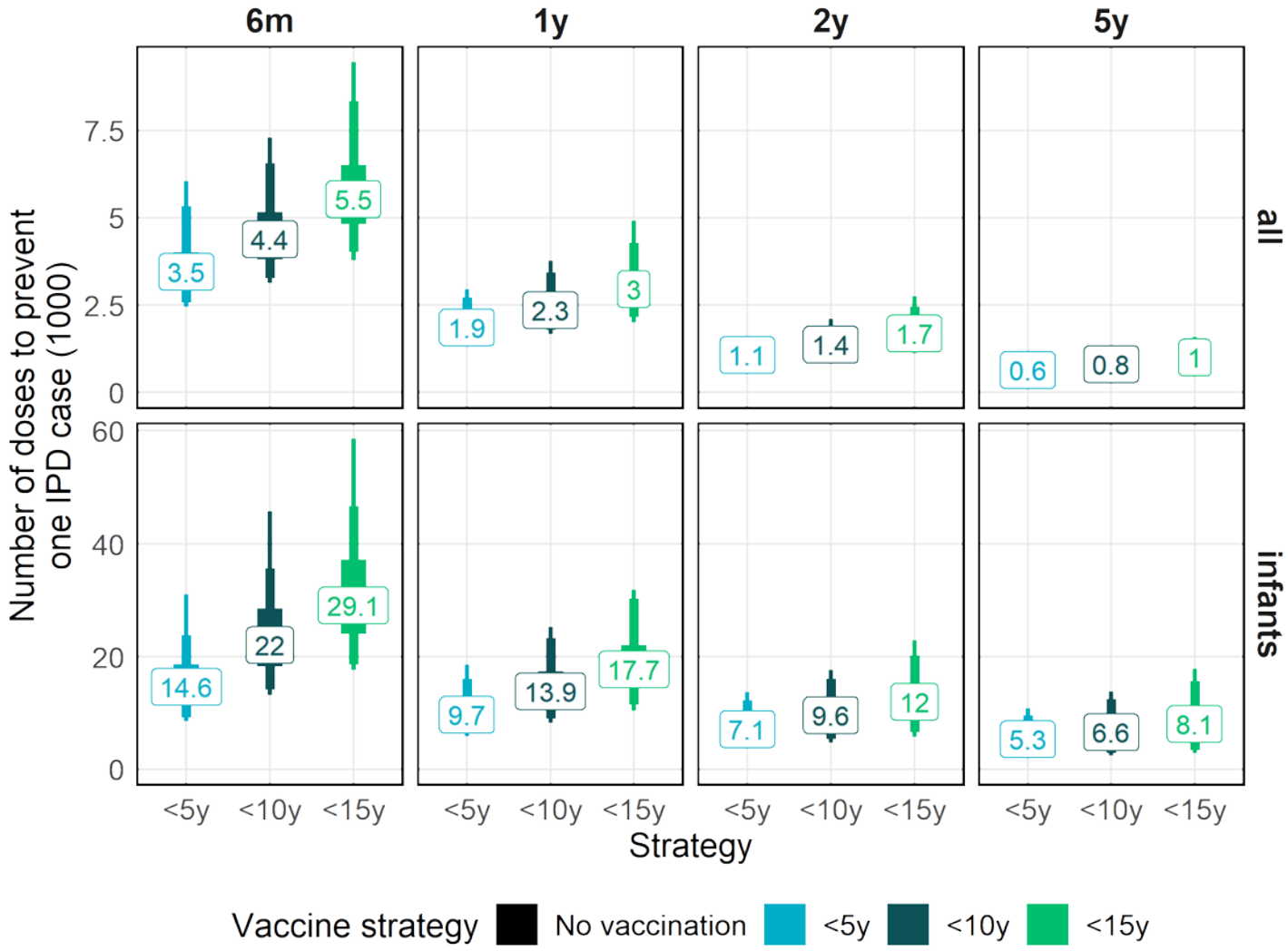
Bentiu PoC


100%
75%
50%
25%
0%
VT carriage prevalence
0y
1/2y
1y
2y
3y
4y
5y
Years since PCV campaign
infants
Vaccine strategy
No vaccination
<5y
<10y
<15y

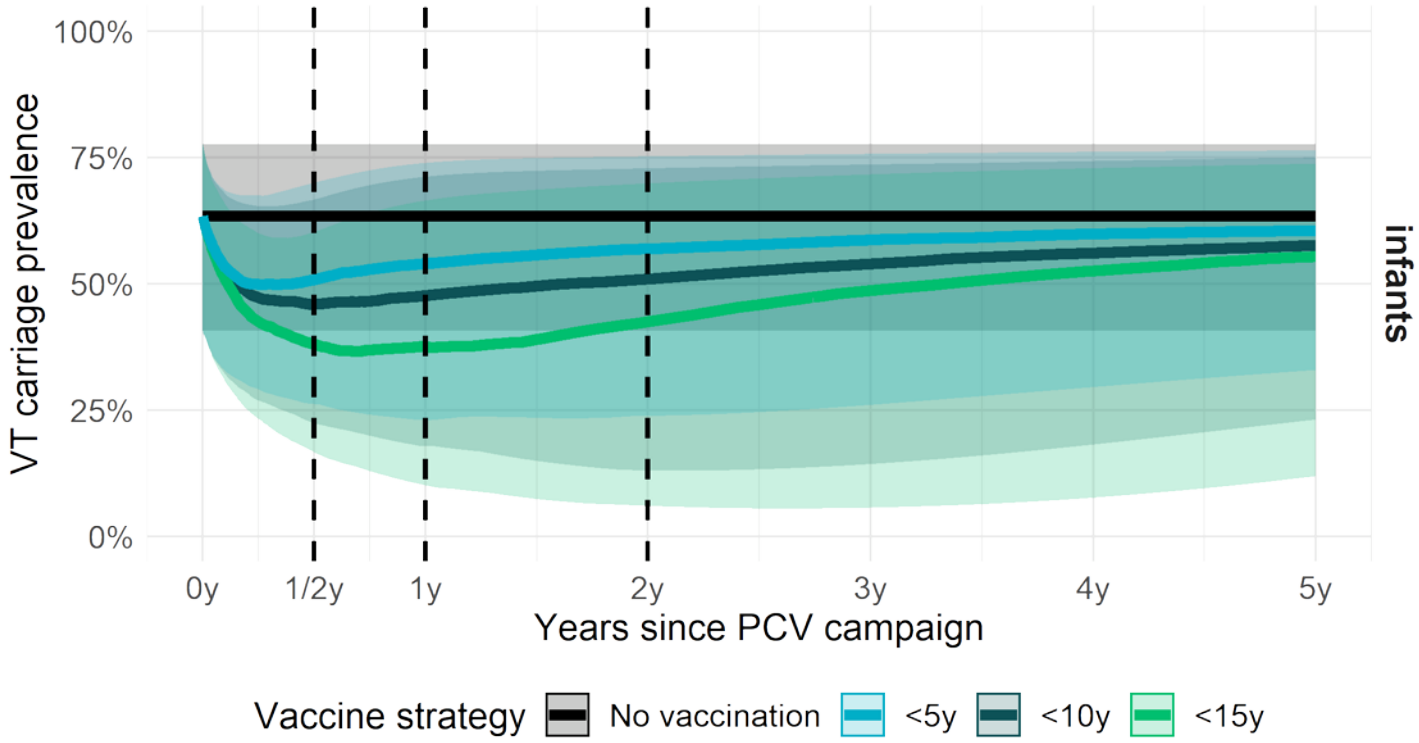
Bentiu PoC


6m
1y
2y
5y
all
infants
Cumulative IPD impact
60%
40%
20%
0%
36
49
53
34
46
50
29
40
44
20
27
29
30
33
35
22
27
29
15
20
22
8
11
13
<5y
<10y
<15y
Strategy
Vaccine strategy
No vaccination
<5y
<10y
<15y

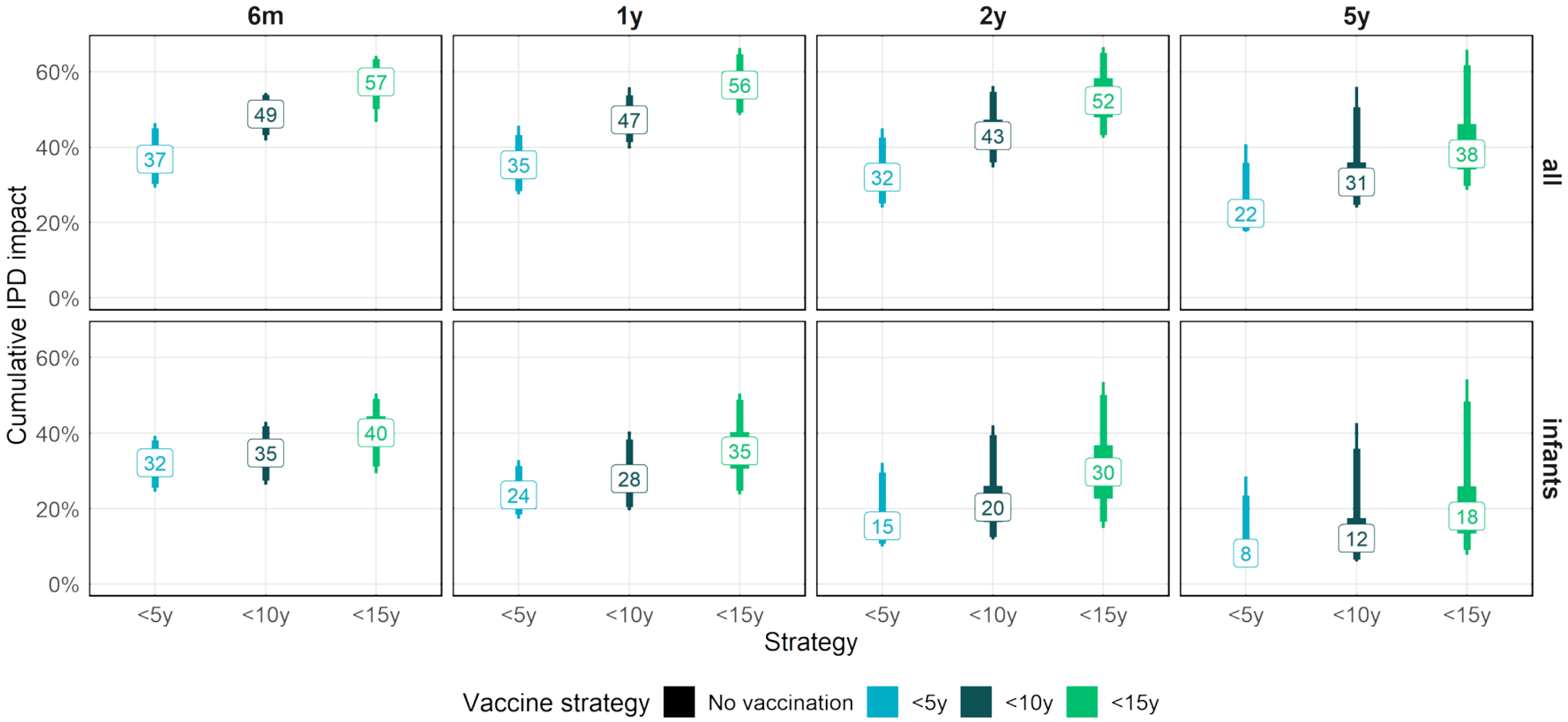
Bentiu PoC


6m
1y
2y
5y
all
infants
Number of doses to prevent one IPD case (1000)
0
2.5
5
7.5
0
20
40
60
3.5
4.4
5.5
1.9
2.3
3
1.1
1.4
1.7
0.6
0.8
1
14.6
22
29.1
9.7
13.9
17.7
7.1
9.6
12
5.3
6.6
8.1
<5y
<10y
<15y
Strategy
Vaccine strategy
No vaccination
<5y
<10y
<15y

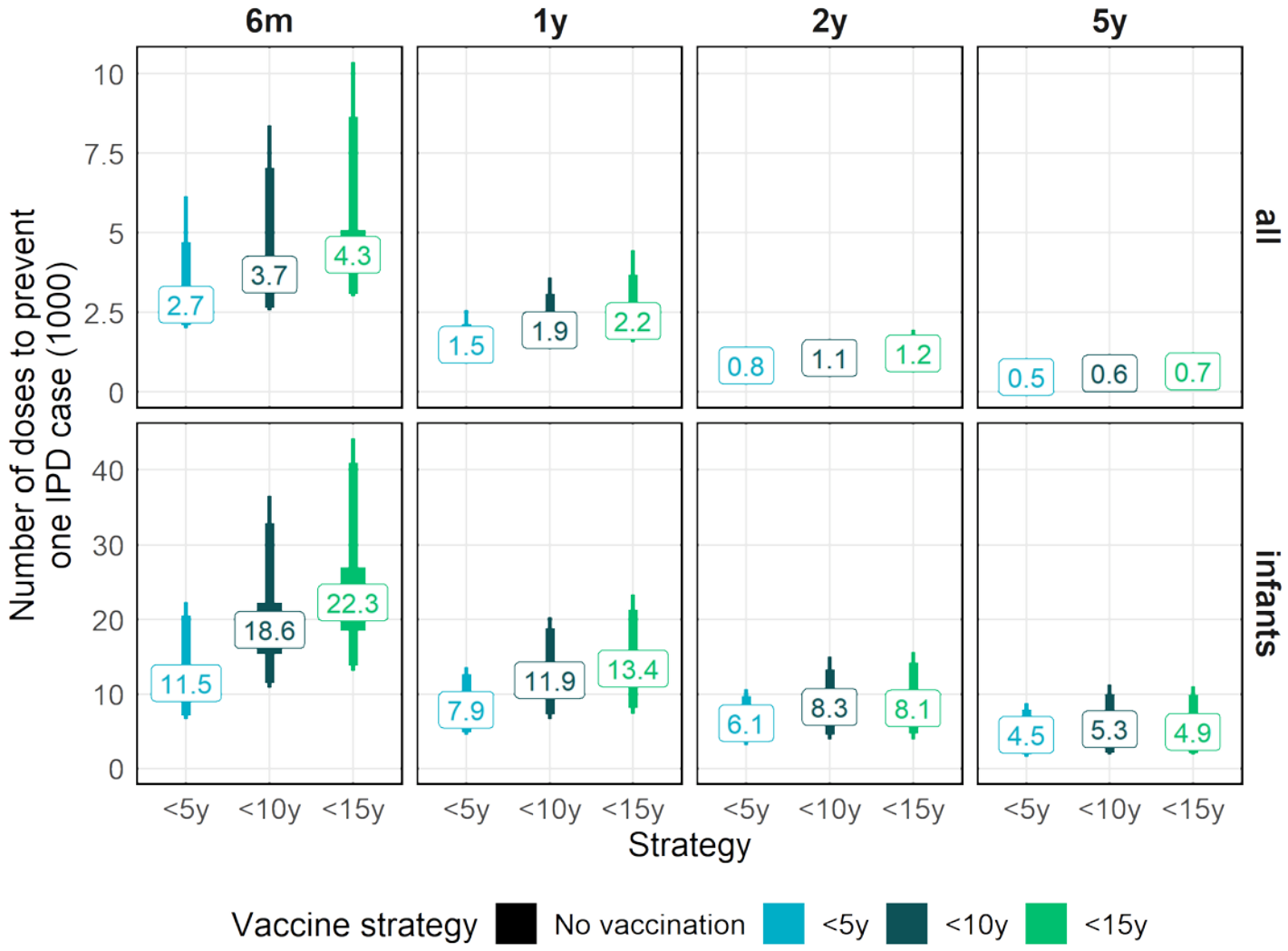
Bambari


100%
75%
50%
25%
0%
VT carriage prevalence
0y
1/2y
1y
2y
3y
4y
5y
Years since PCV campaign
infants
Vaccine strategy
No vaccination
<5y
<10y
<15y

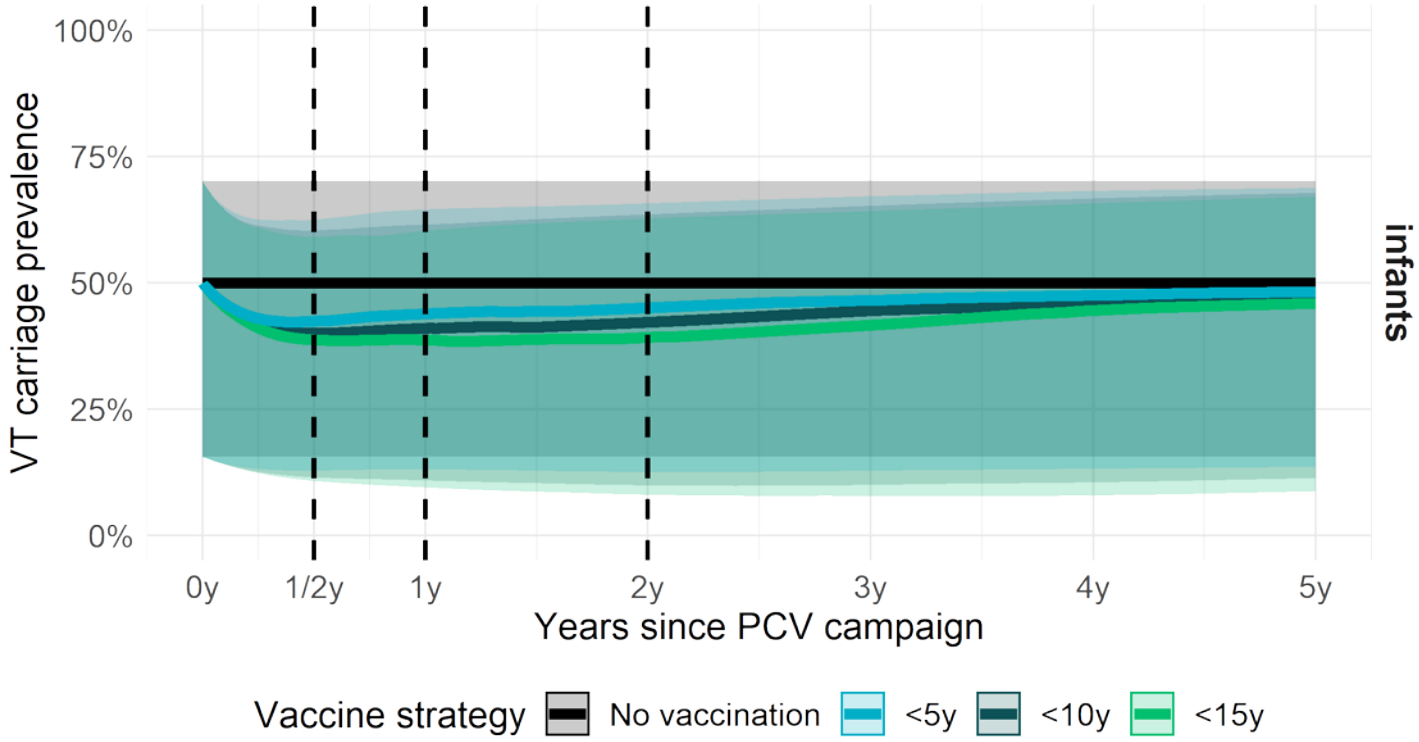
Bambari


6m
1y
2y
5y
all
infants
Cumulative IPD impact
0%
20%
40%
60%
37
49
57
35
47
56
32
43
52
22
31
38
32
35
40
24
28
35
15
20
30
8
12
18
<5y
<10y
<15y
Strategy
Vaccine strategy
No vaccination
<5y
<10y
<15y

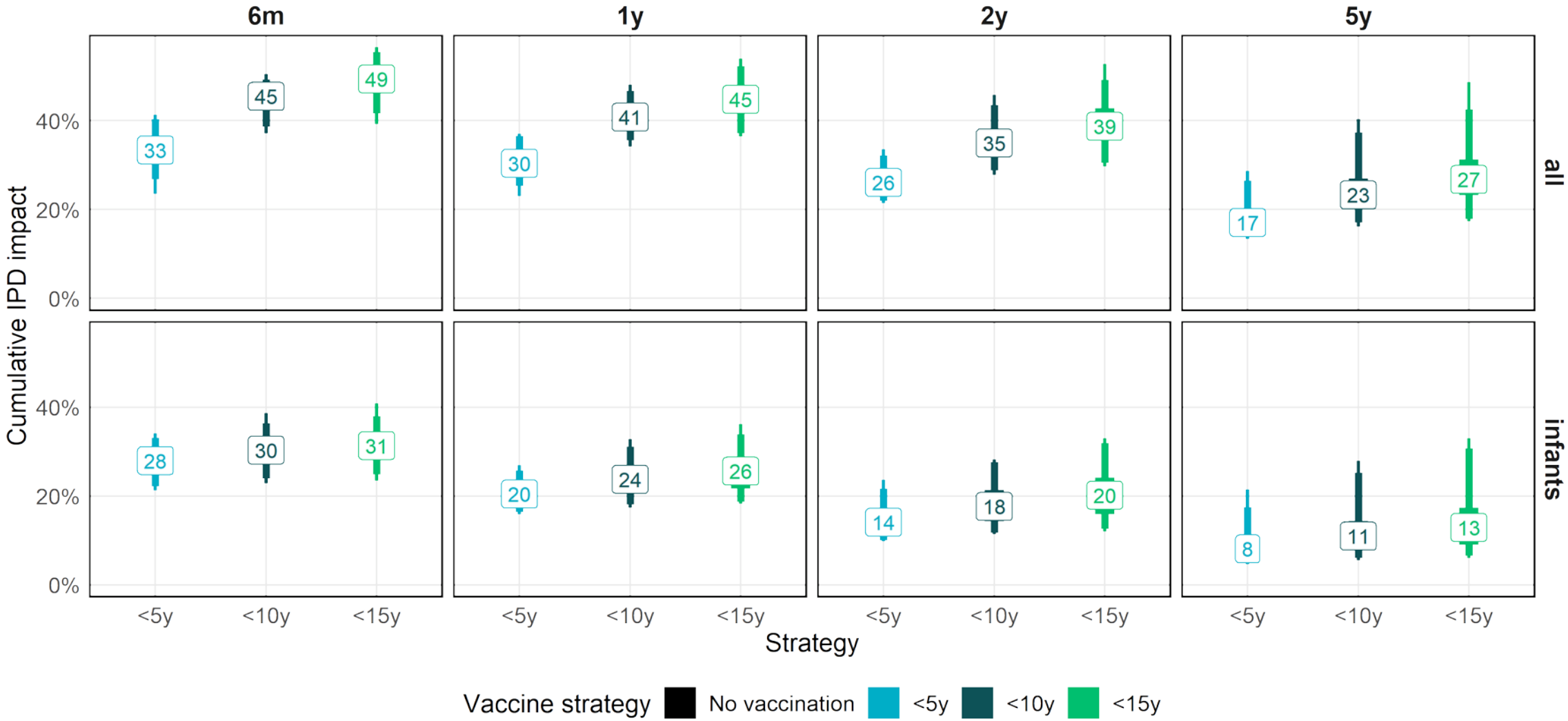
Bambari


6m
1y
2y
5y
all
infants
Number of doses to prevent one IPD case (1000)
10
7.5
5
2.5
0
40
30
20
10
0
2.7
3.7
4.3
1.5
1.9
2.2
0.8
1.1
1.2
0.5
0.6
0.7
11.5
18.6
22.3
7.9
11.9
13.4
6.1
8.3
8.1
4.5
5.3
4.9
<5y
<10y
<15y
Strategy
Vaccine strategy
No vaccination
<5y
<10y
<15y

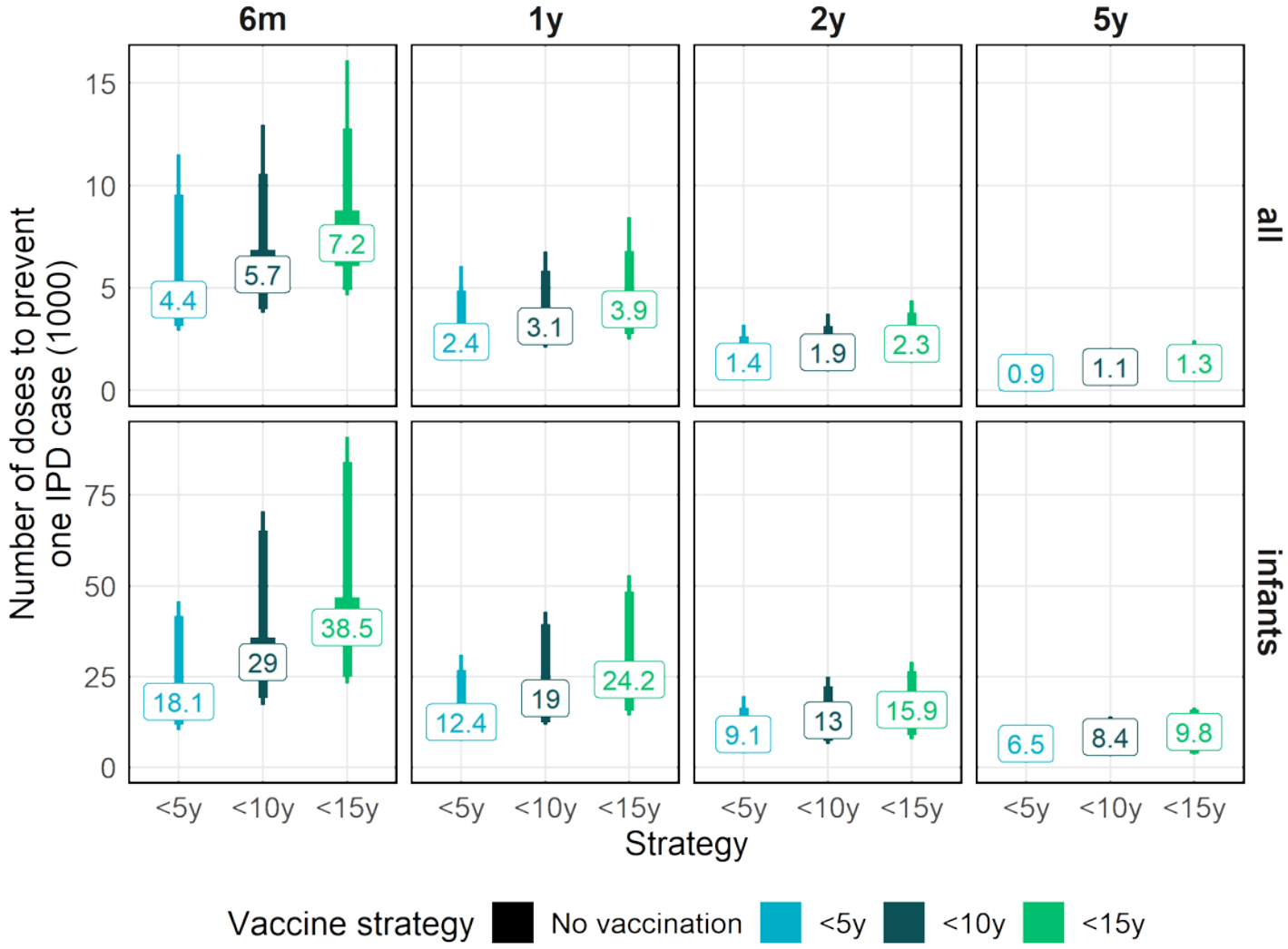
Maiduguri, 2016



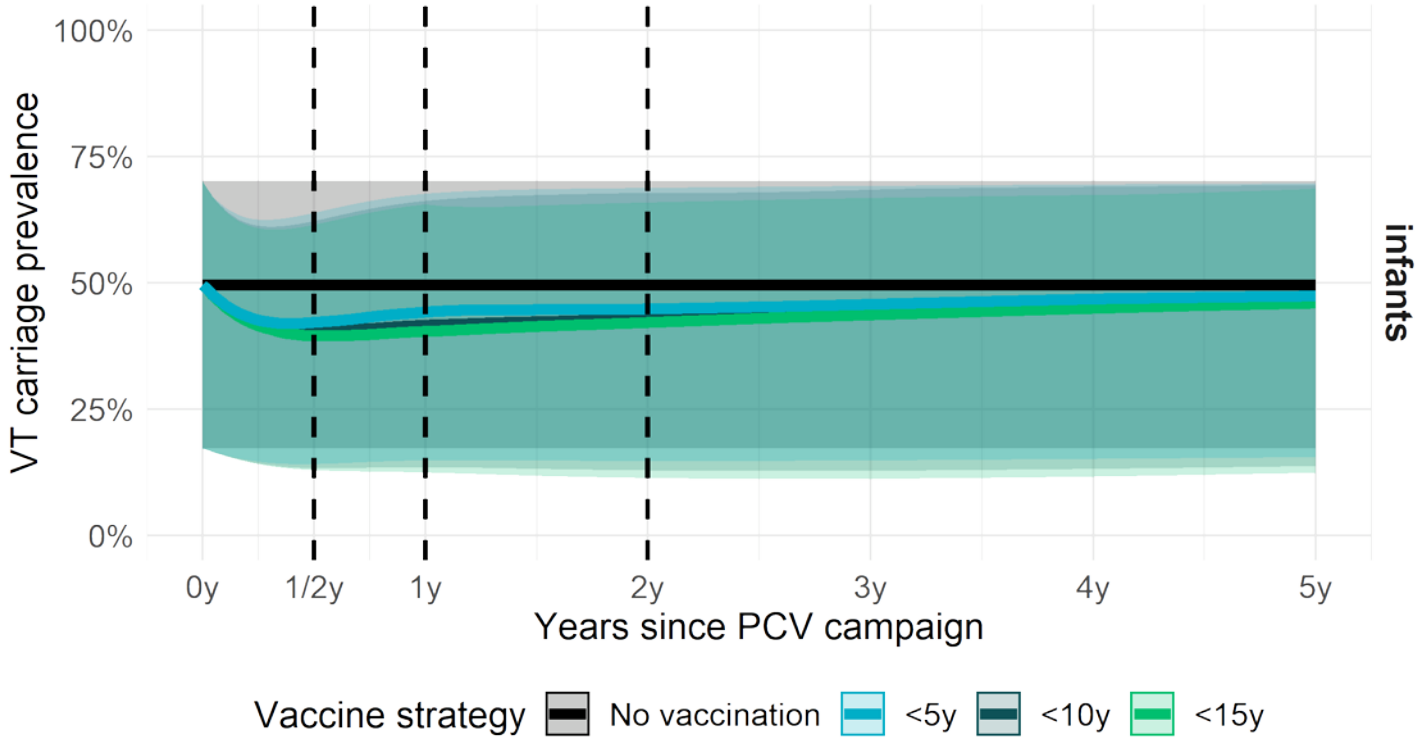
Maiduguri, 2016



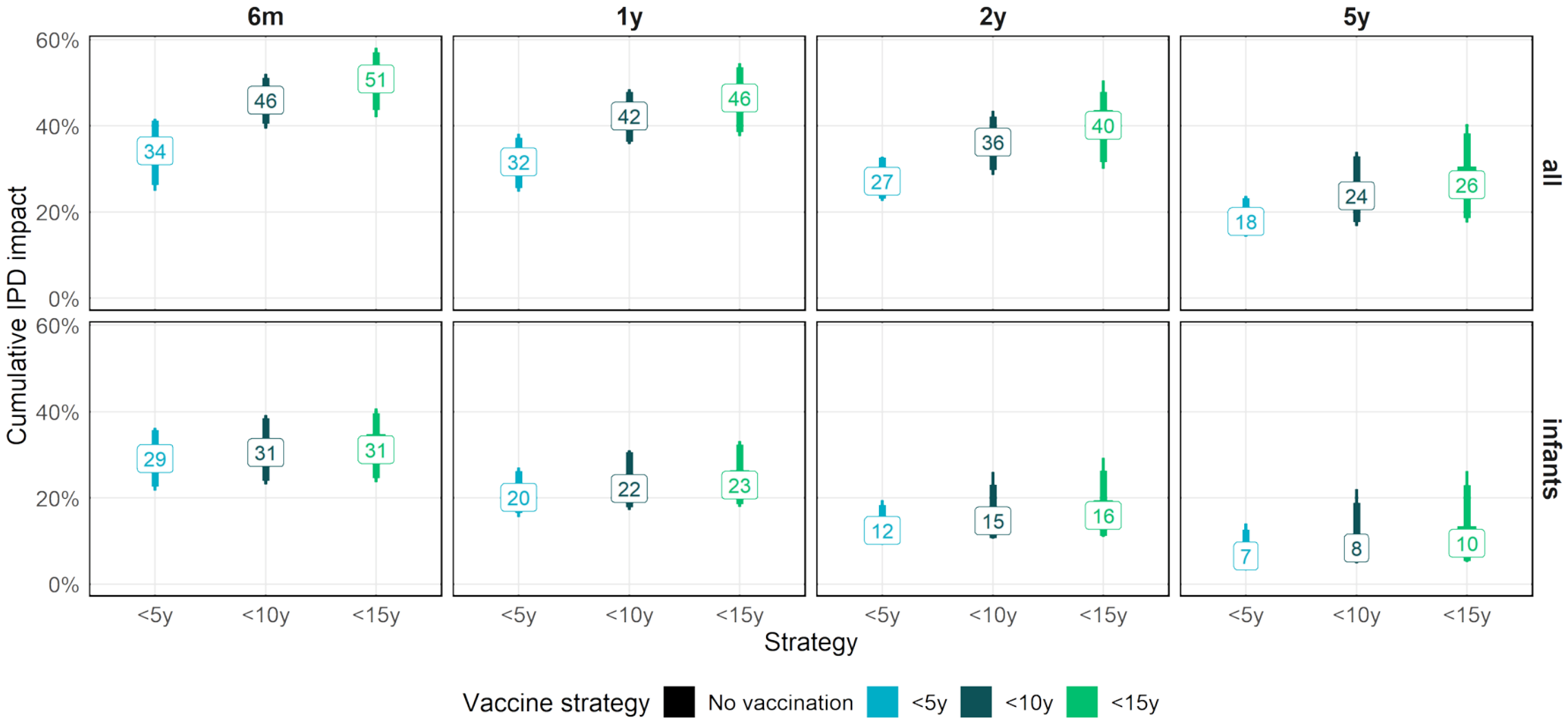
Maiduguri, 2016



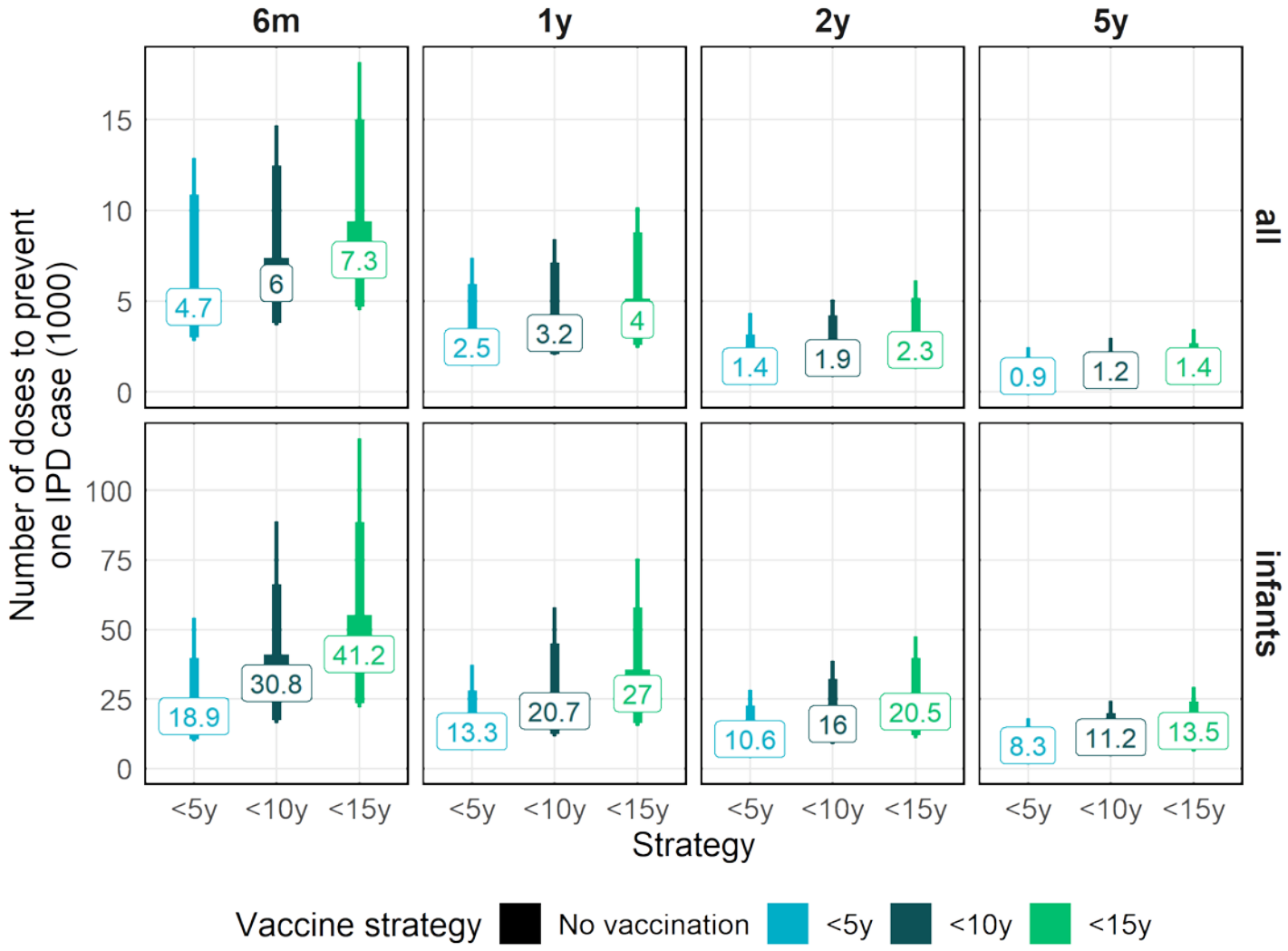
Maiduguri, 2019



Maiduguri, 2019



Maiduguri, 2019



Key background documents to this session are available at the Sharepoint or the links below:

1. Paper on Pneumococcal conjugate vaccine use during humanitarian crises

2. Collected social contact data which is a key input parameter in our transmission model: https://www.sciencedirect.com/science/article/pii/S1755436522000652

Evaluating the Effectiveness of a Pneumococcal Immunisation Campaign in a Camp for internally displaced people (EEPICC)

A non-randomised, quasi-experimental phase IV intervention study

Version:

3.0 (29 April 2022)

Amendments since previous version: added sequencing and phylogenetic analysis of baseline nasopharyngeal swab samples.

Sponsor:

London School of Hygiene and Tropical Medicine

Funders:

Bill and Melinda Gates Foundation

Elhra's Research for Health in Humanitarian Crises (R2HC) Programme

Global Challenges Research Fund, UK Research and Innovation

Pfizer

LSHTM ethics reference:

26414

ClinicalTrials.gov reference:

NCT04945681

Signatures

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the International Council for Harmonisation Good Clinical Practice (ICH GCP) and/or Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, the Sponsor's (and any other relevant) Policies and Standard Operating Procedures (SOPs), and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor: **SIGNATURE BY RGIO TO BE OBTAINED**

Name:	Role:
Signature:	Date:

Chief Investigator:

Name:	Francesco Checchi	Date:	29 April 2022
Signature:			

Notice

This protocol describes the EEPICC study and provides information about procedures for entering participants. The protocol should not be used as a guide for vaccination, testing, infection control or other routine health services and activities; every care was taken in its drafting, but corrections or amendments may be necessary.

Problems relating to this study should be referred, in the first instance, to the main contacts.

This study will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, protocol and all applicable local regulations.

Main contacts

Chief investigators:

Name: Prof Francesco Checchi

Address: Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

Email: Francesco.checchi@lshtm.ac.uk

Tel./whatsapp +44 78 3298 7548

Name: Prof Stefan Flasche

Address: Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

Email: Stefan.flasche@lshtm.ac.uk

Tel./whatsapp +44 74 2594 6656

Co-investigators:

Name: Kevin van Zandvoort

Address: Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

Email: Kevin.Van-Zandvoort@lshtm.ac.uk

Tel./whatsapp +44 73 0726 6245

Name: Dr Catherine Satzke

Address: Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Road, Parkville, Victoria 3052, Australia

Email: Catherine.Satzke@mcri.edu.au

Name: Prof Kim Mulholland

Address: Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Road, Parkville, Victoria 3052, Australia

Email: Kim.Mulholland@lshtm.ac.uk

Name: Abdirahman Ibrahim Buqul

Address: Republic of Somaliland Ministry of Health Development, Hargeisa, Somaliland

Email: buqulmph@gmail.com

Tel./whatsapp +252 6 3441 3202

Name: Mohamed Yusuf

Address: Republic of Somaliland Ministry of Health Development, Hargeisa, Somaliland

Email: yuusuf285@yahoo.com

Name: Dr Mohammed Omer Bobe

Address: Save the Children, Hargeisa, Somaliland

Email: mohamed.bobe@savethechildren.org

Name: Dr Catherine McGowan

Address: Save the Children, 1 St John's Lane, London EC1M 4AR UK

Email: c.mcgowan@savethechildren.org.uk

Name: Emma Diggle

Address: Save the Children, 1 St John's Lane, London EC1M 4AR UK

Email: E.Diggle@savethechildren.org.uk

Contact for general queries:

For general queries, supply of trial documentation, and collection of data, please contact:

Name: Kevin van Zandvoort

Address: Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

Email: Kevin.Van-Zandvoort@lshtm.ac.uk

Tel: +44 7 307 266 245

Contact for clinical queries:

Clinical queries should be directed to Prof Francesco Checchi (see contacts above) who will direct the query to the appropriate person.

Study sponsor:

The London School of Hygiene and Tropical Medicine is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Research Governance and Integrity Office:

London School of Hygiene & Tropical Medicine
Keppel Street
London WC1E 7HT
Tel: +44 207 927 2626
Email: RGIO@lshtm.ac.uk

Study funders:

This study is primarily funded by the Bill and Melinda Gates Foundation. Pre-vaccination activities are co-funded by Elhra's Research for Health in Humanitarian Crises (R2HC) Programme, which aims to improve health outcomes by strengthening the evidence base for public health interventions in humanitarian crises. The R2HC programme is funded by the UK Government (DFID), the Wellcome Trust, and the UK National Institute for Health Research (NIHR). Microbiological analysis is partly funded by the Global Challenges

Research Fund (GCRF), UK Research and Innovation. The sequencing of pneumococci is funded through a Robert Austrian Research Award funded by Pfizer.

Table of contents

Signatures 2
Notice 2
Main contacts 3
Study summary 8
Glossary of abbreviations 8
1 Introduction 9
1.1 Background 9
1.2 Study rationale 9
2 Study objectives 11
2.1 Primary objectives 11
2.2 Secondary objectives 11
3 Study design 12
3.1 Overall design 12
3.2 Study outcomes 13
3.2.1 Primary outcomes 13
3.2.2 Secondary outcomes 13
3.3 Sample size 14
3.3.1 Sample size for vaccination campaign and safety outcomes 14
3.3.2 Sample size for nasopharyngeal carriage outcomes 14
3.3.3 Sample size for other outcomes 14
4 Study measurements 14
4.1 Nasopharyngeal carriage outcomes 14
4.1.1 Sample collection 14
4.1.2 Sample transport and microbiological analysis 15
4.1.3 Individual- and household-level data collection 16
4.1.4 Camp-level data collection 17
4.2 Vaccine safety outcomes 18
4.2.1 Detection 18
4.2.2 Follow-up 18
4.3 Vaccination coverage outcome 19
4.4 Secondary clinical outcomes 19
4.5 Modality of data collection 19
4.6 Risks and benefits of measurements 20
5 Selection and withdrawal of participants 22
5.1 Eligibility Criteria 22
5.1.1 Vaccination and vaccination safety evaluation 22
5.1.2 Nasopharyngeal carriage surveys 22
5.2 Withdrawal criteria 23
6 Enrolment procedures 23
6.1 Vaccination and vaccination safety evaluation 23
6.2 Nasopharyngeal carriage surveys 24
6.2.1 Digaale surveys 24
6.2.2 Hargeisa residents survey 25
7 Experimental intervention 25
7.1 Pneumococcal conjugate vaccine 25
7.1.1 Name and description of the vaccine used 25
7.1.2 Regulatory status of the vaccine 25
7.2 Vaccine supply and management at the study site 25
7.3 Preparation and administration of vaccine 26
7.4 Dosage schedule 26
7.5 Risks and benefits of the experimental intervention 27

7.5.1 Vaccine effectiveness 27
7.5.2 Vaccine safety 27
7.5.3 Restrictions on vaccination 28
8 Safety reporting 28
8.1 Definitions 28
8.2 Causality assessment 29
8.3 Reporting procedures 29
8.3.1 Adverse event reporting 29
8.3.2 SUSARs 30
9 Statistics and data analysis 30
9.1 Study precision and power for primary effectiveness outcome 30
9.1.1 Precision of carriage prevalence estimates 30
9.1.2 Study power for varying effect sizes 30
9.1.3 Expected study power 31
9.2 Analysis of outcomes 32
9.2.1 Nasopharyngeal carriage outcomes 32
9.2.2 Vaccine safety outcomes 33
9.2.3 Vaccination coverage outcome 33
9.2.4 Other secondary clinical outcomes 33
10 Study monitoring and governance 34
10.1 Risk assessment 34
10.2 Study monitoring 34
10.2.1 Vaccine-related monitoring 34
10.2.2 Data quality-related monitoring 34
10.2.3 Study protocol violations 34
10.3 Regulatory issues 35
10.3.1 Study authorisation 35
10.3.2 Ethics approval 35
10.3.3 Consent 35
10.3.4 Confidentiality 35
10.3.5 Indemnity 36
10.3.6 Sponsor 36
10.3.7 Funding 36
10.3.8 Audits and inspections 36
10.3.9 Protocol development 36
10.4 Study management and accountability 36
10.5 Publication 37
11 References 38
12 Appendices 41
12.1 List of drugs (generic names) included in measurement of antibiotic prescriptions 41
12.2 Details of mathematical modelling simulations 41
12.3 Carriage survey questionnaire 41
12.4 Adverse events severity grading table 41
12.5 Serious adverse event Case Report Form 41
12.6 List of solicited signs and symptoms to capture adverse events 41
12.7 National Early Warning Score 2 grading of vital signs 41
12.8 Vaccine information sheet 41
12.9 Vaccination informed consent form 41
12.10 Carriage survey information sheet 41
12.11 Carriage survey informed consent form 41
12.12 Carriage survey informed assent form 41
12.13 PNEUMOSIL product leaflet 41
12.14 Risk assessment 41
12.15 Terms of reference of the Study Oversight Committee 41

Study summary

Title	Evaluating the Effectiveness of a Pneumococcal Immunisation Campaign in a Camp for internally displaced people
Design	Non-randomised quasi-experimental phase IV intervention study with a nested Phase II evaluation of safety in older children
Aims	To evaluate the effectiveness of a Pneumococcal Conjugate Vaccine immunisation campaign in an internally displaced population
Primary outcome measures	Age specific pneumococcal vaccine-type nasopharyngeal carriage at baseline, 6, 12, and 24mths after the vaccine campaign Frequency of post-vaccination adverse events and serious adverse events with a possible, probable, likely or definite causal association with the vaccine
Population	Internally displaced persons living in Digaale IDP camp near Hargeisa, Somaliland
Eligibility	Children aged 6 weeks to 59mo (vaccination) with no exclusion criteria for vaccination All age groups (nasopharyngeal carriage)
Vaccine	A single dose of PNEUMOSIL pneumococcal conjugate vaccine will be offered to all children between the ages of 6 weeks and 59mths and a second dose to children 6 weeks to 11mths old four weeks later
Duration	Vaccination activities will take place in the first month, while pneumococcal prevalence will be assessed at baseline, 6, 12, and 24mths after vaccination

Glossary of abbreviations

AE(FI)	Adverse event following immunization
ALRI	Acute lower respiratory infection
AR	Adverse reaction
CRF	Case Report Form
IDP	Internally displaced person / people
IPD	Invasive pneumococcal disease
IRR	Incidence rate ratio
LSHTM	London School of Hygiene & Tropical Medicine
MCRI	Murdoch Children's Research Institute
MoHD	Ministry of Health Development
MSF	Médecins sans Frontières
NVT	Non-vaccine-type pneumococcal serotypes
OR	Odds ratio
PCV	Pneumococcal conjugate vaccine
SAE	Severe adverse event
SAR	Severe adverse reaction
SC	Save the Children
SUSAR	Suspected Unexpected Severe Adverse Reaction
VT	Vaccine-type pneumococcal serotypes
WHO	World Health Organization

1 Introduction

1.1 Background

Every year, about 300-500 million people worldwide are affected by crises resulting from armed conflicts and natural disasters; of these, some 60-70 million are internally displaced or refugees to other countries (United Nations High Commissioner for Refugees, n.d.). These 'humanitarian' crises expose people to a multiplicity of concurrent risk factors for higher transmission and severity of infections, ultimately resulting in excess mortality, with death rates among children under 5 years up to 50 times greater than baseline during acute emergencies. Predictably, the highest death rates are observed among camp-living internally displaced people (IDPs), who typically experience overcrowding, poor water and sanitation, insufficient nutrient intake and disrupted or altogether absent health services. Very high death rates may also occur during the displacement journey.

Not much is known about the specific burden of acute respiratory infections or pneumonia in crisis settings, but one review (Bellos et al., 2010) suggests they are consistently among the top three causes of morbidity and mortality. On a global level, *Streptococcus pneumoniae* (the pneumococcus) contributes a substantial aetiologic fraction of pneumonia burden, though with important geographical variation (Wahl et al., 2018). There is no published information on the population burden of pneumococcus in humanitarian crises, but theoretical reasoning suggests a high potential for excess morbidity and mortality in such settings, resulting from increased carriage (e.g. through overcrowding and impaired immunity among malnourished persons) and disease progression / case-fatality (e.g. through malnutrition, lack of healthcare, exposure to household fuel particulates and secondary pneumonia during frequent measles outbreaks). Moreover, we believe that some of these risk factors (e.g. acute malnutrition) could also extend the age distribution of pneumococcal infection and disease in either or both directions (van Zandvoort et al., 2019).

Pneumococcal conjugate vaccination (PCV) is an evidence-based intervention to reduce pneumococcal burden. PCVs are widely available in routine immunization programmes around the world. In addition to direct protection against pneumococcal disease, PCVs also elicit indirect protection through interrupted transmission of vaccine-targeted serotypes (VT). In most places where PCVs are used at high coverage, the marked reduction in VT transmission has expanded the benefit beyond vaccinees alone (Klugman et al., 2018). Though the vaccine is being rolled out across most resource-poor countries, to date it has seen limited use in humanitarian responses, and, furthermore, with variable strategies in terms of dosage and target ages (van Zandvoort et al., 2019). On the other hand, the recently (2017) established 'Humanitarian Mechanism' for procurement and delivery of vaccines at affordable prices to humanitarian actors has removed a critical barrier to PCV humanitarian use, namely its cost (World Health Organization, 2017a). To date, the Mechanism has been used mainly by Médecins Sans Frontières to vaccinate children in countries including the Central African Republic, Niger, Nigeria, South Sudan, and Syria.

Making the most of the availability of PCV to reduce morbidity and mortality in crisis settings requires greater awareness by humanitarian actors and more systematic decision-making on vaccination strategies. Critically, however, it also requires more evidence on which PCV vaccination strategies would be appropriate for these settings, and, specifically, for displaced populations.

1.2 Study rationale

In an ongoing study (ESPICC, 2018-2021) funded by ELRHA/R2HC and UK Research and Innovation, the London School of Hygiene & Tropical Medicine (LSHTM), Save the Children (SC), Médecins Sans Frontières (MSF) and the Murdoch Children's Research Institute (MCRI) are collaborating to collect pneumococcal carriage and social mixing data from a crisis-affected population, build mathematical models based on these data to predict the impact on carriage and disease of different PCV strategies, and estimate the cost-effectiveness of alternative strategies.

As part of the above project, a carriage and social mixing survey (van Zandvoort et al., 2021) was conducted in October 2019 in Digaale IDP camp (population 3000) in Somaliland, where SC provides nutritional and educational services. This survey found high crude death rates among all age groups (33 per 1000 per year)

and children under 5yo (57 per 1000 per year) in Digaale, with high (>50%) cumulative incidence estimates of self-reported medically attended pneumonia in children under 5yo. Prevalence of pneumococcal risk factors (overcrowding, polluting cooking fuels, physical contact rates, malnutrition) was also high. Initial data (unpublished) from that survey suggest that pneumococcal carriage prevalence was 43% in all age-groups, 75% in children <24mo, 73% in children 24-59mo, and 46% in 5-14yo.

PCVs have not yet been introduced in Somaliland, and have never been received by the IDPs living in Digaale, though the country has begun the process of seeking Gavi support for their future roll-out. Mathematical modelling analysis (unpublished) relying on a transmission dynamic model was conducted using age-specific demographic, carriage and contact pattern data collected during the 2019 survey in Digaale to explore different target age groups for vaccination. This analysis suggests that a PCV campaign targeting children up to 59mo (i.e. approximately 20% of the population) would substantially reduce VT transmission and prevalence (Figure 1 and Appendix 12.2). Even in the absence of routine immunization, the model projects a reduction in VT prevalence through herd protection sustained over several years, and benefiting both the vaccinated age cohorts and unvaccinated newborns. This is expected to result in a substantial reduction in invasive pneumococcal disease burden, though with differences in effect dependent on the actual age-specific prevalence of carriage in Digaale.

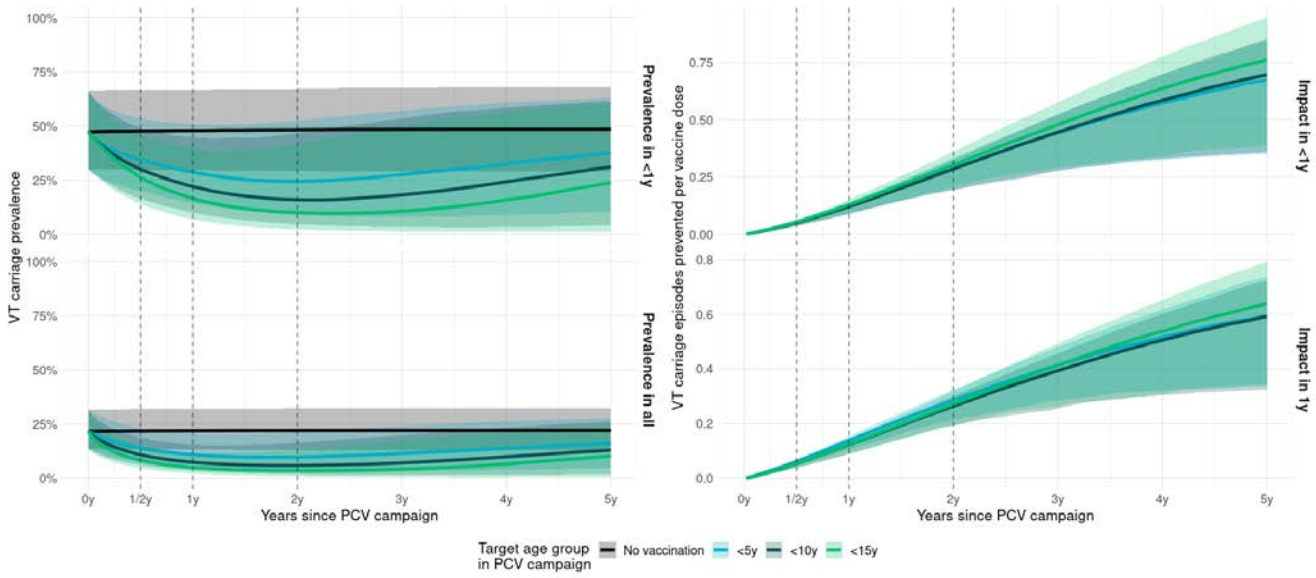


Figure 1. Left panel: Modelled longitudinal impact of simulated PCV campaigns targeting children aged up to 59mo, as well as higher age cut-offs, in Digaale IDP camp. Right panel: Modelled longitudinal efficiency of simulated PCV campaigns in Digaale IDP camp. Campaigns are assumed to achieve 85% vaccination coverage in each age group.

Notably, modelling analysis also suggests that expanding the target age for vaccination to children up to 10 or 14yo would result in even higher and longer-lasting effects on VT carriage and consequent disease burden (Figure 1). Accordingly, the previous version of this study protocol specified this expanded age cut-off. The Ministry of Health Development (MoHD) and Save the Children International in Somaliland have, however, both advised that, given the current landscape of low routine vaccination coverage (<20% for diphtheria, pertussis and tetanus toxoid dose 3) and challenges with vaccine hesitancy and uptake in older age groups, it would be unfeasible and possible counter-productive to target ages ≥ 5yo. As such, this revised protocol adopts the latter cut-off.

While modelling indicates that a PCV campaign could be effective, this study will directly test that hypothesis by implementing a PCV mass vaccination campaign in children and evaluating its impact on pneumococcal carriage prevalence in the short and medium term. To our knowledge this is the first-ever evaluation of such a strategy in a crisis-affected population and may thus contribute critical evidence towards reaching more specific global recommendations for PCV use in these settings. It will also contribute improved understanding of pneumococcal burden in displaced populations, and add to a growing body of evidence on the effect of

the vaccine in different settings, particularly when used in a campaign modality. The vaccination campaign will be preceded by a repeat baseline carriage survey, so to capture changes since the COVID-19 pandemic.

Lastly, the study is expected to contribute to formulating a national PCV vaccination strategy for Somaliland: to this end, we include in this protocol one additional survey of pneumococcal carriage to be conducted among resident, non-displaced people in Hargeisa, the capital of Somaliland: this survey, to be conducted in parallel with the pre-campaign baseline survey in Digaale, will generate evidence upon which to predicate a vaccination strategy for the majority of non-displaced Somaliland citizens, and on the relative differences in carriage patterns between IDPs and non-displaced people in otherwise similar settings.

The study will use the PNEUMOSIL vaccine (Serum Institute, India), one of the three currently World Health Organisation-prequalified PCVs. This vaccine has been selected because it is expected to become the main PCV in use in low-income countries, owing to its cost and design to specifically target serotypes highly prevalent in low-income countries, and given the wider landscape of PCV development (Merck, 2021; Pfizer, 2021). The PNEUMOSIL vaccine label currently covers children aged below 24mo. As such, this study also contains a nested evaluation of the vaccine's safety in children aged 24-59mo.

2 Study objectives

2.1 Primary objectives

1. Estimate the effectiveness of a PCV mass vaccination campaign against vaccine-type (VT) carriage of *S. pneumoniae* in children aged below 24mo, in the short term (6mths and 12mths after vaccination) and mid-term (24mths after vaccination);
2. Document the safety of the PNEUMOSIL pneumococcal conjugate vaccine in children aged 24-59mo; note that the low sample size of the study is unlikely to permit detection of rare adverse events following immunization.

2.2 Secondary objectives

3. Estimate the effect of the PCV campaign on secondary carriage outcomes, including VT carriage in older age groups, NVT carriage in different age groups and bacteriological density of VT and NVT infections by age group, compared to baseline;
4. Compare age-specific prevalence of pneumococcal carriage, serotype distribution and proportion of samples carrying genotypic markers of antimicrobial resistance between internally displaced people and the non-displaced host population, prior to vaccination;
5. Estimate the effect of the PCV campaign on secondary clinical outcomes, including the incidence of hospitalisations due to acute lower respiratory infection (ALRI) among children aged below 24mo and outpatient antibiotic prescription among children aged below 5yo at 6, 12, and 24mths after vaccination, compared to baseline;
6. Estimate the coverage of the full PCV dosing regimen and of at least one dose among the target population, following completion of the mass vaccination campaign, by age group;
7. Estimate the clustering of strains of the most prevalence pneumococcal serotype in displaced children living in Digaale and non-displaced children living in Hargeisa.
8. Use mathematical models parameterized by the study estimates to evaluate strategies to sustain high population immunity in the long-term among similar populations, through repeat campaigns or routine vaccination activities;

Throughout this protocol, we define the effect of vaccination as the sum of direct and indirect protection afforded by vaccination against acquisition of VT carriage. VT serotypes are defined as 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F, namely those that the PNEUMOSIL vaccine is design to provide immunity against.

3 Study design

3.1 Overall design

This study is a non-randomized quasi-experimental Phase IV intervention study with a nested Phase II evaluation of safety in children aged above the age limit in whom PNEUMOSIL is currently approved. The target age group (children up to 59mo) in Digaale IDP camp will be vaccinated in a mass campaign modality. Concurrently, a baseline, cross-sectional pneumococcal carriage survey in Digaale as well as resident, non-displaced communities in Hargeisa, the capital of Somaliland (henceforth 'Hargeisa residents'), will be conducted. In Digaale only, the population will be followed-up for two years, with post-vaccination carriage surveys conducted at 6, 12, and 24mths.

Sequential survey results will be compared in a before-versus-after analysis to the pre-vaccination surveys done in October 2019 and immediately prior to the vaccination campaign, using both statistical and mathematical models to estimate vaccine effectiveness. Data on individual-, household- and camp-level variables will be collected to adjust the effect of vaccination for potential confounding. Additionally, health-facility incident data on ALRI hospitalisations and antibiotic prescriptions will be collected for both the baseline and post-vaccination periods. A schematic of these study activities is provided below (Figure 2).

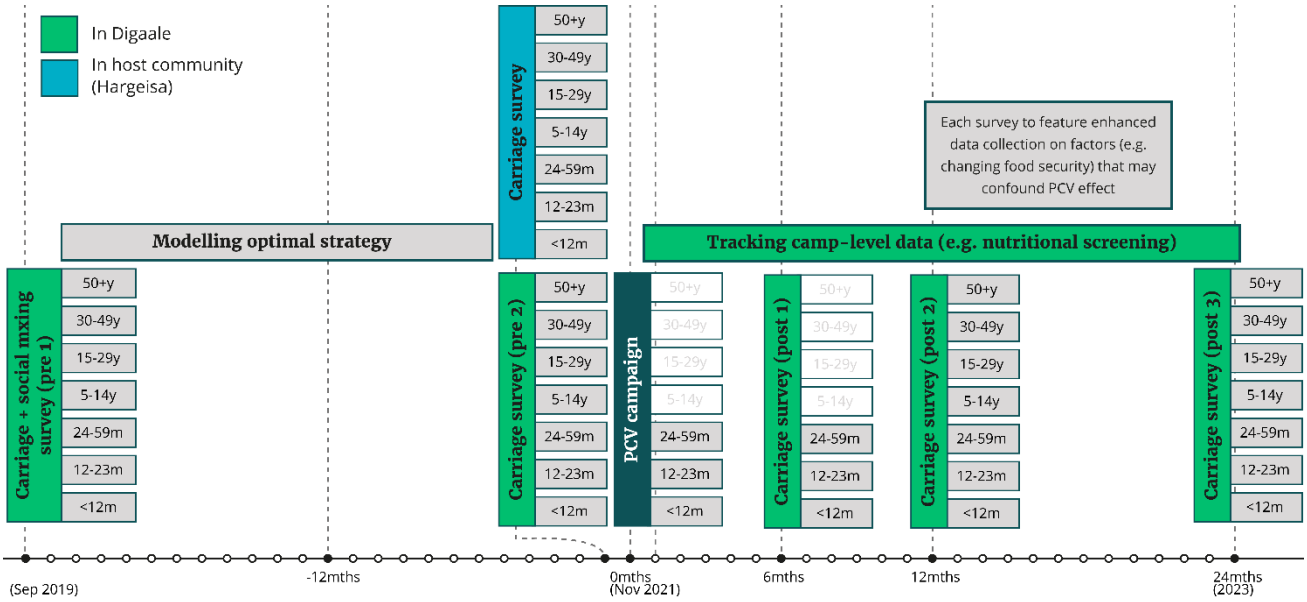


Figure 2. Schematic of study activities.

Not shown in the schematic is data collection on vaccine safety: this will include (i) exhaustive data collection among all children targeted for vaccination on a set ('solicited') list of signs and symptoms corresponding to common AEs, both prior to vaccination (to generate a quasi-experimental, locally valid control) and following each or the only dose of vaccination; and (ii) both active (through observation post-vaccination) and passive detection of SAEs over a period of 3mths following each or the only dose of vaccination, with investigation, follow-up to resolution and causality assessment of each SAE, and comparison of the incidence of SAEs during pre-defined 'at-risk' and 'not-at-risk' periods (corresponding to when SAEs caused by PCV are biologically expected based on existing evidence) using the self-controlled case series method.

3.2 Study outcomes

3.2.1 Primary outcomes

The following outcome will be measured in Digaale IDP camp (all time points) and among Hargeisa residents (baseline only):

- Number and proportion of children aged below 24mo who have nasopharyngeal carriage of one or more colonies of VT *Streptococcus pneumoniae* serotypes, by age group (6 weeks to 11mo, 12 to 23mo) at baseline, 6, 12 and 24mths post receipt of the first or only PCV dose.

The following outcomes will be measured in Digaale IDP camp only:

- Number and proportion of vaccine recipients who experience solicited local and systemic adverse events (AE) over a 7-day period before receipt of the first or only PCV dose and immediately after receipt of the first or only PCV dose, by typology of AE, severity and age group (6 weeks to 11mo, 12 to 23mo, 24 to 59mo);
- Number and proportion of vaccine recipients who experience solicited or unsolicited severe adverse events (SAE) following receipt of the first or only PCV dose, by typology, severity, likelihood of causal association with PCV, expectedness, age group (below 24mo, 24 to 59mo) and timing of onset of the SAE.

3.2.2 Secondary outcomes

The following outcomes will be measured in Digaale IDP camp (all time points) and among Hargeisa residents (baseline only):

- Number and proportion of older children and adults with nasopharyngeal carriage of one or more colonies of VT *Streptococcus pneumoniae* serotypes, by age group (24-59mo, 5 to 14yo, 15 to 29yo, 30 to 49yo, 50yo and above) at baseline, 6, 12 and 24mths post receipt of the first or only PCV dose;
- Number and proportion of children and adults with nasopharyngeal carriage of one or more colonies of NVT *Streptococcus pneumoniae* serotypes, by age group (6 weeks to 11mo, 12 to 23mo, 24-59mo, 5 to 14yo, 15 to 29yo, 30 to 49yo, 50yo and above) at baseline, 6, 12 and 24mths post receipt of the first or only PCV dose;
- Mean bacteriological density of VT and NVT *Streptococcus pneumoniae* infections among children and adults with at least one infecting colony in the nasopharynx, by age group (6 weeks to 11mo, 12 to 23mo, 24-59mo, 5 to 14yo, 15 to 29yo, 30 to 49yo, 50yo and above) at baseline, 6, 12 and 24mths post receipt of the first or only PCV dose;
- Number and proportion of children and adults with nasopharyngeal carriage of one or more colonies of *Streptococcus pneumoniae* serotypes containing at least one marker of antimicrobial resistance, by age group (6 weeks to 11mo, 12 to 23mo, 24-59mo, 5 to 14yo, 15 to 29yo, 30 to 49yo, 50yo and above) at baseline.

The following outcomes will only be measured in Digaale IDP camp:

- Monthly number and incidence rate of hospitalisations due to syndromically defined acute lower respiratory infection (ALRI) among children aged below 24mo at baseline (24mths prior to receipt of the first or only PCV dose) and during the 24mths post receipt of the first or only PCV dose;
- Monthly number and incidence rate of antibiotic prescriptions at outpatient care among children aged below 59mo at baseline (24mths prior to receipt of the first or only PCV dose) and during the 24mths post receipt of the first or only PCV dose; antibiotics are defined as per the World Health Organization's Model List of Essential Medicines (Appendix 12.1);
- Proportion of the target population who receive the specified dosing schedule of pneumococcal conjugate vaccine during the vaccination campaign, by age group (6 weeks to 11mo, 12 to 23mo, 24-59mo, 5 to 14yo, 15 to 29yo, 30 to 49yo, 50yo and above) and gender.

The following outcome will be measured in Digaale IDP camp and among Hargeisa residents (baseline only):

- Phylogeny of sequenced DNA of the most common pneumococcal serotype, collected from children aged 6 weeks to 59mo.

3.3 Sample size

3.3.1 Sample size for vaccination campaign and safety outcomes

All eligible children aged below 59mo in Digaale (estimated as 600-700) will be offered PCV and will be subject to vaccination safety evaluation. This is for ethical reasons, in order to detect infrequent adverse events and because mathematical modelling simulations (Section 9.1 and Appendix 12.2) suggest that less-than-exhaustive vaccination may provide an insufficient pool of vaccinated children in the smallest age groups to sample for the primary carriage outcome and thus achieve the desired study power of ≥ 80% to observe the hypothesised effect on the primary carriage outcome.

3.3.2 Sample size for nasopharyngeal carriage outcomes

Table 1 shows the target sample size by age group for each nasopharyngeal carriage survey, including the survey conducted in 2019 and that to be done among Hargeisa residents. To minimise burden to study participants, the 6mths survey will only collect nasopharyngeal samples from children in the age groups most at risk of PCV-avertable pneumococcal disease: this is deemed sufficient to parameterise mathematical models of overall camp-level transmission, and fulfils the primary objective of the study. Note however that all surveys will collect household-level information. The basis for sample size calculation and expected study power are detailed in Section 9.1 and Appendix 12.2. The sample size for the survey among Hargeisa residents is inflated by 50% to account for an expected design effect of ≈ 1.5.

Table 1. Target sample size by age group for repeat cross-sectional nasopharyngeal carriage surveys. Numbers in parentheses indicate effective sample size in the October 2019 survey (see Section 6.2 for plans to achieve sample size under this protocol).

Location:	Digaale		Hargeisa residents	Digaale		
Timing:	Oct 2019	0mths	0mths	6mths	12mths	24mths
<12mo	100 (22)	100	150	100	100	100
12-23mo	100 (43)	100	150	100	100	100
24-59mo	100 (88)	100	150	100	100	100
5-14yo	100 (77)	100	150	0	100	100
15-29yo	100 (56)	100	150	0	100	100
30-49yo	100 (68)	100	150	0	100	100
≥ 50yo	100 (100)	100	150	0	100	100
Total	*700 (454)*	*700*	*1050*	*300*	*700*	*700*

3.3.3 Sample size for other outcomes

Data collection on the incidence of hospitalisations and antibiotic prescriptions will be exhaustive, i.e. for the entire Digaale camp population.

4 Study measurements

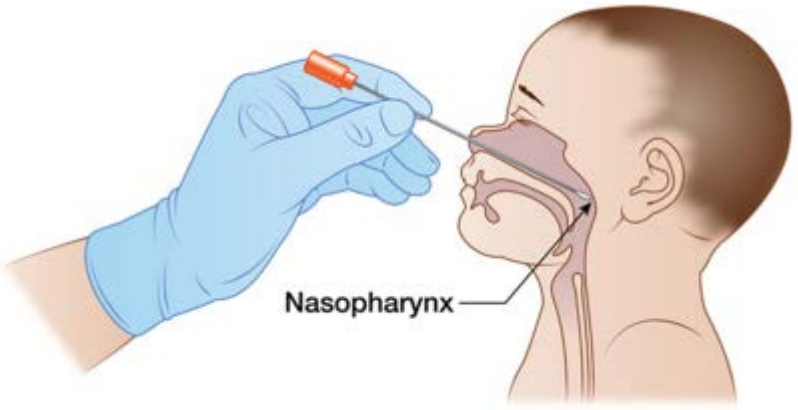
4.1 Nasopharyngeal carriage outcomes

4.1.1 Sample collection

Pneumococcal carriage is a necessary cause of invasive pneumococcal disease (IPD). Invasiveness is serotype-dependent, and is generally higher for the serotypes included in PCVs. While overall pneumococcal carriage prevalence generally stays the same after (routine) vaccination, an effect on disease burden results

from the reduction in VT infections and their ecological replacement by relatively less pathogenic NVT serotypes.

Nasopharyngeal (NP) swab samples will be collected to estimate the prevalence of pneumococcal carriage. Sampling from the nasopharynx is recommended over that from the oropharynx in infants and children. Swabs will consist of nylon or Dacron materials, as these are preferred to maintain sensitivity in further molecular analyses. Swabbing will be done by trained medical doctors or nurses according to WHO guidelines (Satzke et al., 2013), summarised in Figure 3.



"Hold the infant or young child's head securely. Tip their head backwards slightly and pass the swab directly backwards, parallel to the base of the NP passage. The swab should move without resistance until reaching the nasopharynx, located about one-half to two-thirds the distance from the nostril to ear lobe. If resistance occurs, remove the swab and attempt again to take the sample entering through the same or the other nostril. Failure to obtain a satisfactory specimen is often due to the swab not being fully passed into the nasopharynx. Once the swab is in location, rotate the swab 180°, or leave in place for 5 s to saturate the swab tip; remove the swab slowly. All swabs should be processed; however, to assist with interpreting the results, investigators should record whether the procedure was acceptable or suboptimal. Recording if secretions are present on the swab and whether the swab was potentially contaminated (e.g. touched by the investigator or dropped on the ground) may also be helpful in interpretation."

Figure 3. Recommended procedure to collect nasopharyngeal swab samples.

Immediately after collection, NP swabs will be aseptically placed in tubes containing storage medium (skim milk tryptoneglucose-glycerol or STGG), which will have been stored at +4°C prior to use. Swabs will be inserted near the bottom of the STGG medium, raised slightly, after which the swab's shaft will be cut off using sterile scissors and the tube's lid will be closed. The tube will then be placed in a cool box (wet ice) for storage during the day. At the end of each data collection day, swabs will be transferred to a <-20°C freezer. As soon as possible thereafter and after a maximum of seven days, swabs will be transported to a ULT freezer (-80°C) at the Somaliland National Tuberculosis Laboratory.

4.1.2 Sample transport and microbiological analysis

Upon completion of each survey, samples will be randomly split into two equal size batches and shipped by air to MCRI in Melbourne, Australia. Shipments will be labelled as UN3373 (Category B – biological substance). Samples will be shipped out of Hargeisa International Airport using a prequalified shipping solution that utilizes Phase Change Materials to maintain frozen temperatures for up to 5 days. The Schaumaplast Thermocon Classic 15 will be used for this initial shipment (https://www.thermocon-coldchain.com/en/produkt/thermocon-classic-15/). During transit, samples will be placed in a cryobox with dry ice for the remainder of the journey to Melbourne. Arrangements will be made with the courier to top up dry ice if needed.

After transport to MCRI, nasopharyngeal swabs will be tested for pneumococcal serotypes using DNA Microarray with an additional culture amplification step. This technique has 100% sensitivity to detect the major pneumococcal serotypes present in the swab, and 99% sensitivity to detect minor pneumococcal serotypes. It has a positive predictive value of 100% (Satzke et al., 2015). The microarray can also quantify

the relative abundance of the serotypes present and determine the presence of genetic markers associated with antibiotic resistance, including against tetracyclines and macrolides.

A total of 150 pneumococcal isolates identified from the baseline survey only will be selected for DNA sequencing, 75 from children in each population (displaced individuals in Digaale and non-displaced individuals in Hargeisa). Analyses will focus on the most prevalent serotype(s) in children younger than five years of age as detected using MicroArray, and isolates will be selected using a simple random sampling approach. DNA will be extracted using QIAGEN QIACube HT, and sequenced using 2x150bp paired-end sequencing on the NovaSeq 6000 (Illumina). The sequencing will be used to assess the clustering of strains between Digaale and Hargeisa, but will also allow a more specific identification of the antibiotic resistance profile of the selected pneumococci. All microbiological analyses will be conducted at MCRI.

4.1.3 Individual- and household-level data collection

All carriage surveys will also collect individual- and household-level data that are direct or proxy measures of potential confounders and effect modifiers of the association between vaccination and VT carriage.

Data collected as part of the carriage survey for each child aged up to 59mo being sampled only will include:

- Anthropometric measurements of children aged 6 to 59mo, collected according to SMART guidelines (SMART, 2017) and including weight, height (or length for children below 85cm / under 24mo), age in months, middle-upper-arm circumference (MUAC) and presence of bilateral oedema on the dorsum of both feet, as defined by sustained pitting after three seconds thumb pressure. Weight will be measured using an electronic scale to the nearest 0.1Kg and height/length to the nearest cm using a measuring board. MUAC strips will be used to measure MUAC in mm. If a child is physically disabled, this will be reported (i.e. missing limbs may bias weight estimates);
- Breastfeeding status;
- Completion of the recommended dosage of measles, pertussis and haemophilus influenzae type B vaccines, as per local routine immunisation schedule.

Data collected as part of the carriage survey for each participant being sampled, irrespective of age, will include:

- Health service utilisation:
  - Whether the participant was seen in a formal health facility during the previous two weeks;
  - Whether the participant was unwell with respiratory symptoms during the previous two weeks (may confound pneumococcal detection from swab sample);
  - Any antibiotic consumption during the previous two weeks (may confound pneumococcal detection from swab sample);
- Proxy data for contact patterns:
  - School or work attendance;
  - Class or workplace size;
  - Most common mode of transportation;

Data collected on each household included in the carriage survey will include:

- GPS coordinates (to track survey uptake and identify households who need to be revisited);
- Exposure to indoor air pollution:
  - Cooking fuel used;

- Presence of ventilation in cooking area;
- Presence of infants when cooking;
- Fuel used to heat shelter;
- Tobacco use in household;

- Food security (dietary diversity):
  - Households will be asked to recall the foods that they consumed in the previous seven days from a pre-defined list of items. Each item is given a score of 0 to 7, depending on the number of days on which it was consumed. These will be used to calculate food consumption scores, a standardized proxy indicator that represents the dietary diversity, energy and macro and micro (content) value of the food that people eat (World Food Programme, 2009);
- Quality of shelter:
  - Leakage;
  - Presence of draught;
- Proxy data for contact patterns:
  - Household size and age/gender composition;
  - Door-to-door distance from nearest dwelling (approximate in metres);
  - History of in- and out migration within the camp or from/to other areas of Somaliland since the previous survey;
  - Perceived change in contact behaviour compared to pre-COVID-19 patterns;
- Water, sanitation and hygiene conditions:
  - Use of facemasks and hand sanitizers;
  - Water source most commonly used in the household (piped water: piped into dwelling, piped into compound, yard, or plot, piped into neighbour, public tap/standpipe; dug well: protected well, unprotected well, e.g. shallow well; water from spring: protected spring, unprotected spring, rainwater collection, tanker truck, cart with small tank/drum, surface water, e.g. river, dam, lake, pond, stream; bottled water; other);
  - Availability and use of soap.

The survey questionnaire is found in Appendix 12.3.

4.1.4 Camp-level data collection

The following data will be collected for the entire population of camp residents in order to capture confounders or effect modifiers of the association between vaccination and carriage:

- Aggregate data on the number of outpatient consultations for acute respiratory infection, ALRI and/or influenza-like illness, collected from Digaale camp's single primary health care facility, and stratified by age group (<12mo, 12-23mo, 24-59mo, 5-14yo, 15-29yo, 30-49yo, ≥ 50yo) and month, collected at baseline (vaccination campaign) for a retrospective period of 24mths, and at 6mths, 12mths and 24mths post-initiation of the vaccination campaign, each time covering the entire retrospective period since the previous time point of data abstraction;
- Aggregate number and proportion of all children aged 0-59mo consulting at Digaale camp's primary health care facility who have a MUAC reading of 115 to 124mm (orange) and < 115mm (red), out of all children tested, per month, collected at baseline (vaccination campaign) for a retrospective period of 24mths, and at 6mths, 12mths and 24mths post-initiation of the vaccination campaign, each time covering the entire retrospective period since the previous time point of data abstraction.

4.2 Vaccine safety outcomes

4.2.1 Detection

In the context of vaccine safety evaluation, AEs will comprise events due to the vaccine product itself, vaccine quality, vaccination error, vaccination anxiety or coincidental events. All solicited (i.e. through proactive ascertainment of specific signs and symptoms) and unsolicited AEs will be coded using the Medical Dictionary for Regulatory Activities (version 24.0 or later) and classified by type (injection-site, systemic, vital signs) as well as severity (grade 1: mild to grade 5: fatal: Appendix 12.4). SAEs are defined as AEs of grade 3-5. More detailed definitions are provided in Section 8.1.

AEs will be detected through the following activities:

- All vaccinees will be observed for 30 minutes post injection so as to detect, manage and document immediate AEs, including severe reactions; a trained study clinician will be on site, equipped with essential drugs and supplies for management for anaphylactic reactions;
- During the vaccination campaign and up to 7 days following its conclusion (or 7 days after the last second dose of PCV is administered, for infants <12mo), caregivers of vaccinated children will be able to contact a 24 days/7 hours activated local toll-free phone number if they have concerns on vaccine safety or observe AEs in vaccinated children; a clinician monitoring the phone number will provide advice on healthcare seeking, record systematic information on the AEs and initiate further investigation if the event meets the SAE definition or a severity grading below 3 cannot be confirmed;
- During each day of the vaccination campaign, and up to 7 days following its conclusion (or 7 days after the last second dose of PCV is administered, for infants <12mo), end-of-working-day visits to Digaale camp primary healthcare facility will take place to identify, based on conversation with attending clinicians, any instances of children having presented during the day with clinical events meeting the SAE definition; for any such event, further investigation will be initiated; after this 7-day period, the primary healthcare facility will be visited once weekly for a period ending 3mths after receipt of the last single dose (and 3mths after receipt of the last second dose for infants only) to identify any further SAEs among children presenting to the facility, and initiate further investigation;
- Members of the Vaccination Committee, comprising various IDP representatives of both genders (Section 10.4), will be asked to serve as focal points receiving information from the community on any serious illness following vaccination, and report this information to the study team during the same 3mths period;
- The referral inpatient paediatric facilities used by the IDPs will also be contacted regularly over 3mths to identify any children who may have not been seen at Digaale primary health facility prior to hospital admission (this activity is also required for measurement of the related secondary clinical outcome: Section 4.4);
- Onset of a systematic list of ‘solicited’ signs and symptoms (Appendix 12.6) will be ascertained among all children eligible for and consenting to vaccination, based on caregiver recall, at two time points: (i) during the month prior to the start of the vaccination campaign, with a ‘recall’ period of 7 days, and (ii) exactly 7 days after receipt of each or the only dose, with the recall period being the week since the dose was administered. At both time points, data collection will take place at the household.

4.2.2 Follow-up

All SAEs (including events for which a severity grading below 3 is not initially clear) detected through any of the above activities, or through any other means, but within the maximum 3mths period for SAE detection (see above), will be subject to systematic individual investigation and data collection using a standardised Case Report Form (CRF; Appendix 12.5) and will be actively followed up by a study clinician, in close coordination with the Chief Investigator, until resolution (survival without sequelae or with sequelae, death). Follow-up activities will depend on the nature of the SAE, and are constrained by the extent of diagnostics and medical investigations available in Somaliland. Generally, the study team will:

- Ensure that any child with a SAE experiences no financial or transport barriers to access care up to tertiary level available in country (Hargeisa), including treatment for the emergent medical condition that constitutes the SAE, with the exception of any elective treatment costs;
- Ensure that any child with a SAE receives all locally available investigations that are deemed medically useful to understand the cause and nature of the SAE, including laboratory examinations such as biochemistry, microbiology, differential blood count, etc.;
- Collect copies of all medical charts, investigation reports and any other relevant documents that may be helpful to support the CRF and final assessment of severity, causality and expectedness (Sections 8.2, 8.3.2).

4.3 Vaccination coverage outcome

The population targeted for vaccination will be listed exhaustively, by household, in preparation for the vaccination campaign. Names, ages and addresses of each child within the vaccination age group will be collected onto an electronic register, and the number of doses received by each child listed on the register will be noted during the vaccination campaign. Further children who come forward for vaccination, and may have been omitted from listing, will be added to the register. The register will also serve as a sampling frame for the carriage surveys, and will be updated ahead of each survey. After the campaign, an administrative estimate of vaccination coverage will be computed by tallying the number of children who receive all doses and at least a single dose, out of the number targeted, by age group (6 weeks old to 11mo; 12 to 23mo; 24 to 59mo). Section 9.2.3 provides more detailed definitions of coverage.

4.4 Secondary clinical outcomes

The following existing aggregate data will be collected for the entire camp population:

- Number of children aged 0-23mo admitted to a paediatric inpatient facility with a primary diagnosis of ALRI, pneumonia or invasive bacterial disease, by age group (0-11mo, 12-23mo) and month, collected at baseline (vaccination campaign) for a retrospective period of 24mths, and at 6mths, 12mths and 24mths post-initiation of the vaccination campaign, each time covering the entire retrospective period since the previous time point of data abstraction; camp residents utilise a small number of nearby hospitals in Hargeisa, each of which will be visited to abstract data from historical admission registers;
- Number of antibiotic prescriptions given out at the pharmacy of Digaale camp's primary health care facility to children under 5yo, by month and if possible by age group (0-11mo, 12-23mo, 24-59mo), collected at baseline (vaccination campaign) for a retrospective period of 24mths, and at 6mths, 12mths and 24mths post-initiation of the vaccination campaign, each time covering the entire retrospective period since the previous time point of data abstraction; the list of drugs considered antibiotics for the purpose of this outcome is in Appendix 12.1.

4.5 Modality of data collection

All data other than nasopharyngeal swabs will be collected using the Open Data Kit (ODK) software on electronic tablets. This software will be programmed to automatically skip irrelevant questions and perform plausibility checks, thereby increasing the internal validity of the study. Tablets will not require any internet access in the field, but will be charged overnight and synchronised with the server regularly. Several additional tablets will be available in case of technological failure.

Questionnaires will be developed in English, then translated to Somali and back-translated to English to ensure internal validity. They will be tested on focus groups of community members prior to initiation of data collection.

4.6 Risks and benefits of measurements

Children may benefit from anthropometric measurement, as those identified as severely malnourished will be referred to the nearest facility for nutritional therapy. Individuals may experience discomfort from the nasopharyngeal swab. The community of Digaale as a whole may benefit from improved humanitarian and public services resulting from estimation of the prevalence of acute malnutrition and routine vaccination coverage, and, more in the long term, benefit from earlier-than-foreseen introduction of PCV.

Aside from disrupting study activities, ongoing COVID-19 incidence poses a number of health risks for staff and people involved in both the PCV campaign and other data collection activities. Somaliland has recently started vaccinating their healthcare workers and some high-risk populations with COVID-19 vaccines procured through the Covax Initiative. Health professionals and enumerators are expected to be vaccinated ahead of study activities, but the general population in Digaale may not be. Mitigations against known COVID-19 risks, to be implemented ahead of and during data collection, are outlined in Table 2.

Table 2. COVID-19 related risk and mitigation strategies.

Activity	Risk	Mitigation
Community engagement for vaccination	SARS-CoV-2 transmission during community stakeholder meetings.	▪ Meetings take place outdoors. ▪ Participants are seated at least 2 metres apart. ▪ All community engagement staff are fully vaccinated for COVID-19. ▪ All involved wear face coverings.
	SARS-CoV-2 transmission during community mobilisation ahead of vaccination.	▪ No group activity is held. Instead, vaccination community mobilisation are done door to door, by standing outdoors at least 2 metres from camp residents. ▪ All community engagement staff are fully vaccinated for COVID-19. ▪ All involved wear face coverings. ▪ Any loudspeakers are thoroughly disinfected before being passed on to other staff, and before and after each session.
Vaccination campaign	SARS-CoV-2 transmission during vaccine registration and administration.	▪ All vaccination takes place door to door, outside the household. ▪ All vaccination staff are fully vaccinated for COVID-19. ▪ Vaccination clerks wear face masks and maintain 2 metres distance. ▪ Vaccinators wear face masks, aprons and gloves. These are discarded after each household has been vaccinated; hands are washed and disinfected. Any vaccination equipment (e.g. chairs, seats) is also disinfected. ▪ Any adults involved in holding or comforting children are handed a face mask to wear during vaccination. ▪ Vaccinators prepare and load syringes away from the patient, and position themselves sideways with respect to the patient (i.e. facing the patient's arm, not his/her face).
Survey data collection	Nasopharyngeal swabbing is known to result in aerosol formation and thus places staff at high risk of SARS-CoV-2 transmission.	▪ All swabbing takes place outdoors, as per either of the following modalities: ▪ in a designated temporary 'corner' or open tent near the health facility, but at least 10 metres away from the outpatient sitting area; after each swab, the patient's sitting area is disinfected; an additional staff member regulates traffic to and from the swabbing point; ▪ outside the household, at least 2 metres from other household members. ▪ Any adults involved in holding or comforting children are handed a face mask to wear. ▪ Any potential participants who have symptoms of COVID-19 (cough, fever, sore throat) are excluded from swabbing. ▪ All study staff involved in swabbing wear PPE (goggles, face mask, apron, gloves). All disposable PPE items are changed after each swab; goggles are disinfected using spray. Hands are washed and disinfected. ▪ All study staff involved in swabbing are fully vaccinated for COVID-19. All are aged < 40 years (subject to any Somaliland legislation barring age discrimination).
	SARS-CoV-2 transmission during household questionnaires.	▪ All data collection takes place outside the shelter. Data collection staff maintain a distance of at least 2 metres during data collection. ▪ Data collection staff wear masks or face coverings. ▪ All data collectors are fully vaccinated for COVID-19. All data collectors are aged < 40 years (subject to any Somaliland legislation barring age discrimination).

Activity	Risk	Mitigation
Swab management	Infection of study staff while handling swabs prior to deep freezing.	▪ Single-use gloves, discarded after each swab is collected and placed within the collection container. Hand disinfection after gloves are discarded.

5 Selection and withdrawal of participants

5.1 Eligibility Criteria

5.1.1 Vaccination and vaccination safety evaluation

Inclusion criteria for receipt of the vaccine and data collection on safety outcomes will be:

1. Resident in Digaale;
2. Aged between 6 weeks old and 59mo on the day of first dose receipt;
3. The parent or caregiver is able to comprehend and comply with study requirements and procedures;
4. Voluntary written/thumb-printed informed consent for vaccination provided by a parent or caregiver;
5. The child must have a fixed, identifiable residence within the camp.

Exclusion criteria will be:

1. Known hypersensitivity to any component of any of the EPI vaccines, including diphtheria toxoid, in the child or any sibling;
2. History of allergic disease or history of a serious reaction to any prior vaccination in the child or any sibling;
3. History of anaphylactic shock, regardless of cause;
4. History of long-term treatment (defined as 14 or more consecutive days) with immunosuppressants or other immune modifying drugs, including glucocorticoids, but excluding topical and inhaled glucocorticoids.

Criteria for postponement of vaccination (as applied on the day of vaccination) will be:

1. Any abnormal (grade ≥ 1) vital sign, according to the National Early Warning Score 2 system (Appendix 12.7); in practice only axillary temperature will be systematically measured (axillary temperature of ≥ 37.5°C constitutes grade ≥ 1), but other criteria may be assessed based on clinical suspicion;
2. Any moderate or severe (grade ≥ 2) acute illness, as per AE severity grading;
3. A MUAC reading below 115mm in children aged 6 to 59mo, or clinical suspicion of severe acute malnutrition in children aged below 6mo, as determined by a designated study clinician;
4. Known history or diagnosis of thrombocytopenia or any coagulation disorder, or ongoing treatment with anticoagulant therapy.

Children meeting postponement criteria 1 and 2 will become eligible for vaccination 48 hours after their abnormal vital signs or illness have resolved to grade 0. Children meeting postponement criterion 3 will become eligible upon discharge from a therapeutic nutritional programme for severe acute malnutrition, whether cured or not cured but discharged due to failure to gain weight. Children meeting postponement criterion 4 will be assessed by a designated study clinician, who will determine their eligibility for vaccination, if necessary in consultation with experts and the Chief Investigator.

5.1.2 Nasopharyngeal carriage surveys

Inclusion criteria will be:

1. The participant has a fixed, identifiable residence in the study area (Digaale or Hargeisa, respectively), and expects to be available during the period of data collection;
2. Age (depending on the target age groups for the survey in question: see Section 3.1);
3. The participant and/or their parent/caregiver are able to comprehend and comply with study requirements and procedures;

4. Voluntary written/thumb-printed informed consent as provided by the individual, or a parent or caregiver for children aged less than 18yo, accompanied by assent of children aged 12-17yo.

Exclusion criteria will be:

1. Any head or facial injuries that would contraindicate swabbing of the nasopharynx.
2. [For the carriage survey in Hargeisa only:] Internally displaced person or refugee, defined as a national of Somaliland or of another country who has moved to Hargeisa within the last 5 years and who was forced or obliged to flee or to leave their home or place of habitual residence as a result of or in order to avoid the effects of food insecurity, armed conflict, situations of generalised violence, violations of human rights or other natural or human-made disasters.

5.2 Withdrawal criteria

The right of the participant to refuse to participate without giving reasons will be upheld at all times.

All participants are free to withdraw at any time from the any study procedure without giving reasons and without prejudicing further treatment or support.

Data or samples already collected will not be destroyed if participants choose to withdraw, unless requested by the participant or his/her caregiver.

6 Enrolment procedures

6.1 Vaccination and vaccination safety evaluation

Teams consisting of one female and one male home visitor will identify children falling within the eligibility criteria for vaccination about 2-3 weeks prior to the vaccination campaign, by systematic block-by-block visitation of the camp's shelters and households (Figure 4) and registration of all such children. Registration will occur in the presence of an adult (aged ≥ 18yo) household member who is a parent or caregiver for the children. If no such adult is present, of if the household is empty on visitation, the team will arrange a better time for the visit or return up to twice during the following week.

Consent will be initially sought only for vaccination and vaccination safety evaluation (Appendices 12.8 and 12.9); further consent for study data collection will be obtained separately (see below) so as to not deprive the population of PCV if they have concerns about other components of the study. Criteria for postponement of vaccination will be determined immediately prior to planned vaccination, and any children who are severely ill or have signs of severe acute malnutrition will be referred for further care; a dedicated vaccination team will ensure that they are offered vaccination once they become eligible.

For a duration of 1 week after the end of vaccination in the camp, a 'catch-up' team will be on site to offer PCV to anyone found to have missed the campaign dose, based on the list of registered children established before the campaign. This team will also re-visit all households that could not be included during the initial registration (e.g. because they were travelling during previous visits) and invite any eligible children to receive vaccination.

Four weeks after the first dose, infants aged <12mo at the time of first dose receipt will be offered a second PCV dose, again through house-to-house visits.

All children who are initially registered for vaccination will also be included in baseline data collection on the frequency of solicited AEs. All children who receive at least one PCV dose will be included in data collection for all other safety outcomes.

6.2 Nasopharyngeal carriage surveys

6.2.1 Digaale surveys

Following vaccination registration, the team will seek consent and older child assent for participation in the baseline survey. Ahead of each post-vaccination survey, teams will again visit each shelter and household systematically, block by block, to offer participation in the upcoming survey. If no adult caregiver is present, but neighbours report that the shelter has been occupied at any time during the previous 2 weeks, the team will return once during the following week.

The purpose of the study will be explained to the participant and/or their parent/caregiver. An information sheet (Appendix 12.10) will be left with the household. The team will emphasise the social benefit and confidentiality of the results. Consent and older child assent (Appendices 12.11 and 12.12) will be asked for all elements of the study: the survey, including anthropometric measurements (if applicable), and the swabbing procedure. Consent at this stage will be obtained at the household level. If consent is given, all household members will be listed by age group that the survey aims to recruit a sufficient sample size for (see above); data from the 2019 survey on population size, age distribution and unavailable households will be combined with the target sample size per age group to automatically generate an *a priori* probability of sampling for each household member, which will be used to select the individuals for nasopharyngeal swabbing and individual data collection, based on a random number generator and an automated sampling algorithm pre-loaded onto ODK survey instruments. Sampling probabilities will be calculated for each household member as:

$$\frac{n_a}{qN_a}$$

Where n_a is the target sample size in age group *a*, N_a is the estimated population size in age group *a* in the 2019 survey, and *q* is the proportion of non-vacant shelters that could not be included in the 2019 survey.

Individual household members and caregivers of children selected for the survey will be asked to confirm verbally that they consent and assent (for older children) to swabbing, anthropometric measurement and individual data collection. This 'advance' survey team will set up a convenient time for actual survey data collection, based on the availability of people in the household who are selected for swabbing. At the scheduled time of data collection, consent will be confirmed in writing, participants will be swabbed and all other individual- and household-level survey data will be collected. The survey team will emphasise the safe but potentially uncomfortable nature of the swabbing procedure by showing participants a swab and illustrating a visual image on the information sheet. If some of the selected individuals are not present, the household will be revisited once at a mutually convenient time.

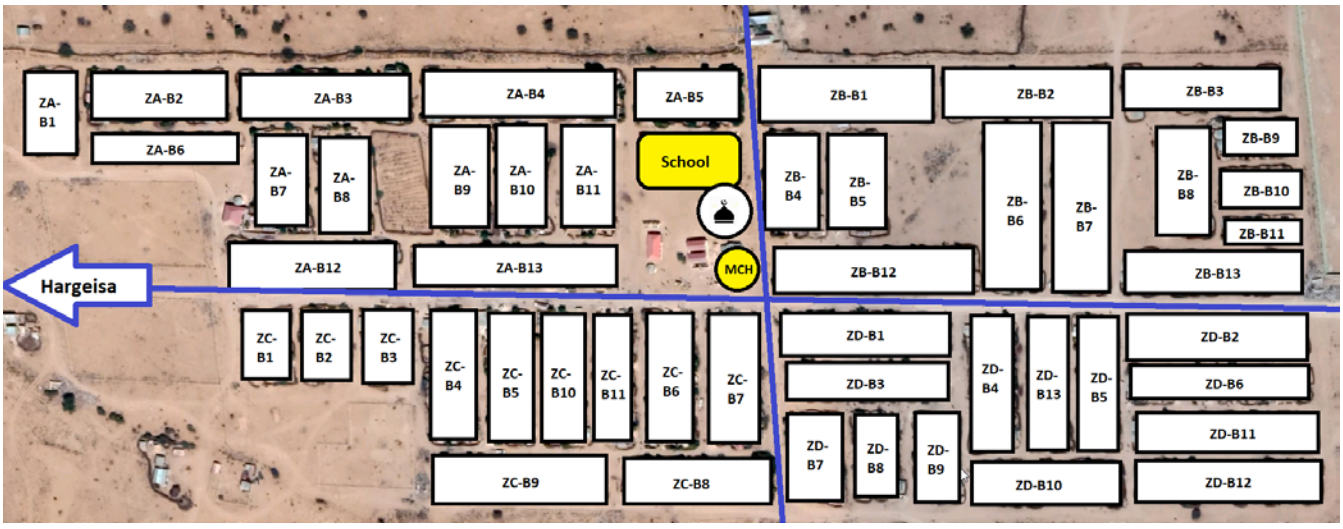


Figure 4. Map of Digaale IDP camp. A school, mosque, and health facility (MCH) are located in the centre of the camp. Shelters are grouped in different blocks (addresses starting with ZA, ZB, ZC, and ZD).

6.2.2 Hargeisa residents survey

For the carriage survey in Hargeisa, we will use the existing sampling frame created for the Somaliland Health and Demographic Survey 2020 (DHS), and sample individuals using a two-stage cluster sampling design. Listing of dwelling structures for the 2020 survey was done during February 2018 to December 2019 for each of several neighbourhoods of the city or primary sampling units (PSUs); since that time no significant displacement has been reported among Hargeisa residents.

The number of dwelling structures per PSU, as per DHS 2020, ranges between 50 and 149. We will assume that the estimated sizes of each PSU have remained unchanged, and not update this sampling frame. To achieve the intended sample size, given the expected age distribution per household, we will select 20 PSUs and 13 households (dwelling structures) per PSU. PSUs will be selected through probability proportional to size, while households will be selected systematically from the DHS list, with sampling step based on the PSU size. Further procedures for consent, selection of individuals to be swabbed and other data collection will be as per the Digaale surveys.

7 Experimental intervention

7.1 Pneumococcal conjugate vaccine

7.1.1 Name and description of the vaccine used

The study will offer vaccination with PNEUMOSIL, commercial name for Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10-Valent). PNEUMOSIL is manufactured and supplied by the Serum Institute of India. Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10-valent) is a sterile suspension of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F individually conjugated by using 1-cyano-4-dimethylamino pyridinium tetrafluoroborate chemistry (CDAP) to non-toxic diphtheria CRM197 protein. The polysaccharides are chemically activated and then covalently linked to the protein carrier CRM197 to form the glycoconjugate. Individual conjugates are compounded and then polysorbate 20 and aluminium phosphate are added to formulate the vaccine. The potency of the vaccine is determined by the quantity of the saccharide antigens and the saccharide-to-protein ratios in the individual glycoconjugates. The vaccine meets the requirements of WHO, Indian Pharmacopoeia (IP) and British Pharmocopoeia (BP) when tested by the methods outlined in WHO Technical Report Series 977, IP and BP.

The package insert of the vaccine (summary of product characteristics) is found in Appendix 12.13 and can be downloaded here: https://extranet.who.int/pqweb/content/pneumosil%C2%AE-0. PNEUMOSIL is stored at between 2°C and 8°C. It must not be frozen. One dose consists of 0.5 ml.

7.1.2 Regulatory status of the vaccine

PNEUMOSIL is WHO prequalified since 18/12/2019 (*PNEUMOSIL*®, 2020). No PCV has been licensed for use within Somaliland. It is indicated for active immunization against invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F in infants and toddlers from 6 weeks up to 2 years of age. The use of vaccine should be determined on the basis of relevant recommendations and take into consideration the disease impact by age and regional epidemiology.

The study will be carried out under a Clinical Trial Authorisation (CTA) from the Ministry of Health Development in Somaliland. The vaccine will therefore only be used by the named investigators and designated study staff, for the participants specified in this protocol, and solely within the scope of this study.

7.2 Vaccine supply and management at the study site

PNEUMOSIL will be supplied in a 5-dose (multi-dose) vial, in cartons containing 50 labelled vials and 1 product leaflet. Each vial label will include the following information: name of the medicinal product,

composition, dose and fill volume, route of administration, lot number, manufacturing date, retest dates, and storage condition.

The MoHD of Somaliland will receive PNEUMOSIL on its arrival to Somaliland; all vaccines will be stored at 2°C to 8°C in dedicated refrigerators that are safe, locked, and not accessible to unauthorized personnel. The refrigerators will be under continuous temperature monitoring with maintenance of daily temperature logs, and connected to a power source with a reliable back-up system.

The anticipated amount of vaccine needed for a particular day of the campaign will be transported to the field site in a cold box with continuous temperature monitoring. The temperature of vaccines will be monitored during shipment, storage and transportation to the field sites with electronic temperature loggers to ensure that temperature deviations do not occur. Vaccines will not be used until the temperature of the vaccines throughout transit has been confirmed to be within acceptable limits.

It is the responsibility of designated study personnel to ensure that vaccine has not been exposed to temperatures outside the allowed range during transport, storage at the facility or transport to the vaccination site prior to being dispensed for vaccination. Should there be a deviation outside the allowed temperature range, the affected vaccine(s) will be quarantined. Expert opinion will be sought to determine the action to be taken, based on the magnitude and duration of the temperature deviation. Such action may include safe destruction of the quarantined vaccine.

At the end of each day of vaccination, any opened, unused vaccine vials will be destroyed. Remaining unopened vials will be returned to the storage facility. At the end of the vaccination campaign, any leftover vaccine will be remitted to the Ministry of Health Development, who will take the final decision on use of these doses: if feasible, vaccine may be donated to the nearest inpatient nutritional therapeutic feeding centre for vaccination of children below 24mo upon discharge, on a sequential basis until supply is exhausted. All drug accountability procedures, including cold chain monitoring will be documented and are the responsibility of the study team.

7.3 Preparation and administration of vaccine

A limited number of appropriately trained study personnel will be responsible for preparing study vaccine doses and handling all drug accountability procedures.

As PNEUMOSIL is a suspension containing an adjuvant, each vial will be shaken vigorously immediately prior to use to obtain a homogenous, whitish turbid liquid in the vaccine container. The vial will be inspected immediately prior to use, and discarded if the vial or its contents appear in any way unusual.

Vaccination will be performed intramuscularly, with care to avoid injection into or near nerves and blood vessels. The preferred injection sites will be the anterolateral aspect of the thigh in infants (aged <12mo) and the deltoid muscle of the upper arm in older children.

7.4 Dosage schedule

Children aged 6 weeks old to 11mo on the day of the first vaccine dose will receive 2 doses of PNEUMOSIL, spaced by 4 weeks. Children aged 12 to 59mo will receive a single dose.

This is a deviation from the current WHO recommendation for PCV use in catch-up campaigns at the time of its first introduction, which currently specifies a schedule of 3 doses for children below 12mo, 1 or 2 doses for children aged 12-23mo and 1 dose for older children aged up to 59mo (World Health Organization, 2019).

The WHO Framework for Decision Making on Vaccination in Acute Humanitarian Emergencies (World Health Organization, 2017b) states that a PCV campaign should be considered for a target age-group of 6 weeks to 59mo, though it notes that the exact target age group and dosage schedule should be based on epidemiological and feasibility considerations, with reduced dosages an ethically viable option depending on logistics and access constraints. The WHO “Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019” (World Health Organization, 2019) states that age-

appropriate schedules of PCV vaccination should be used for children <12mo, and considered for children <59mo, as indicated by the situation.

While our dosing strategy is in line with WHO recommendations for children 12mo and older, in this study infants 6 weeks to 11mo will receive 2, rather than 3 doses as recommended by the WHO. This is considered a viable trade-off between the limited ability to provide multiple doses in populations affected by crises and the evidence that 2 doses in infancy afford a non-inferior antibody response and comparable direct protection during the first year of life to 3 doses (Goldblatt et al., 2006; Lewnard et al., 2020; Russell et al., 2010). The Goldblatt et al. study in particular shows that for PCV9 the IgG (correlate for protection against invasive disease) response after 2 doses in infants is non-inferior to that after 3 doses (which is why a 2 dose priming schedule has been used in the UK rather than the 3 dose series as proposed by the manufacturer at the time). Moreover, it is expected based on mathematical modelling analysis (Section 1.2, Appendix 12.2) that the indirect effects of vaccinating older children on pneumococcal risk among infants will compensate any loss in effectiveness due to the latter receiving two doses only.

Although PNEUMOSIL is only licensed for use in children aged 6 weeks to 23mo, safety in other age groups has been assessed in early, limited sample-size phase 1 and 2 trials. No severe adverse effects were found in older individuals (Clarke et al., 2020; PATH, 2019). Furthermore, other PCVs are licensed for use up to 5 years and are administered to older children at high risk, for example in the United States (Centers for Disease Control and Prevention, 2021). PNEUMOSIL's vaccine technology and composition are very similar to those of other PCVs.

7.5 Risks and benefits of the experimental intervention

7.5.1 Vaccine effectiveness

PCVs are a safe and effective intervention to protect against IPD (Klugman et al., 2018). Their efficacy is estimated to be 89% against IPD caused by VT in children under 24mo who received their complete schedule (Pavia et al., 2009). In addition, their efficacy against carriage of VT has been estimated as 50% 2 years after vaccination (Le Polain De Waroux et al., 2015), resulting in substantial reductions in transmission and thus indirect protection in the population if high coverage is achieved.

The combination of direct and indirect effects of the intervention are therefore expected to afford a substantial reduction in pneumococcal disease burden within the Digaale population, improved nutritional status (as a result of reduced incidence and severity of childhood illness), reduced indirect and direct expenditure for outpatient and/or inpatient treatment, and more favourable long-term developmental outcomes for children.

7.5.2 Vaccine safety

The risks associated with the PNEUMOSIL vaccine are very low, and similar to those of other injectable vaccines included in routine immunization programmes. In safety assessments of the vaccine, the vast majority of reactions observed following vaccination were of mild or moderate severity and were of short duration. In the largest study in infants, the most common adverse reactions observed after primary vaccination were tenderness at the injection site, fever and irritability, reported for approximately 49%, 52% and 32% of all infants, respectively. The profile of adverse reactions was similar in adults, as assessed in Phase 1 (PCV10-001) and Phase 1/2 (VAC-017) studies. In adults, the most common reactogenicity event (RE) after a single dose of PNEUMOSIL was pain, as reported in 70.6% and 58.8% of adults in the respective studies. Headache was the most common systemic RE after vaccination and was reported for 17.6% of adults who received PNEUMOSIL in both trials. Only one grade ≥ 2 local RE was reported in the PNEUMOSIL group in either trial (grade 3 tenderness). No grade ≥ 2 systemic RE was reported in any children 24mo or older or any adult who received PNEUMOSIL in these studies (Clarke et al., 2020; PATH, 2019, 2020). In evaluations of other PCV vaccines (PCV7 and PCV13), the typology and frequency of adverse events among older children and adults were similar to those in young children.

Table 3 summarises the frequency of adverse reactions (i.e. events considered as related to vaccination) noted after PNEUMOSIL vaccination among children 6 weeks to 23mo:

Table 3. Frequency of known adverse vaccine reactions.

Typology of disorder	Frequency	Adverse reactions
Gastrointestinal disorders	Uncommon	Diarrhoea
General disorders and administration site conditions	Very common	Pain, Fever ≥ 37.5ºC (axillary)
	Common	Erythema, Swelling/induration
	Uncommon	Fever > 39ºC (axillary)
Metabolism and nutrition disorders	Common	Decreased appetite
Nervous system disorders	Common	Drowsiness
Psychiatric disorders	Very common	Irritability
Skin and subcutaneous tissue disorders	Common	Rash

Very common = ≥1/10 vaccinees; Common = ≥1/100 vaccinees but < 1/10 vaccinees; Uncommon = ≥1/1000 vaccinees but < 1/100 vaccinees; Rare = ≥1/10,000 vaccinees but < 1/1,000 vaccinees.

Using the frequency ranges above, Table 4 lists the expected number of vaccine-related adverse events among all vaccinated children in Digaale (assuming that 85% of a total of 700 children younger than 59mo are vaccinated), as well as the expected number of coincidental non-vaccine related deaths of all causes that would occur within the first 3mths after vaccination, calculated by applying the age-specific crude death rate measured during the 2019 survey to the total number of vaccinated children.

Table 4. Expected frequencies of vaccine related adverse events and non-vaccine related coincidental deaths among vaccine recipients in Digaale.

Type	Frequency	Adverse event	Estimate	Low	High
Vaccine related adverse events	Common	Erythema, Swelling/induration	40	5	70
	Common	Decreased appetite	40	5	70
	Common	Drowsiness	40	5	70
	Common	Rash	40	5	70
	Uncommon	Diarrhoea	5	0	10
	Uncommon	Fever > 39C (axillary)	5	0	10
	Very common	Pain, Fever > 37.5C (axillary)	375	70	680
	Very common	Irritability	375	70	680
Coincidental non-vaccine related deaths		Deaths in children <59mo from all causes (not related to vaccine) within the 3mths after vaccination	3	1	6

7.5.3 Restrictions on vaccination

See section 5.1.1 for eligibility and postponement criteria for vaccination. Study staff will individually follow up children whose vaccination needs to be postponed, determine when they become eligible and offer them vaccination accordingly.

There are no known interactions between PNEUMOSIL and other vaccines or medical products. Vaccine recipients may receive all medications and procedures deemed necessary based on good medical practice in Somaliland. If the recipient is to receive another injectable vaccine simultaneously, the vaccines should always be given at different injection sites.

8 Safety reporting

8.1 Definitions

Table 5 lists definitions used by the study of different categories of adverse events occurring among vaccine recipients. The definition of AE will be extended to pre-vaccination data collection on solicited signs and symptoms, though it is understood that these are inherently not temporally associated with vaccination.

Table 5. Definitions for safety reporting related terms.

Term	Definition
Adverse Event (AE), Adverse Event Following Immunisation (AEFI)	Any untoward medical occurrence in a child who has received a dose of PNEUMOSIL, including occurrences which are not necessarily caused by or related to PNEUMOSIL. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the vaccine and the process of vaccination, whether or not considered related to the vaccine.
Adverse Reaction (AR)	Any AEFI for which a causal relationship between the vaccine and the AEFI is at least a reasonable possibility, i.e. the relationship cannot be ruled out.
Serious Adverse Event (SAE)	A serious adverse event is any AEFI with severity grade 3 to 5, i.e. for which at least one of the following applies: ▪ Results in death ▪ Is life-threatening ▪ Requires inpatient hospitalisation or prolongation of existing hospitalisation ▪ Results in persistent or significant disability/incapacity ▪ Consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the vaccine recipient or require an intervention to prevent one of the above consequences.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to the vaccine, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information set out in the summary of product characteristics (SmPC) for PNEUMOSIL (Appendix 12.13).

8.2 Causality assessment

An assignment of causality (i.e. likelihood that there is a causal association between vaccination and the adverse events) will be made by the Chief Investigator using the definitions in Table 6, for any SAE. If any doubt about the causal relationship exists, the Chief Investigator will seek advice from a panel of clinicians not connected with the study and with expertise in paediatric vaccination. In the event that no agreement is reached on causality by experts consulted, the Chief Investigator's decision as well as other points of view will be reported.

Table 6. Definitions that will be applied when establishing causality between vaccine administration and a serious adverse event.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the vaccine). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the vaccine). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

8.3 Reporting procedures

8.3.1 Adverse event reporting

A designated study clinician on site will be the focal point to whom any study staff becoming aware of a potential SAE during collection of solicited AEs, or through any other means, will immediately (within the same working day) report any such event. The study clinician will review all such events for likely severity, based on the information initially available. AEs with severity grade 1 or 2 will not be reported individually,

unless the study clinician cannot confirm that severity grading is below 3; instead, they will be included in aggregate analysis (Section 9.2.2).

SAEs, defined as grade 3 or above, will be reported by the study clinician to the Chief Investigator within 24 hours of detecting the event. The Chief Investigator will in turn report each SAE to the Study Oversight Committee within the following 48 hours. The instrument of reporting will be the SAE CRF (Appendix 12.5), signed and dated and inclusive of anonymised copies of relevant treatment documents and investigations (Section 4.2.2), containing as much detail on the event as is available at a given time, and progressively supplemented when outstanding information is collected. Each SAE CRF will be completed by the Chief Investigator with the final assessment of severity, causality and expectedness, if needed after consultation with a panel of Somali clinicians and paediatricians experienced in vaccine evaluation.

8.3.2 SUSARs

All SAEs classified as SUSARs will be subject to expedited reporting to the Ministry of Health Development in Somaliland, the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK, the vaccine manufacturer and all ethics committees who have reviewed this protocol, within the required reporting timescales.

9 Statistics and data analysis

9.1 Study precision and power for primary effectiveness outcome

9.1.1 Precision of carriage prevalence estimates

A sample of 100 persons per age group within any of the nasopharyngeal carriage surveys will allow estimation of the point prevalence of pneumococcal carriage within a single age group with a precision (size of a one-sided confidence interval) of 2-10%, depending on the actual pneumococcal prevalence and using a confidence level of 95%.

9.1.2 Study power for varying effect sizes

The power to observe a difference in nasopharyngeal carriage depends on (i) the sample size, (ii) the baseline prevalence, and (iii) the effect size following vaccination. Assuming the target sample size (Section 3.3.2) is achieved and an α-level of 0.05, Figure 5 shows the expected study power ($1 - \beta$) to detect a relative difference in VT carriage prevalence between baseline and any time point following the vaccination campaign, within any single age-group and for varying initial prevalence.

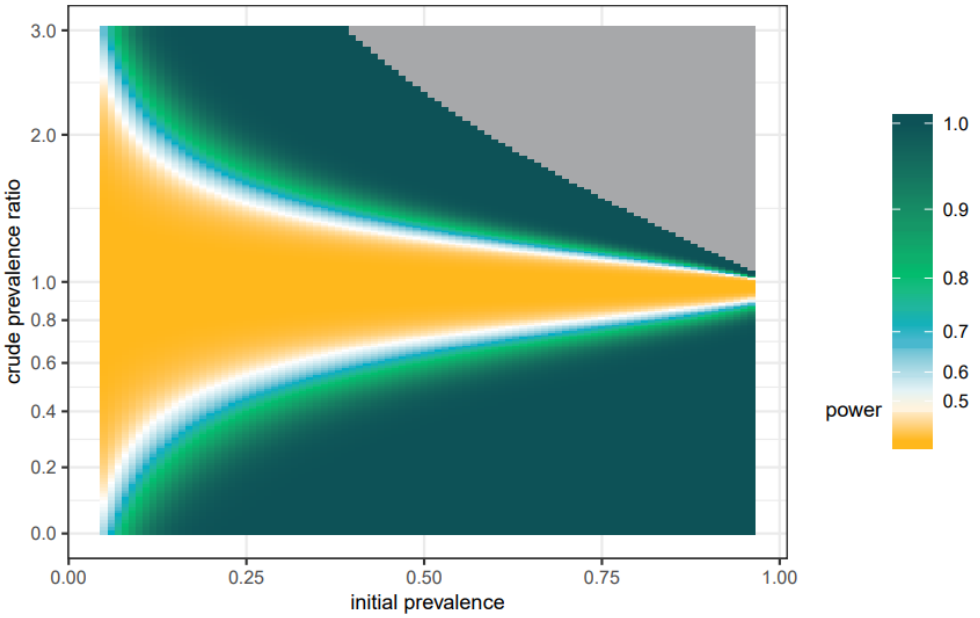


Figure 5. Power to detect a crude difference in carriage within a single age group, for different initial pre-vaccination prevalence levels (x-axis), and different ratios of pre- versus post-vaccination VT carriage prevalence (y-axis). Power estimates assume 100 individuals in both pre- and post-vaccination evaluation groups.

9.1.3 Expected study power

Because the effect of interest includes both direct and indirect protection, and is dependent on social contact patterns among different age groups, a transmission dynamic model of VT and NVT pneumococcal carriage (Appendix 12.2) was parameterised using 2019 survey findings (including the age-specific prevalence of VT and NVT carriage, the population structure, birth, death and migration rates, and the social contact pattern matrix for Digaale) to simulate the expected effect (reduction in VT carriage at any evaluation points in children <24mo: Figure 1) and study power to detect it. Briefly, the model groups all (over 100 known) pneumococcal serotypes into two classes: VT and NVT. The population is stratified into compartments according to their pneumococcal colonization status: those who are susceptible (not carrying any pneumococcal serotype), and those who carry at least one VT and/or at least one NVT. Susceptible individuals can acquire carriage when they come into contact with a VT or NVT carrier, while carriers will lose their infection and become susceptible again after several weeks (depending on their age), based on an assumed rate of infection clearance. The model is based on a model by Flasche et al used to evaluate PCV catch-up campaigns in Kenya (Flasche et al., 2017) .

Three sample size scenarios were subjected to simulation:

- A pessimistic scenario in which the effective sample size is 22 infants aged <12mo and 43 children aged 12-23mo at all pre- and post-vaccination evaluation points;
- A realistic scenario in which the effective sample size is 44 infants aged <12mo and 86 children aged 12-23mo at all pre- and post-vaccination evaluation points;
- An optimistic scenario in which the target sample size of 100 infants per age group is reached at all pre- and post-vaccination evaluation points.

The model assumes that 85% of children in the target age group have been vaccinated. Figure 6 shows expected power in each scenario. Although the power to detect a difference is suboptimal (below 80%) in the pessimistic scenario at the 6mths post-vaccination evaluation point, the model projects that the study should have reasonable power to detect a difference at the first (6mths post PCV campaign) evaluation point, and good power at the subsequent evaluation points (12mths and 24mths post PCV campaign), even when sample size is lower than desired (under the realistic scenario).

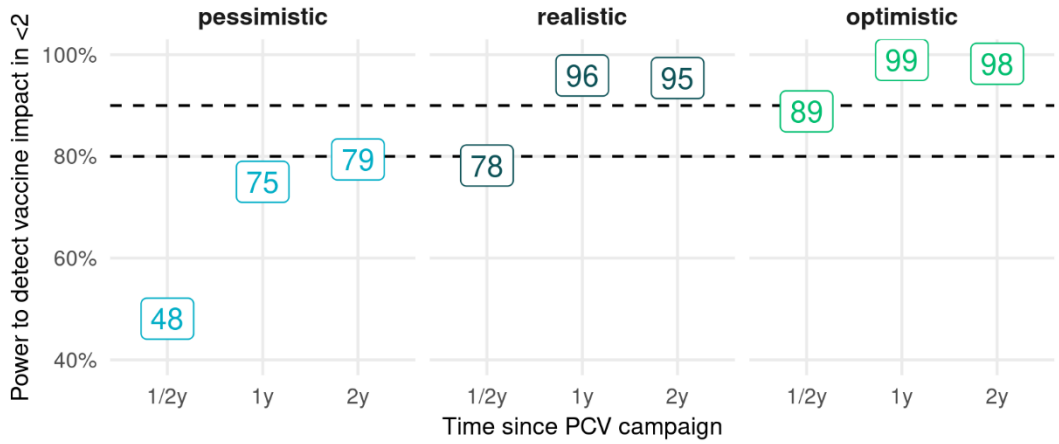


Figure 6. Expected power to detect the modelled difference in carriage before versus after vaccination in children aged <24mo, at different planned evaluation timepoints (6mths, 12mths and 24mths following vaccination), and for three different sample size scenarios.

Figure 7 shows the expected precision (at the 95% confidence level) of expected effect estimates under different sample size scenarios. In the realistic scenario, our model projects that we should be able to measure the primary outcome with 18% (12% to 26%) precision.

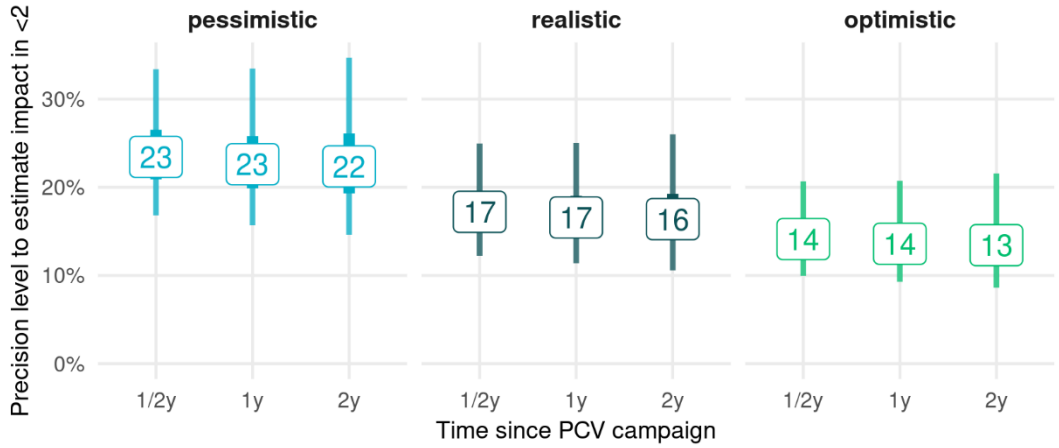


Figure 7. Precision around effect estimates (reduction in carriage among children <24mo), at different planned evaluation timepoints (6mths, 12mths and 24mths following vaccination), for three different sample size scenarios.

9.2 Analysis of outcomes

9.2.1 Nasopharyngeal carriage outcomes

For either the primary outcome or any secondary carriage outcome, generalised linear models will be fitted to estimate prevalence or mean colonisation density and their confidence intervals, for any age group. For Hargeisa residents, because of the cluster sampling design, the observed intra-cluster correlation coefficient will be used to estimate robust standard errors.

Generalised linear mixed models assuming a binomial distribution, with household as the random effect, will be fitted to estimate the odds ratio (OR) of VT or NVT carriage at 6, 12 or 24mths after vaccination, compared to baseline and for any age group. Vaccine effectiveness will be estimated from the model fixed effects as $1 - OR$. All models will be adjusted for camp-, household- and individual-level potential confounders identified statistically and *a priori* through a directed acyclic graph. Effect modifications will be explored. For density of pneumococcal colonies, we will assume a Gaussian distribution or, in case of censored data, another appropriate distribution (e.g. tobit), with transformations if required.

The above statistical approach will also be used to compare the odds of carriage among Digaale IDPs versus Hargeisa residents, based on respective baseline surveys.

For the 150 pneumococcal isolates that will be sequenced, genomes will be typed using PopPUNK (https://poppunk.net/), and phylogenies inferred using the Gubbins algorithm (http://nickjcroucher.github.io/gubbins/). A population level who-infected-whom analysis will then be conducted to assess clustering of strains in children in both populations (Senghore et al., 2022).

We will also use transmission dynamic mathematical modelling to understand the observed impact of vaccination and explore alternative vaccination strategies. The transmission model described above will be updated with the most recent demographic data and fitted to observed age-specific pre-PCV and post-PCV carriage estimates from the carriage surveys using a Markov Chain Monte Carlo algorithm. The model will also be adapted to allow the transmission of multiple pneumococcal strains, which will then be fit to the estimated proportion of strains shared between the two populations at study baseline. This will enable us to quantify and parameterize the transmission rate between the two populations. The fitted model will then be used to predict waning of impact in the absence of follow-on vaccination activities, and a range of strategies for initial PCV campaign vaccination and maintenance of direct and indirect immunity thereafter. Resulting effect estimates will be combined with projected costs of each candidate strategy (based on MoHD standard budgets) to evaluate efficiency and cost-effectiveness.

9.2.2 Vaccine safety outcomes

The frequency of solicited AEs and solicited or unsolicited SAEs will be tabulated by age group, severity grading, timing, dose and, for SAEs, assessed causal likelihood.

For solicited AEs, a generalised linear mixed model assuming a Poisson or negative binomial distribution, with individual child as the random effect, will be fitted to compute the incidence rate ratio (IRR) of specific or all solicited AEs post- versus pre-vaccination. A similar model and a difference-of-differences approach will be used to compare the change in frequency of AEs in the 6 weeks to 23mo age group to that in the 24 to 59mo age group, so as to explore any significant difference in AE risk between the two age groups (a direct comparison of the two age groups is not deemed advisable as these age groups are likely to experience different background rates of coincidental AEs not related to the vaccine).

To further explore any excess risk of SAEs resulting from the vaccine, a self-controlled case series analysis (Petersen et al., 2016) will be conducted: briefly, this method only includes SAE cases in analysis, and computes the IRR of SAEs comparing incidence during assumed ‘at-risk’ period during which SAEs caused by the vaccine are plausibly expected (to be defined after review of safety data for PCVs, including post-licensure pharmaco-surveillance) to incidence during the remainder of the SAE surveillance period (3mths). A statistically significant IRR > 1 provides evidence of excess, vaccine-attributable risk. The analysis will be adjusted for age, gender and other potential confounders, as available. This analysis will, however, only be attempted if a sufficient number of SAEs occurs.

9.2.3 Vaccination coverage outcome

Vaccination coverage will be defined alternatively as the number of children who received the intended PCV dosage, divided by (i) children consenting to and deemed eligible for vaccination during registration or mop-up (‘partial’ coverage) or (ii) all children identified within the eligible age group and living in the camp, as per initial or mop-up registration (‘total’ coverage). The coverage of a single dose will also be computed. Coverage will be tabulated by age group, gender and other baseline household characteristics.

9.2.4 Other secondary clinical outcomes

The effect of vaccination at camp level on the incidence of hospitalisations for ALRI and the rate of antibiotic prescriptions will be quantified using an interrupted time series approach (Kontopantelis et al., 2015), in which a generalised linear model of the monthly count of incidence or prescription events during the 24mths before

and after vaccination, offset by the log of population at risk, will be fitted. The model will be adjusted for any confounding variables collected at camp level. The interrupted time series approach quantifies effect by analysing the change in level and slope of the trend being observed before and after the intervention, and is particularly appropriate for quasi-experimental designs without any control (i.e. no-intervention) groups.

10 Study monitoring and governance

10.1 Risk assessment

A detailed risk assessment is found in Appendix 12.14. In brief, the study will feature two main sources of risk:

1. Vaccination with PNEUMOSIL, whose risks are described in Section 7.5.2;
2. Exposure of study staff to higher-than-routine risk of COVID-19 infection due to mass vaccination activities and, in particular, nasopharyngeal swabbing. Swabbing, done in a very similar way to how COVID-19 testing is conducted, results in aerosolization of COVID-19 and other respiratory pathogens, and thus can increase the risk of transmission. Mitigation measures are described in Section 4.6.

10.2 Study monitoring

10.2.1 Vaccine-related monitoring

The quality of vaccination cold chain will be monitored from receipt of vaccine into Somaliland to its administration through temperature logs.

Adherence to standard procedures for vaccine administration will be enforced through spot checks of vaccination teams, with a pilot phase of vaccination in a limited fraction of the camp to enable sufficient observation of practice and identification of any non-adherence to procedure warranting remedial steps.

Activities for detecting AEFI are described in Section 4.2. In addition, a Vaccination Support Committee composed of Digaale community representatives will be constituted, and contacted once daily to identify and address negative feedback and concerns by households during the vaccination campaign and related study activities.

10.2.2 Data quality-related monitoring

A study coordinator will be present full-time during data collection, and will perform spot checks and direct observations of carriage survey teams, focussing on quality of swabbing, anthropometric measurements and questionnaire administration.

Data will be entered electronically directly on the field. Electronic forms will automatically perform range and consistency checks, and prompt data collectors to rectify any entries.

At the end of each data collection day, data will be synchronized and registered participants will be matched with completed informed consent forms. Further manual checks (e.g. on completeness of data entry and digit preference) will be done each evening after data collection by generating descriptive statistics on the collected data, and if necessary data collectors will be retrained or more closely supervised for the remainder of data collection.

10.2.3 Study protocol violations

Violations of study protocol (including but not limited to failure to obtain or document consent; inclusion of participants who do not meet all inclusion criteria or meet one or more exclusion criterion; unsafe practices during vaccination or swabbing; breach of participant confidentiality) will be reported within 24 hours to the Chief Investigator, who will also systematically report all such violations, along with accompanying detail, to

the Study Oversight Committee; the latter will advise on recommended actions (e.g. exclusion of any data from analysis; interruption of data collection; etc.). Reporting of all study protocol violations to the Study Oversight Committee will occur within 48 hours of the Chief Investigator becoming aware of the violation.

10.3 Regulatory issues

10.3.1 Study authorisation

Authorisation for this study, and for off-label use of PNEUMOSIL, will be sought from the Ministry of Health Development, Republic of Somaliland.

10.3.2 Ethics approval

Ethical approval will be sought from the Ethics Committee of the London School of Hygiene and Tropical Medicine, the Ethics Committee at the Republic of Somaliland Ministry of Health Development, and the Ethics Committee of Save the Children UK.

10.3.3 Consent

Informed consent will be obtained prior to the participants undergoing procedures that are specifically for the purposes of the study. Consent instruments are found in Appendices 12.8, 12.9, **Error! Reference source not found.**, 12.10, 12.11 and 12.12.

Consent to take part in the study will be sought from each participant only after a full explanation has been given, an information sheet offered and time allowed for consideration. Participants will be provided the opportunity to ask questions and to potentially delay participation until a later vaccination round. Written or thumb-print participant consent will be obtained, including assent of older children (≥ 12yo) accompanied by consent from their caregivers. Consent will cover vaccination and vaccine safety evaluation, as well as data collection for carriage surveys (including nasopharyngeal swabbing), with specific consent for storage and possible further analysis of swab samples or derivates thereof.

The right of the participant to refuse to participate without giving reasons will be respected. All participants will be free to withdraw at any time from the study without giving reasons and without prejudicing further services to themselves or their families. The Chief Investigator is responsible for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

10.3.4 Confidentiality

Participants' identifiable data will be stored securely and their confidentiality protected in accordance with the UK Data Protection Act 2008 and any applicable Somaliland legislation. As required by the LSHTM Research Data Management Policy, the study team will create a Data Management Plan which will be reviewed by the LSHTM Research Data Manager.

Data will be collected on PIN-protected Android tablets. Data will be collected and managed locally using the LSHTM ODK instance. ODK-level encryption will be enabled to prevent unauthorised or otherwise unlawful access to the survey meta-data and/or data. Survey responses will be entered directly into the tablets and uploaded once an internet connection is available. All survey data and metadata will be deleted from the tablets upon completion of each round of data collection (e.g. first carriage survey, second carriage survey). Consent forms and a study 'key' linking UIDs to participant names will be scanned and uploaded directly to an LSHTM network drive via LSHTM MyFiles (formerly Filr); these documents will be stored on the shared network drive space to which only members of the LSHTM study team have access.

Study data will be stored on the LSHTM ODK server until data collection is complete. The data will then be moved to the LSHTM dedicated secure server provided LSHTM staff have access to the LSHTM offices. As the secure server cannot be accessed offsite, and in the event that home working continues, it may be

necessary to store data on a shared network drive with appropriate permissions to restrict access to the study team.

The original data will be archived for a period of ten years as per the LSHTM Data Management Policy (Retention and Disposal Schedule). The LSHTM Library, Archive & Open Research Services will be the custodian of these data. Data that have been archived will be stored on the LSHTM secure server (as per the LSHTM Data Management Policy).

Anonymised datasets and associated metadata will be provided to the funder (as per our grant agreement) and will be made available to the public via the LSHTM data repository. If the non-public data are subsequently deemed to have historical significance and further utility, an additional retention period with the LSHTM Research Data Manager may be agreed.

10.3.5 Indemnity

The London School of Hygiene & Tropical Medicine holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

10.3.6 Sponsor

The London School of Hygiene & Tropical Medicine will act as the main sponsor for this study. Delegated responsibilities will be assigned locally.

10.3.7 Funding

The Bill and Melinda Gates Foundation is funding the vaccination activities and evaluation in this study. Carriage surveys are co-funded by the Bill and Melinda Gates Foundation, Elhra's Research for Health in Humanitarian Crises (R2HC) Programme, and the Global Challenges Research Fund, UK Research and Innovation.

10.3.8 Audits and inspections

The study may be subject to audit by the London School of Hygiene and Tropical Medicine under their remit as sponsor, and other regulatory bodies to ensure adherence to Good Clinical Practice.

10.3.9 Protocol development

This protocol was developed by the following investigators who are responsible for the development of, and agreeing to, the final protocol:

Professor Francesco Checchi, Francesco.Checchi@lshtm.ac.uk

Professor Stefan Flasche, Stefan.Flasche@lshtm.ac.uk

Kevin van Zandvoort, Kevin.Van-Zandvoort@lshtm.ac.uk

Dr Catherine McGowan, Catherine.McGowan@lshtm.ac.uk

Subsequent changes to the final protocol will require the agreement of the Study Oversight Committee.

10.4 Study management and accountability

A Study Coordination Team, consisting of the LSHTM investigators and a representative each from Save the Children UK and Save the Children International (Somaliland field office) has been constituted, and will meet

fortnightly at a minimum during study preparation, daily during the vaccination campaign, and monthly in between periods of data collection after the vaccination campaign. The Study Coordination Team is chaired by the LSHTM Chief Investigator and is tasked with leading the implementation of study activities, as per protocol.

In addition, a Study Oversight Committee, composed of technical experts from Save the Children, MCRI, the Ministry of Health Development of Somaliland and one external independent expert will be appointed, and will meet regularly, with LSHTM providing a secretariat function, to review study progress and advise on any changes to the study protocol. Its terms of reference are found in Appendix 12.15.

Within Digaale, a Vaccination Committee composed of community representatives will be constituted to advise on community engagement and uptake, help disseminate important messages and provide a first point of contact to gather negative or positive feedback and concerns from the community. The Committee will primarily be active ahead of and during the vaccination campaign, but will be consulted as part of planned carriage surveys, as needed.

10.5 Publication

Findings will be published in scientific journals and presented at scientific conferences as well as non-technical dissemination events hosted in Somaliland by the MoHD, and globally as a collaboration of all study partners. Co-authorship will be offered based on International Committee of Medical Journal Editors criteria. Other individuals who made important contributions will be acknowledged. Dissemination of findings to the Digaale community will occur through the Vaccination Committee. Fully anonymized data will be made available through public (open-access) databases.

11 References

Bellos, A., Mulholland, K., O'Brien, K. L., Qazi, S. A., Gayer, M., & Checchi, F. (2010). The burden of acute respiratory infections in crisis-affected populations: A systematic review. *Conflict and Health*, *4*(1), 3. https://doi.org/10.1186/1752-1505-4-3

Centers for Disease Control and Prevention. (2021, February 25). *Pneumococcal Vaccination | CDC*. https://www.cdc.gov/vaccines/vpd/pneumo/index.html

Clarke, E., Bashorun, A. O., Okoye, M., Umesi, A., Badjie Hydara, M., Adigweme, I., Dhere, R., Sethna, V., Kampmann, B., Goldblatt, D., Tate, A., Weiner, D. H., Flores, J., Alderson, M. R., & Lamola, S. (2020). Safety and immunogenicity of a novel 10-valent pneumococcal conjugate vaccine candidate in adults, toddlers, and infants in The Gambia—Results of a phase 1/2 randomized, double-blinded, controlled trial. *Vaccine*, *38*(2), 399–410. https://doi.org/10.1016/j.vaccine.2019.08.072

Flasche, S., Ojal, J., Le Polain de Waroux, O., Otiende, M., O'Brien, K. L., Kiti, M., Nokes, D. J., Edmunds, W. J., & Scott, J. A. G. (2017). Assessing the efficiency of catch-up campaigns for the introduction of pneumococcal conjugate vaccine: A modelling study based on data from PCV10 introduction in Kilifi, Kenya. *BMC Medicine*, *15*(1). https://doi.org/10.1186/s12916-017-0882-9

Goldblatt, D., Southern, J., Ashton, L., Richmond, P., Burbidge, P., Tasevska, J., Crowley-Luke, A., Andrews, N., Morris, R., Borrow, R., Cartwright, K., & Miller, E. (2006). Immunogenicity and Boosting After a Reduced Number of Doses of a Pneumococcal Conjugate Vaccine in Infants and Toddlers. *The Pediatric Infectious Disease Journal*, *25*(4), 312–319. https://doi.org/10.1097/01.inf.0000207483.60267.e7

Klugman, K. P., Dagan, R., Malley, R., & Whitney, C. G. (2018). Pneumococcal conjugate vaccine and pneumococcal common protein vaccines. In *Plotkin's Vaccines* (7th ed.). Elsevier.

Kontopantelis, E., Doran, T., Springate, D. A., Buchan, I., & Reeves, D. (2015). Regression based quasi-experimental approach when randomisation is not an option: Interrupted time series analysis. *The BMJ*, *350*, h2750. https://doi.org/10.1136/bmj.h2750

Le Polain De Waroux, O., Flasche, S., Prieto-Merino, D., Goldblatt, D., & Edmunds, W. J. (2015). The Efficacy and Duration of Protection of Pneumococcal Conjugate Vaccines Against Nasopharyngeal Carriage: A Meta-regression Model. *The Pediatric Infectious Disease Journal*, *34*(8), 858–864. https://doi.org/10.1097/INF.0000000000000717

Lewnard, J. A., Givon-Lavi, N., & Dagan, R. (2020). Dose-specific Effectiveness of 7- and 13-Valent Pneumococcal Conjugate Vaccines Against Vaccine-serotype Streptococcus pneumoniae Colonization in Children. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *71*(8), e289–e300. https://doi.org/10.1093/cid/ciz1164

Merck. (2021). *Merck Announces U.S. FDA Approval of VAXNEUVANCE™ (Pneumococcal 15-valent Conjugate Vaccine) for the Prevention of Invasive Pneumococcal Disease in Adults 18 Years and Older Caused by 15 Serotypes*. Merck.Com. https://www.merck.com/news/merck-announces-u-s-fda-approval-of-vaxneuvance-pneumococcal-15-valent-conjugate-vaccine-for-the-prevention-of-invasive-pneumococcal-disease-in-adults-18-years-and-older-caused-by-15-serot/

PATH. (2019). *A Phase 1/2, Prospective,Randomized, Active-Controlled, Double-Blind, Age De-escalation Study to Evaluate the Safety, Tolerability, Immunogenicity of Serum Institute of India's PCV10 in Healthy Adults, Toddlers, and Infants* (Clinical Trial Registration results/NCT02308540). clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/results/NCT02308540

PATH. (2020). *A Phase 3, Randomized, Double-Blind Study of the Safety, Tolerability, Lot-to-Lot Consistency, Immunogenicity & Non-Interference With Concomitant Vaccinations of Serum Institute of PNEUMOSIL in Healthy Infants in The Gambia* (Clinical Trial Registration No. NCT03197376). clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03197376

Pavia, M., Bianco, A., Nobile, C. G. A., Marinelli, P., & Angelillo, I. F. (2009). Efficacy of Pneumococcal Vaccination in Children Younger Than 24 Months: A Meta-Analysis. *Pediatrics*, *123*(6), e1103–e1110. https://doi.org/10.1542/peds.2008-3422

Petersen, I., Douglas, I., & Whitaker, H. (2016). Self controlled case series methods: An alternative to standard epidemiological study designs. *BMJ*, *354*, i4515. https://doi.org/10.1136/bmj.i4515

Pfizer. (2021). *U.S. FDA Approves PREVNAR 20™, Pfizer's Pneumococcal 20-valent Conjugate Vaccine for Adults Ages 18 Years or Older | Pfizer*. https://www.pfizer.com/news/press-release/press-release-detail/us-fda-approves-prevnar-20tm-pfizers-pneumococcal-20-valent

PNEUMOSIL®. (2020, July 17). WHO - Prequalification of Medical Products (IVDs, Medicines, Vaccines and Immunization Devices, Vector Control). https://extranet.who.int/pqweb/content/pneumosil%C2%AE-0

Russell, F. M., Carapetis, J. R., Satzke, C., Tikoduadua, L., Waqatakirewa, L., Chandra, R., Seduadua, A., Oftadeh, S., Cheung, Y. B., Gilbert, G. L., & Mulholland, E. K. (2010). Pneumococcal Nasopharyngeal Carriage following Reduced Doses of a 7-Valent Pneumococcal Conjugate Vaccine and a 23-Valent Pneumococcal Polysaccharide Vaccine Booster. *Clinical and Vaccine Immunology : CVI*, *17*(12), 1970–1976. https://doi.org/10.1128/CVI.00117-10

Satzke, C., Dunne, E. M., Porter, B. D., Klugman, K. P., Mulholland, E. K., & PneuCarriage project group. (2015). The PneuCarriage Project: A Multi-Centre Comparative Study to Identify the Best Serotyping Methods for Examining Pneumococcal Carriage in Vaccine Evaluation Studies. *PLOS Medicine*, *12*(11), e1001903. https://doi.org/10.1371/journal.pmed.1001903

Satzke, C., Turner, P., Virolainen-Julkunen, A., Adrian, P. V., Antonio, M., Hare, K. M., Henao-Restrepo, A. M., Leach, A. J., Klugman, K. P., Porter, B. D., Sá-Leão, R., Scott, J. A., Nohynek, H., & O'Brien, K. L. (2013). Standard method for detecting upper respiratory carriage of Streptococcus pneumoniae: Updated recommendations from the World Health Organization Pneumococcal Carriage Working Group. *Vaccine*, *32*(1), 165–179. https://doi.org/10.1016/j.vaccine.2013.08.062

Senghore, M., Chaguza, C., Bojang, E., Tientcheu, P.-E., Bancroft, R. E., Lo, S. W., Gladstone, R. A., McGee, L., Worwui, A., Foster-Nyarko, E., Ceesay, F., Okoi, C. B., Klugman, K. P., Breiman, R. F., Bentley, S. D., Adegbola, R., Antonio, M., Hanage, W. P., & Kwambana-Adams, B. A. (2022). Widespread sharing of pneumococcal strains in a rural African setting: Proximate villages are more likely to share similar strains that are carried at multiple timepoints. *Microbial Genomics*, *8*(2). https://doi.org/10.1099/mgen.0.000732

SMART. (2017). *Standardized Monitoring and Assessment for Relief and Transitions Manual 2.0*.

United Nations High Commissioner for Refugees. (n.d.). *Figures at a Glance*. Retrieved October 8, 2020, from https://www.unhcr.org/figures-at-a-glance.html

van Zandvoort, K., Bobe, M. O., Hassan, A. I., Abdi, M. I., Ahmed, M. S., Warsame, M. Y., Wais, M. A., Diggle, E., Satzke, C., Mulholland, K., Egeh, M. M., Hassan, M. M., Hergeeye, M. A., Eggo, R. M., Checchi, F., & Flasche, S. (2021). *Social contacts and other risk factors for respiratory infections among internally displaced people in Somaliland. Data and analyses.* (v1.0.0") [R]. https://doi.org/10.5281/zenodo.5225141

van Zandvoort, K., Checchi, F., Diggle, E., Eggo, R. M., Gadroen, K., Mulholland, K., McGowan, C. R., le Polain de Waroux, O., Rao, V. B., Satzke, C., & Flasche, S. (2019). Pneumococcal conjugate vaccine use during humanitarian crises. *Vaccine*, *37*(45), 6787–6792. https://doi.org/10.1016/j.vaccine.2019.09.038

Wahl, B., O'Brien, K. L., Greenbaum, A., Majumder, A., Liu, L., Chu, Y., Lukšić, I., Nair, H., McAllister, D. A., Campbell, H., Rudan, I., Black, R., & Knoll, M. D. (2018). Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: Global, regional, and national estimates for 2000–15. *The Lancet Global Health*, *6*(7), e744–e757. https://doi.org/10.1016/S2214-109X(18)30247-X

World Food Programme. (2009). *Emergency Food Security Assessment Handbook (EFSA)—Second Edition*. https://www.wfp.org/publications/emergency-food-security-assessment-handbook

World Health Organization. (2017a). *The Humanitarian Mechanism*. http://www.who.int/immunization/programmes_systems/sustainability/The_Humanitarian_Mechanism_ToRs.pdf?ua=1

World Health Organization. (2017b). *Vaccination in Acute Humanitarian Emergencies. A framework for decision making.*

World Health Organization. (2019). Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. *Weekly Epidemiological Record*, *94*(8), 85–104.

12 Appendices

12.1 List of drugs (generic names) included in measurement of antibiotic prescriptions

12.2 Details of mathematical modelling simulations

12.3 Carriage survey questionnaire

12.4 Adverse events severity grading table

12.5 Serious adverse event Case Report Form

12.6 List of solicited signs and symptoms to capture adverse events

12.7 National Early Warning Score 2 grading of vital signs

12.8 Vaccine information sheet

12.9 Vaccination informed consent form

12.10 Carriage survey information sheet

12.11 Carriage survey informed consent form

12.12 Carriage survey informed assent form

12.13 PNEUMOSIL product leaflet

12.14 Risk assessment

12.15 Terms of reference of the Study Oversight Committee

Considerations for Pneumococcal Conjugate Vaccine (PCV) Product Choice

Disclaimer: WHO does not endorse the use of specific branded products over others; this publication may not be used for any commercial or promotional purposes.

Background

This document summarizes current technical and programmatic information on WHO prequalified PCV products to facilitate informed country choices for PCV introduction or product switch for childhood immunization programmes. Three PCV products are prequalified by the World Health Organization (WHO) for use in infants and children. They include the 13-valent PCV manufactured by Pfizer (PCV-13, Prev(e)nar®), a 10-valent PCV manufactured by GlaxoSmithKline (PCV-10^{GSK}, Synflorix®), and a 10-valent PCV manufactured by Serum Institute of India (PCV-10^{SII}, PNEUMOSIL®). Manufacturers are expected to seek WHO prequalification for additional higher valent PCV products in the future. This summary of considerations may be updated in the future to address new products.

This document is based on published sources except for content related to the newest prequalified product, PNEUMOSIL®, where the manufacturer provided the unpublished Clinical Study Report confidentially. The document should not be viewed as formal WHO recommendations or guidelines.

WHO Position on Pneumococcal Vaccines in Infants and Children

The 2019 WHO position paper[1] presents the current policy recommendations for pneumococcal conjugate vaccines in infants and children. The document does not express preference among prequalified PCV products but does not reference PCV-10^{SII} or data specific to this product given that it was prequalified in December 2019 after the paper's publication. Despite the most recent product not being mentioned, the 2019 policy recommendations are considered applicable to PCV-10^{SII}. The position paper states:

- "Both PCV10 and PCV13 have substantial impacts against pneumonia, vaccine type (VT) invasive pneumococcal disease (IPD), and nasopharyngeal (NP) carriage" in a variety of settings".
- "The choice of product to be used in a country should be based on programmatic characteristics, vaccine supply, vaccine price, the local and regional prevalence of vaccine serotypes and antimicrobial resistance patterns".
- "PCV13 may have an additional benefit [over PCV-10^{GSK}] in settings where disease attributable to serotype (ST) 19A or ST 6C is significant".

[1] Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. Weekly epidemiological record (Relevé épidémiologique hebdomadaire). 2019;94(8):85–104.

Vaccine Characteristics

In considering the biological characteristics of the three prequalified PCV products, a key difference is the number and selection of STs included. Additionally, differences in carrier proteins, conjugation method, and preservatives are shown in Table 1.

Table 1: Biological characteristics of available pneumococcal conjugate vaccines

			Pneumococcal Serotype (ST)													
Product	**Carrier protein(s)**	**Conjugation method & Preservative**	**1**	**3**	**4**	**5**	**6A**	**6B**	**6C**	**7F**	**9V**	**14**	**18C**	**19A**	**19F**	**23F**
PCV-10^{GSK} Synflorix®	Protein D (PD), tetanus toxoid (TT), diphtheria toxoid (DT)	*Conjugation:* CDAP* *Preservative:* 1-dose vial – none 2-dose vial – none 4-dose vial – 2-phenoxyethanol	■		■	■	■	■		■	■	■	■		■	■
PCV-10^{SII} PNEUMOSIL®	CRM197	*Conjugation:* CDAP* *Preservative*: 1 dose vial – none 5 dose vial – thimerosal	■			■	■	■		■	■	■		■	■	■
PCV-13 Prevnar®	CRM197	*Conjugation:* Reductive amination *Preservative*: 1-dose vial – none 4-dose vial – 2-phenoxyethanol	■	▒	■	■	■	■	■	■	■	■	■	■	■	■

* CDAP: 1-cyano-4-dimethylaminopyridinium tetrafluoroborate

■	ST included in vaccine
	ST not included in vaccine
■	ST not included in vaccine but some evidence of cross-protection
▒	**ST3** included in PCV-13 but no conclusive evidence for protection

Safety

- The safety profiles of both PCV-10^{GSK} and PCV-13 have been reviewed as part of the WHO prequalification process and by the Global Advisory Committee on Vaccine Safety (GACVS). Both products have accrued extensive post-marketing safety surveillance data, and both are assessed as having excellent safety profiles.
- Clinical trial data for PCV-10^{SII} were reviewed during the WHO prequalification process; the product was well tolerated and has a comparable safety profile to the other prequalified PCVs[2].

[2] Public Assessment Summary Report. Pneumococcal Conjugate Vaccine, (adsorbed, 10-valent), Serum Institute of India Pvt. Ltd. 17 December 2019. https://extranet.who.int/pqweb/content/pneumosil%C2%AE-0

PCV Performance

Efficacy/effectiveness or immunogenicity

- Measurements of disease effectiveness following PCV use in routine use settings, measured at the community level, do not meaningfully distinguish PCV-10^{GSK} from PCV-13
    - Both products show high levels of immunogenicity, reduction in VT IPD, all cause pneumonia, chest x-ray (CXR) confirmed pneumonia, and VT colonization (the effector of herd effect)
- Efficacy data for PCV-10^{SII} are not available, but efficacy is expected to be equivalent to PCV-13 and PCV-10^{GSK} based on immunogenicity data showing non-inferiority[2,3,4].

Serotype-specific coverage

Available local, regional, and global pneumococcal disease surveillance data should be considered as part of a decision to switch or introduce a new PCV product. The proportion of IPD in children under 5 years of age, caused by STs included in the available PCVs, by region, before PCV introduction is similar across the three products, as shown in the figure below.

ST 3 (contained in PCV-13 only):

- Data on PCV-13 impact on ST 3 are inconclusive, with most studies showing no impact.

ST 6A, 19A (contained in PCV-13 and PCV-10^{SII}):

- PCV13 stimulates strong immune response to ST 6A and 19A as well as demonstrated impact on ST 19A and 6A IPD in both immunized and unimmunized age groups.
- PCV-10^{SII} was also shown to stimulate strong immune responses for ST 6A and 19A in phase 3 trials but disease impact data are not yet available.
- For PCV-10^{GSK}, while reduction in disease from ST 6A has been documented in immunized populations, there is no conclusive evidence of cross-protection for ST 19A. Little to no impact on unimmunized individuals (i.e. indirect protection) has been observed for these STs following PCV-10^{GSK} implementation.

ST 6C (possible cross-protection conferred by ST 6A, contained in PCV-13 and PCV-10^{SII})

- Some studies have shown a significant impact of PCV13 on ST 6C IPD and on carriage[1].
- Given that PCV-10^{SII} contains ST 6A, it may provide impact on ST 6C disease, but impact data are not yet available.

[3] Clarke E, Bashorun A, Adigweme I et al. Immunogenicity and safety of a novel ten-valent pneumococcal conjugate vaccine in healthy infants in The Gambia: a phase 3, randomised, double-blind, non-inferiority trial. Lancet Infectious Diseases. 2021. https://doi.org/10.1016/S1473-3099(20)30735-0

[4] Clinical Study Report PCV-10-003. A Phase 3, Randomized, Double-Blind Study to Evaluate the Immunogenicity, Safety and Tolerability of Serum Institute of India's 10-valent Pneumococcal Conjugate Vaccine (PNEUMOSIL®) in Healthy Indian Infants. Serum Institute of India Pvt. Ltd. 24 June 2020.

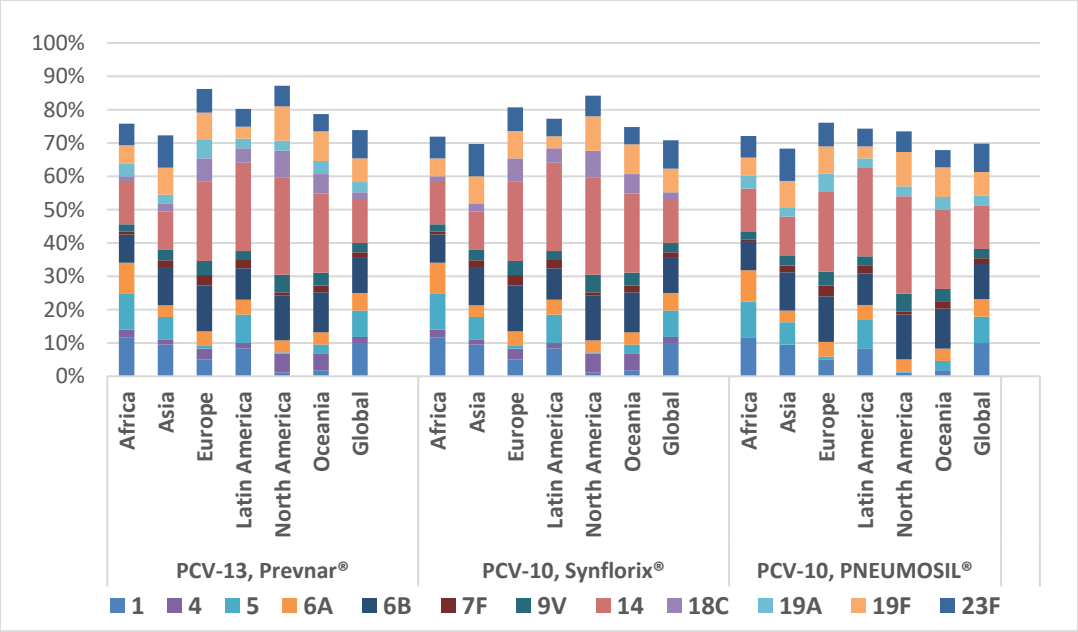


Figure: Proportion of invasive pneumococcal disease (IPD) in children under 5 years of age before PCV introduction, caused by vaccine serotypes (ST) included in available PCV products, by region. Data adapted from Johnson et al, 2010. PLoS Med 7(10): e1000348.

This figures shows that prior to PCV introduction, similar proportions of IPD were caused by the ST included in each of the three vaccine products. Please note that this pre-PCV distribution may vary from the percent reduction of ST-specific disease that might be observed after PCV introduction. ST shown include ST included in the product plus ST where evidence of cross-protection has been observed. This applies to ST 6A impact observed for Synflorix®. Evidence of ST 6C cross protection by PCV-13 has been observed but the percent IPD due to this ST are not available from the pre-PCV period and cannot be quantified.

Programmatic Considerations

- Several programmatic characteristics are similar or identical between the three PCV products (e.g. presentation, administration, formulation, storage temperature, vaccine vial monitor (VVM), wastage rate).
- Other important factors —such as cold chain and storage space, doses per container, and price—differ by product and may require additional planning for countries choosing to switch or incorporate multiple products (Table 2).
- Training of immunization staff is required for use of all PCV products prior to introduction and may be required for situations where a product and/or presentation switch is undertaken.

Table 2: Vaccine presentation, administration, storage and cold chain requirements

	PCV-10^{SII}	PCV-10^{SII}	PCV-13	PCV-13	PCV-10^{GSK} *
Presentation	1 dose/vial, liquid	5 doses/vial, liquid	1 dose/vial, liquid	4 doses/vial, liquid	4 doses/vial, liquid
Dose quantity	←----------0.5 ml----------→				
Dose measurement needed	No	Yes	No	Yes	Yes
Vaccine vial monitor type	←----------Type 30----------→				
Open vial handling[5]	n.a.	May be kept for use up to 28 days if stored at 2-8°C	n.a.	May be kept for use up to 28 days if stored at 2-8°C	May be kept for use up to 28 days if stored at 2-8°C
Shelf-life	←----------36 months, 2 - 8 °C----------→				
Cold chain volume per fully immunized person (cm3)	53	11	37.8	11.7	8

*This table shows product presentations supplied by Gavi. PCV-10^{GSK} 1 and 2 dose vials are also WHO prequalified[6]

Recommended vaccination schedules

- Per the 2019 position paper, WHO recommends a 3-dose schedule administered either as 2 primary doses plus a booster dose (2p+1) or as 3 primary doses without a booster (3p+0), starting as early as 6 weeks of age. For the 2p+1 schedule, an interval of ⩾8 weeks is recommended between the 2 primary doses, but the interval may be shortened if there is a compelling programmatic reason to do so. The booster dose should be given between 9–18 months of age. If the 3p+0 schedule is used, a minimum interval of 4 weeks should be maintained between doses.
- In choosing between the 2p+1 and 3p+0 schedules, countries should consider programmatic factors, including timeliness of vaccination and expected coverage.
- PCV-10 ^{SII} clinical trial data support its use in a 3p+0 schedule. Additional data from trials in India and the Gambia assessing the immunogenicity of the 2p+1 schedule are expected soon.

Co-Administration

- Based on the Gambian phase 3 trial[3], PCV-10 ^{SII} was shown not to interfere with the performance of pentavalent vaccine (diphtheria, tetanus, whole-cell pertussis, hepatitis B, and *Haemophilus influenzae* type b) when given at the same time.
- WHO recommends that despite the lack of comprehensive data on the immunogenicity, effectiveness and safety of all possible combinations of PCV and other routine vaccines, co-administration for programmatic reasons appears to be acceptable[1].

[5] WHO policy statement: multi-dose vial policy (MDVP): handling of multi-dose vaccine vials after opening, Revision 2014. https://apps.who.int/iris/handle/10665/135972

[6] https://extranet.who.int/pqvdata/PreviewVaccine.aspx?nav=0&ID=384

Interchangeability

- A 2019 review of evidence on PCV interchangeability synthesized data on children who completed PCV schedules with mixed products to inform policies on PCV procurement and product switching[7]. Available evidence suggests that countries can use PCVs interchangeably in routine programmes when continuing the entire series with the same product is not feasible.
- Given limited evidence on interchangeability, once a PCV vaccination programme has been initiated, product switching may be recommended in the event of substantial changes in the epidemiological or programmatic factors that determined the original choice of product, such as increase in the burden of disease from a serotype(s) better covered by an available alternative vaccine formulation**[1].**

Cost and financial considerations

- PCV pricing varies by product and procurement method. PCV public market prices per dose for PCV-10^{GSK} and PCV13 range from $3 USD for Gavi countries[8] through UNICEF (and the AMC) to $132 USD in the USA[9]. PCV-10^{SII} has the lowest Gavi price of all PCVs ($2.95 USD, 1 dose/vial; $2.00 USD, 5 doses/vial)[10] and is expected to be the lowest-price option for non-Gavi countries, though data on non-Gavi pricing are not yet available.
- The table below provides an overview of median price per dose for PCV-10^{GSK} and PCV13 by income and procurement group.[11]

	UNICEF Supply Division – Gavi eligible country purchases	UNICEF Supply Division – MIC procuring purchases	PAHO Revolving Fund purchases	Self- procured MIC purchases	Self-procured HIC purchases
PCV* Median price/dose (USD)	$3.05	$9.39	$14.50	$18.29	$45.44

*PCV13 and PCV10^{GSK}

- WHO publishes annually Vaccine Purchase Data[12] reported by countries through the WHO/UNICEF Joint Reporting Form. This database is available for countries to be able to

[7] IVAC. Pneumococcal Conjugate Vaccine (PCV) Interchangeability: Evidence Dossier. 2019. https://www.jhsph.edu/ivac/wp-content/uploads/2020/03/Evidence-dossier-PCV-Interchangeability_Global_Dec-2019.pdf

[8] https://www.gavi.org/sites/default/files/document/2020/Gavi-PCV-vaccines-profiles-july-2020.pdf

[9] Global Market Study: Pneumococcal Conjugate (PCV) And Polysaccharide (PPV) Vaccines. https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module2/Pneumococcal_Vaccine_Market_Study-June2020.pdf?ua=1

[10] https://www.gavi.org/sites/default/files/document/2020/Gavi-PCV-vaccines-profiles-july-2020.pdf

[11] 2020 Global Vaccine Market Report https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module2/2020_Global_Vaccine_Market_Report.pdf?ua=1

[12] WHO Vaccine Purchase Data: https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module1/en/

compare prices paid for different vaccines by procurement method, income group and other characteristics. This includes prices reported by self- procuring countries.

- PATH has developed a tool for comparison of costs for all available PCV products that countries may find useful for cost considerations[13].
- PCV-10^{GSK} and 13 have generally been found to be cost effective; PCV-10^{SII} is expected to be cost effective or cost saving, but cost effectiveness data specific to PCV-10 ^{SII} are very limited as it has not been used broadly outside of clinical trials.

Availability and supply

- Based on the latest available information, sufficient consolidated PCV supply exists globally to support current and emerging demand in the coming years[9].
- PCV-10 ^{SII} is prequalified as of 2019 and is available for procurement support from Gavi (through UN agencies) or for direct procurement from the manufacturer.
- At country level, sufficient supply for any PCV product for routine introduction will depend on the product preference, target population and dose requirement, timing of introduction, and global demand for the preferred product.

Prioritization among new vaccine introduction decisions

The WHO CAPACITI tool[14] is available to support standardized country decision making and comparison of multiple product choice options for introduction, product switch, or schedule changes.

Additional materials that can be used to inform product switches:

1. Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019 https://apps.who.int/iris/bitstream/handle/10665/310968/WER9408.pdf?ua=1
2. Gavi-supported PCV profiles to support country decision making. July 2020. https://www.gavi.org/sites/default/files/document/2020/Gavi-PCV-vaccines-profiles-july-2020.pdf
3. Pneumococcal Conjugate Vaccine (PCV) Interchangeability: Evidence Dossier. 2019. https://www.jhsph.edu/ivac/wp-content/uploads/2020/03/Evidence-dossier-PCV-Interchangeability_Global_Dec-2019.pdf
4. PCV Product Assessment, April 2017. Published by Johns Hopkins University, International Vaccine Access Center. https://www.jhsph.edu/ivac/resources/pcv-product-assessment/
5. Global Market Study: Pneumococcal Conjugate (PCV) And Polysaccharide (PPV) Vaccines. https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module2/Pneumococcal_Vaccine_Market_Study-June2020.pdf?ua=1

[13] PATH. Pneumococcal conjugate vaccine cost calculator. https://www.path.org/resources/pneumococcal-conjugate-vaccine-cost-calculator/

[14] https://decidehealth.world/index.php/en/capaciti

6. Pneumococcal conjugate vaccine cost calculator
   https://www.path.org/resources/pneumococcal-conjugate-vaccine-cost-calculator/

Acknowledgements

This document was written by the WHO Department of Immunization, Vaccines, and Biologicals (IVB) with contributions from the WHO regional new vaccines focal points and in consultation with current members of the SAGE Working Group on Pneumococcal Vaccines and the Gavi Pneumococcal and Rotavirus Vaccines Working Group (PROWG).

Considerations for pneumococcal conjugate vaccine (PCV) product choice
ISBN 978-92-4-003060-2 (electronic version)
ISBN 978-92-4-003061-9 (print version)
© World Health Organization 2021. Some rights reserved. This work is available under the CC BY-NC-SA 3.0 IGO licence.

9789240030602

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

22 FEBRUARY 2019, 94th YEAR / 22 FÉVRIER 2019, 94e ANNÉE
No 8, 2019, 94, 85–104
http://www.who.int/wer

Contents

85 Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019

Sommaire

85 Vaccins antipneumococciques conjugués chez les nourrissons et les enfants de moins de 5 ans: note de synthèse de l'OMS – février 2019

Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019

Introduction

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale vaccination programmes. They summarize essential background information on diseases and vaccines and conclude with the current WHO position on the use of vaccines worldwide.

The papers are reviewed by external experts and WHO staff and endorsed by the WHO Strategic Advisory Group of Experts (SAGE) on Immunization (http://www.who.int/immunization/sage/en). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) method is used to assess the quality of the available evidence systematically. The SAGE decision-making process is reflected in "evidence-to-recommendation" tables. The processes followed for the preparation of vaccine position papers are described at: http://www.who.int/immunization/position_papers/position_paper_process.pdf. The position papers are intended for use mainly by national public health officials and managers of immunization programmes. They may also be of interest to international funding agencies, vaccine advisory groups, vaccine manufacturers, health professionals, researchers, the scientific media and the general public.

Vaccins antipneumococciques conjugués chez les nourrissons et les enfants de moins de 5 ans: note de synthèse de l'OMS – février 2019

Introduction

Conformément à son mandat, qui prévoit qu'elle conseille les États Membres en matière de politique sanitaire, l'OMS publie une série de notes de synthèse régulièrement mises à jour sur les vaccins et les associations vaccinales contre les maladies ayant une incidence sur la santé publique internationale. Ces notes, qui portent essentiellement sur l'utilisation des vaccins dans les programmes de vaccination à grande échelle, résument les informations essentielles sur les maladies et les vaccins et présentent en conclusion la position actuelle de l'OMS concernant l'utilisation de ces vaccins à l'échelle mondiale.

Ces notes sont examinées par des experts externes et des membres du personnel de l'OMS, puis approuvées par le Groupe stratégique consultatif d'experts sur la vaccination (SAGE) de l'OMS (http://www.who.int/immunization/sage/fr). La qualité des données disponibles est évaluée de manière systématique au moyen de la méthode GRADE (Grading of Recommendations Assessment, Development and Evaluation). Le processus de décision du SAGE est reflété dans des tableaux illustrant le passage des preuves aux recommandations («evidence-to-recommendation»). La description des procédures suivies pour élaborer les notes de synthèse sur les vaccins est disponible à l'adresse: http://www.who.int/immunization/position_papers/position_paper_process.pdf. Les notes de synthèse s'adressent avant tout aux responsables nationaux de la santé publique et aux administrateurs des programmes de vaccination, mais elles peuvent également présenter un intérêt pour les organismes internationaux de financement, les groupes consultatifs sur la vaccination, les fabricants de vaccins, les professionnels de la santé, les chercheurs, les médias scientifiques et le grand public.

A 23-valent polysaccharide vaccine has been available since the early 1980s, and pneumococcal conjugate vaccines (PCV) have been available since 2009. The focus of this position paper is use of PCV in infants and children <5 years of age; a separate position paper on vaccination of older age groups with conjugate and polysaccharide vaccines will be developed after consideration by SAGE. The present position paper includes data on the effects of the 10- and 13-valent PCVs (PCV10 and PCV13) published up to June 2017 and specifically addresses the dosing schedule, product choice and the value of catch-up vaccination in children under 5 years of age.

Recommendations on the use of PCVs were discussed by SAGE in October 2017. Evidence presented at the meeting can be accessed at: http://www.who.int/immunization/sage/meetings/2017/october/presentations_background_docs/en/.

Background

Epidemiology

Pneumococcal infections can lead to serious invasive diseases such as meningitis, septicaemia and pneumonia, as well as milder but more common illnesses such as sinusitis and otitis media. The causative agent, *Streptococcus pneumoniae*, frequently colonizes the human nasopharynx and is transmitted mainly through respiratory droplets. Infants and young children are the main reservoir of this organism, in whom the cross-sectional point prevalence of nasopharyngeal (NP) carriage ranges from 27% to 85%, with higher carriage rates among children in low- and middle-income countries (LMICs) and in some indigenous populations in high-income countries.[1]

There are >90 known serotypes of *S. pneumoniae*. The distribution of serotypes that cause disease varies over time and by age, disease syndrome, disease severity, geographical region and the presence of antimicrobial-resistant genes. Before the introduction of PCVs in the different WHO regions, 6–11 serotypes accounted for ≥70% of all invasive pneumococcal disease (IPD), defined as morbidity associated with isolation of pneumococci from a normally sterile body site, in children <5 years.[2]

Most illnesses occur sporadically. Outbreaks of pneumococcal disease, although uncommon, may occur in closed institutions, such as in nursing homes and child-care centres; however, large outbreaks of meningitis

Un vaccin polyosidique 23-valent est disponible depuis le début des années 1980, et les vaccins antipneumococciques conjugués (VPC) sont quant à eux disponibles depuis 2009. La présente note de synthèse traite essentiellement de l'utilisation des VPC chez les nourrissons et les enfants de <5 ans; une autre note de synthèse, portant sur la vaccination des groupes plus âgés par les vaccins conjugués et polyosidiques, sera élaborée après examen de la question par le SAGE. La présente note de synthèse contient des données publiées jusqu'en juin 2017 concernant les effets du VPC 10-valent (VPC10) et du VPC 13-valent (VPC13) et aborde dans le détail les questions relatives au schéma d'administration des doses, au choix du produit et à l'utilité de la vaccination de rattrapage chez les enfants de <5 ans.

Les recommandations sur l'utilisation des VPC ont été examinées par le SAGE en octobre 2017. Les éléments présentés lors de cette réunion peuvent être consultés à l'adresse: http://www.who.int/immunization/sage/meetings/2017/october/presentations_background_docs/en/.

Informations générales

Épidémiologie

Les infections à pneumocoques peuvent entraîner des maladies invasives graves telles que la méningite, la septicémie et la pneumonie, ainsi que des affections plus bénignes mais aussi plus courantes, comme la sinusite et l'otite moyenne. L'agent étiologique, *Streptococcus pneumoniae*, colonise souvent le rhinopharynx de l'être humain et se transmet principalement par les gouttelettes respiratoires. Les nourrissons et les jeunes enfants constituent le principal réservoir de cet organisme, l'évaluation transversale de la prévalence ponctuelle dans cette population révélant un taux de portage rhinopharyngé allant de 27% à 85%, avec des taux de portage plus élevés parmi les enfants qui vivent dans les pays à revenu faible ou intermédiaire ou qui appartiennent à certaines populations autochtones dans les pays à revenu élevé.[1]

Il existe >90 sérotypes connus de *S. pneumoniae*. La distribution des sérotypes pathogènes varie au cours du temps, ainsi qu'en fonction de l'âge, du syndrome pathologique, de la gravité de la maladie, de la région géographique et de la présence de gènes résistants aux antimicrobiens. Avant l'introduction des VPC dans les différentes régions de l'OMS, 6 à 11 sérotypes étaient à l'origine de ≥70% de tous les cas de pneumococcie invasive (PI) – pathologie définie par un état morbide associé à un isolement de pneumocoques sur un site normalement stérile de l'organisme – chez les enfants de <5 ans.[2]

La plupart des cas surviennent de manière sporadique. Des flambées de pneumococcie, bien que rares, peuvent se produire au sein de populations confinées, comme dans les maisons de retraite ou les structures d'accueil de la petite enfance. Toutefois,

[1] O'Brien KL, et al. Report from a WHO Working Group: standard method for detecting upper respiratory carriage of Streptococcus pneumoniae. Pediatr Infect Dis J; 2003: 22(2): e1-11.

[2] Johnson HL, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. PLoS Med. 2010;7:pii:e1000348.

[1] O'Brien KL, et al. Report from a WHO Working Group: standard method for detecting upper respiratory carriage of Streptococcus pneumoniae. Pediatr Infect Dis J; 2003: 22(2): e1-11.

[2] Johnson HL, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. PLoS Med. 2010;7:pii:e1000348.

caused by serotype 1 have been reported from the African "meningitis belt".[3, 4, 5]

Of the estimated 5.83 million deaths among children <5 years of age globally in 2015, 294 000 (uncertainty range [UR], 192 000–366 000) were estimated to be caused by pneumococcal infections.[6] An additional 23 300 deaths (UR 15 300–40 700) were estimated to have occurred in children co-infected with HIV. Disease and mortality rates are higher in developing than in industrialized settings, with most deaths occurring in Africa and Asia.

Before widespread introduction of PCVs into national immunization programmes since 2006, the reported mean annual incidence of IPD in children aged <2 years was 44.4/100 000 per year in Europe and 167/100 000 per year in the United States of America.[7, 8] In comparison, the annual incidence of IPD in children <2 years in Africa ranged from 60/100 000 in South Africa to 797/100 000 in Mozambique.[9, 10, 11] Although differences in the reported incidence can be explained partly by differences in the sensitivity of case ascertainment and surveillance (e.g., limited to hospitalized children in some studies but including outpatients with febrile illness in others), the incidence in Africa appeared to be generally higher than that in Europe or North America. The reported incidence rates in Asia and Latin America range between these extremes.[12–20]

d'importantes flambées de méningite dues au sérotype 1 ont été signalées dans la «ceinture africaine de la méningite».[3, 4, 5]

Sur les quelque 5,83 millions de décès survenus en 2015 à l'échelle mondiale parmi les enfants de <5 ans, on estime que 294 000 (plage d'incertitude: 192 000–366 000) étaient imputables aux infections à pneumocoques.[6] À cela s'ajoutent environ 23 300 décès (plage d'incertitude: 15 300-40 700) parmi les enfants co-infectés par le VIH. Les taux de morbidité et de mortalité sont plus élevés dans les régions en développement que dans celles qui sont industrialisées, la plupart des décès étant observés en Afrique et en Asie.

Avant que les VPC ne soient introduits à grande échelle dans les programmes nationaux de vaccination à partir de 2006, l'incidence annuelle moyenne de la PI signalée chez les enfants de <2 ans était de 44,4 pour 100 000 en Europe et de 167 pour 100 000 aux États-Unis.[7, 8] Par comparaison, l'incidence annuelle de la PI chez les enfants de <2 ans en Afrique variait entre 60 pour 100 000 en Afrique du Sud et 797 pour 100 000 au Mozambique.[9, 10, 11] Bien que ces disparités de l'incidence signalée puissent en partie s'expliquer par des différences de sensibilité de la surveillance et de la constatation des cas (par exemple, limitée aux enfants hospitalisés dans certaines études, mais incluant les patients fébriles en soins ambulatoires dans d'autres), l'incidence semble globalement plus élevée en Afrique qu'en Europe ou en Amérique du Nord. Les taux d'incidence signalés en Asie et en Amérique latine varient entre ces deux extrêmes.[12-20]

[3] Yaro S, et al. Epidemiological and molecular characteristics of a highly lethal pneumococcal meningitis epidemic in Burkina Faso. Clin Infect Dis. 2006;43:693–700.

[4] Kwambana-Adams BA, et al. An outbreak of pneumococcal meningitis among older children (≥5 years) and adults after the implementation of an infant vaccination programme with the 13-valent pneumococcal conjugate vaccine in Ghana. BMC Infect Dis. 2016;16(1):575.

[5] Leimkugel J, et al. An outbreak of serotype 1 *Streptococcus pneumoniae* meningitis in northern Ghana with features that are characteristic of *Neisseria meningitidis* meningitis epidemics. J Infect Dis. 2005 Jul 15;192(2):192-9.

[6] Wahl B, et al. Burden of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. Lancet Global Health. 2018;6(7):e744–57.

[7] Isaacman DJ, et al. Burden of invasive pneumococcal disease and serotype distribution among *Streptococcus pneumoniae* isolates in young children in Europe: impact of the 7-valent pneumococcal conjugate vaccine and considerations for future conjugate vaccines. Int J Infect Dis. 2010;14:e197–209.

[8] Black S, et al. Pneumococcal conjugate vaccine and pneumococcal common protein vaccines. In: Plotkin SA, Orenstein WA, Offit P, editors. Vaccines. 5th ed. Philadelphia (PA): WB Saunders Co; 2008:531–67.

[9] Roca A, et al. Invasive pneumococcal disease in children < 5 years of age in rural Mozambique. Trop Med Int Health. 2006;11:1422–31.

[10] Karstaedt AS, et al. Pneumococcal bacteremia during a decade in children in Soweto, South Africa. Pediatr Infect Dis J. 2000;9:454–7.

[11] Cutts FT, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet. 2005;365:1139–46.

[12] Benavides JA, et al. Population-based surveillance for invasive pneumococcal disease and pneumonia in infants and young children in Bogotá, Colombia. Vaccine. 2012;30(40):5886–92.

[13] Arguedas A, et al. Prospective epidemiologic surveillance of invasive pneumococcal disease and pneumonia in children in San José, Costa Rica. Vaccine. 2012;30(13):2342–8.

[14] Andrade AL, et al. Population-based surveillance for invasive pneumococcal disease and pneumonia in infants and young children in Goiânia, Brazil. Vaccine. 2012;30(10):1901–9.

[15] Howidi M, et al. The burden of pneumococcal disease in children less than 5 years of age in Abu Dhabi, United Arab Emirates. Ann Saudi Med. 2011;31(4):356–9.

[16] Lin TY, et al. Summary of invasive pneumococcal disease burden among children in the Asia–Pacific region. Vaccine. 2010;28(48):7589–605.

[17] Owais A, et al. Incidence of pneumonia, bacteremia, and invasive pneumococcal disease in Pakistani children. Trop Med Int Health. 2010;15(9):1029–36.

[3] Yaro S, et al. Epidemiological and molecular characteristics of a highly lethal pneumococcal meningitis epidemic in Burkina Faso. Clin Infect Dis. 2006;43:693–700.

[4] Kwambana-Adams BA, et al. An outbreak of pneumococcal meningitis among older children (≥5 years) and adults after the implementation of an infant vaccination programme with the 13-valent pneumococcal conjugate vaccine in Ghana. BMC Infect Dis. 2016;16(1):575.

[5] Leimkugel J, et al. An outbreak of serotype 1 *Streptococcus pneumoniae* meningitis in northern Ghana with features that are characteristic of *Neisseria meningitidis* meningitis epidemics. J Infect Dis. 2005 Jul 15;192(2):192-9.

[6] Wahl B, et al. Burden of Streptococcus pneumoniae and *Haemophilus influenzae* type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. Lancet Global Health. 2018;6(7):e744–57.

[7] Isaacman DJ, et al. Burden of invasive pneumococcal disease and serotype distribution among Streptococcus pneumoniae isolates in young children in Europe: impact of the 7-valent pneumococcal conjugate vaccine and considerations for future conjugate vaccines. Int J Infect Dis. 2010;14:e197–209.

[8] Black S, et al. Pneumococcal conjugate vaccine and pneumococcal common protein vaccines. In: Plotkin SA, Orenstein WA, Offit P, editors. Vaccines. 5th ed. Philadelphia (PA): WB Saunders Co; 2008:531–67.

[9] Roca A, et al. Invasive pneumococcal disease in children <5 years of age in rural Mozambique. Trop Med Int Health. 2006;11:1422–31.

[10] Karstaedt AS, et al. Pneumococcal bacteremia during a decade in children in Soweto, South Africa. Pediatr Infect Dis J. 2000;9:454–7.

[11] Cutts FT, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet. 2005;365:1139–46.

[12] Benavides JA, et al. Population-based surveillance for invasive pneumococcal disease and pneumonia in infants and young children in Bogotá, Colombia. Vaccine. 2012;30(40):5886–92.

[13] Arguedas A, et al. Prospective epidemiologic surveillance of invasive pneumococcal disease and pneumonia in children in San José, Costa Rica. Vaccine. 2012;30(13):2342–8.

[14] Andrade AL, et al. Population-based surveillance for invasive pneumococcal disease and pneumonia in infants and young children in Goiânia, Brazil. Vaccine. 2012;30(10):1901–9.

[15] Howidi M, et al. The burden of pneumococcal disease in children less than 5 years of age in Abu Dhabi, United Arab Emirates. Ann Saudi Med. 2011;31(4):356–9.

[16] Lin TY, et al. Summary of invasive pneumococcal disease burden among children in the Asia–Pacific region. Vaccine. 2010;28(48):7589–605.

[17] Owais A, et al. Incidence of pneumonia, bacteremia, and invasive pneumococcal disease in Pakistani children. Trop Med Int Health. 2010;15(9):1029–36.

It is difficult to determine the proportion of pneumonia that is due to *S. pneumoniae*. In a compilation of data from studies of lung aspirates from various regions, *S. pneumoniae* was found to be the cause of 78% of 284 lobar pneumonia cases and 13% of 515 bronchopneumonia cases proven to be of bacterial etiology by transthoracic needle aspiration.[21] A systematic Cochrane review of studies on PCVs in children <2 years of age showed a pooled vaccine efficacy of 27% (95% confidence interval [CI], 15%, 36%) against radiologically confirmed pneumonia as defined by WHO, suggesting that at least 27% of radiologically confirmed pneumonia could be caused by *S. pneumoniae*.[22] An analysis of the efficacy of PCV against radiologically confirmed pneumonia in children under 5 years of age indicated that the proportion of pneumonia caused by *S. pneumoniae* is 34% [UR 26-36%];[6] such proportions are considered to be more precise than estimates based on data from studies of laboratory-confirmed cases.

On average, about 75% of cases of IPD, and 83% of cases of pneumococcal meningitis, occur in children aged <2 years, but the incidence and age distribution of cases may vary by country, study method and socio-economic status within countries. Seasonal and climatic trends in both IPD and community-acquired pneumonia have been reported that coincide with the seasonal circulation of influenza and respiratory syncytial viruses, suggesting that these viruses predispose to pneumococcal infection.[23–26]

Pathogen

S. pneumoniae is a Gram-positive, encapsulated diplococcus. The polysaccharide capsule of this bacterium is an essential virulence factor, and pneumococcal serotypes are defined on the basis of differences in its composition. Antibody to the capsular polysaccharide protects against disease. In general, immunity from natural infection or vaccination is serotype-specific, but cross-protection among related serotypes can occur (namely between serotypes 6A/6B, 6A/6C and 19A/19F).

Il est difficile de déterminer la proportion des cas de pneumonie qui sont dus à *S. pneumoniae*. Des données compilées à partir d'études d'aspirats pulmonaires dans différentes régions ont indiqué que *S. pneumoniae* était responsable de 78% des 284 cas de pneumonie lobaire et de 13% des 515 cas de bronchopneumonie dont l'origine bactérienne avait été confirmée par ponction transthoracique.[21] Une revue systématique Cochrane d'études portant sur l'utilisation des VPC chez les enfants de <2 ans a révélé une efficacité vaccinale globale de 27% (intervalle de confiance à 95% [IC]: 15%-36%) contre les pneumonies confirmées par radiologie selon la définition de l'OMS, ce qui laisse supposer qu'au moins 27% des cas de pneumonie confirmés par radiologie pourraient être imputables à *S. pneumoniae*.[22] Une analyse de l'efficacité des VPC contre la pneumonie confirmée par radiologie chez les enfants de <5 ans a indiqué que la proportion de cas de pneumonie dus à *S. pneumoniae* était de 34% [plage d'incertitude: 26-36%];[6] on estime que la précision de ces estimations est meilleure que celle des estimations tirées des études sur les cas confirmés en laboratoire.

En moyenne, environ 75% des cas de PI et 83% des cas de méningite pneumococcique concernent des enfants de <2 ans, mais l'incidence et la distribution des cas selon l'âge peuvent varier selon le pays, la méthode d'étude et la situation socio-économique au sein de chaque pays. Des tendances saisonnières et climatiques ont été observées aussi bien pour la PI que pour la pneumonie contractée dans la communauté; ces tendances coïncidaient avec la circulation saisonnière des virus grippaux et du virus respiratoire syncytial, ce qui porte à croire que ces virus prédisposent à l'infection pneumococcique.[23-26]

Agent pathogène

S. pneumoniae est un diplocoque encapsulé à Gram positif. Sa capsule polyosidique est un facteur de virulence essentiel et les sérotypes pneumococciques sont définis sur la base des différences de composition de cette capsule. Les anticorps dirigés contre les polyosides capsulaires protègent contre la maladie. En général, l'immunité induite par une infection naturelle ou par la vaccination est spécifique au sérotype, mais une protection croisée est possible entre sérotypes apparentés (à savoir sérotypes 6A/6B, 6A/6C et 19A/19F).

[18] Memish ZA, et al. Epidemiology of invasive pneumococcal infection in children aged five years and under in Saudi Arabia: a five-year retrospective surveillance study. Int J Infect Dis. 2010;14(8):e708–12.

[19] Russell FM, et al. Invasive pneumococcal disease in Fiji: clinical syndromes, epidemiology, and the potential impact of pneumococcal conjugate vaccine. Pediatr Infect Dis J. 2010;29(9):870–2.

[20] Arifeen SE, et al. Invasive pneumococcal disease among children in rural Bangladesh: results from a population-based surveillance. Clin Infect Dis. 2009;48 Suppl 2:S103–13.

[21] Vuori-Holopainen E, et al. Reappraisal of lung tap: review of an old method for better etiologic diagnosis of childhood pneumonia. Clin Infect Dis. 2001;32:715–26.

[22] Lucero MG et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. Cochrane Database Systemic Review, 2009, 7:CD004977.

[23] Cilloniz C, et al. Seasonality of pathogens causing community-acquired pneumonia. Respirology. 2017;22(4):778–85.

[24] Numminen E, et al. Climate induces seasonality in pneumococcal transmission. Sci Rep. 2015;5:11344.

[25] Ben-Shimol S, et al. Seasonality of both bacteremic and nonbacteremic pneumonia coincides with viral lower respiratory tract infections in early childhood, in contrast to nonpneumonia invasive pneumococcal disease, in the pre-pneumococcal conjugate vaccine era. Clin Infect Dis. 2015;60(9):1384–7.

[26] Dangor Z, et al. Temporal association in hospitalizations for tuberculosis, invasive pneumococcal disease and influenza virus illness in South African children. PLoS One. 2014;9(3):e91464.

[18] Memish ZA, et al. Epidemiology of invasive pneumococcal infection in children aged five years and under in Saudi Arabia: a five-year retrospective surveillance study. Int J Infect Dis. 2010;14(8):e708–12.

[19] Russell FM, et al. Invasive pneumococcal disease in Fiji: clinical syndromes, epidemiology, and the potential impact of pneumococcal conjugate vaccine. Pediatr Infect Dis J. 2010;29(9):870–2.

[20] Arifeen SE, et al. Invasive pneumococcal disease among children in rural Bangladesh: results from a population-based surveillance. Clin Infect Dis. 2009;48 Suppl 2:S103–13.

[21] Vuori-Holopainen E, et al. Reappraisal of lung tap: review of an old method for better etiologic diagnosis of childhood pneumonia. Clin Infect Dis. 2001;32:715–26.

[22] Lucero MG et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. Cochrane Database Systemic Review, 2009, 7:CD004977.

[23] Cilloniz C, et al. Seasonality of pathogens causing community-acquired pneumonia. Respirology. 2017;22(4):778–85.

[24] Numminen E, et al. Climate induces seasonality in pneumococcal transmission. Sci Rep. 2015;5:11344.

[25] Ben-Shimol S, et al. Seasonality of both bacteremic and nonbacteremic pneumonia coincides with viral lower respiratory tract infections in early childhood, in contrast to nonpneumonia invasive pneumococcal disease, in the pre-pneumococcal conjugate vaccine era. Clin Infect Dis. 2015;60(9):1384–7.

[26] Dangor Z, et al. Temporal association in hospitalizations for tuberculosis, invasive pneumococcal disease and influenza virus illness in South African children. PLoS One. 2014;9(3):e91464.

While a wide variety of serotypes cause non-invasive diseases such as otitis media and sinusitis, fewer cause invasive disease. Serotypes 1, 5, 6A, 6B, 14, 19F and 23F are common causes of IPD globally in children <5 years of age. Before widespread use of PCV, serotypes 1, 5 and 14 together accounted for 28–43% of cases of IPD in children under 5 years worldwide and for about 30% of IPD in 20 of the world's poorest countries; serotypes 19F and 23F were responsible for 9–18% of cases globally. Serotype 18C was common in regions with larger proportions of high-income countries (Europe, North America and Oceania).[2] Some serotypes, such as 6B, 9V, 14, 19A, 19F and 23F, are more likely than others to be resistant to antimicrobials.[27]

Disease

Pneumococcal infection and disease can affect various organ systems. Bloodstream invasion results in bacteraemia that occasionally causes infection at secondary sites, such as the meninges, joints and peritoneum. In other instances, contiguous spread from the nasopharynx can cause diseases such as otitis media or sinusitis. Pneumonia is often caused by aspiration of pneumococci from the nasopharynx and may also be caused by blood-borne spread. When associated with bacteraemia, pneumonia is classified as IPD.[22] As IPD can be diagnosed unambiguously by microbiology, its incidence is frequently used as a measure of the incidence of severe pneumococcal disease in general.

Case fatality rates from IPD in children can be high, ranging up to 20% for septicaemia and 50% for meningitis in LMICs. Long-term neurological sequelae such as hearing loss, mental retardation, motor abnormalities and seizures have been observed in 24.7% (interquartile range, 16.2–35.3%) of survivors of childhood pneumococcal meningitis; the risk of sequelae was 3 times higher among survivors in Africa and Asia than among those in Europe.[28] Pneumococcal middle-ear infection and sinusitis are less severe clinical manifestations, but they are considerably more common health problems worldwide and represent a high economic burden, particularly in countries where out-of-pocket expenditure constitutes a large proportion of health expenditure. They also result in significant consumption of antimicrobials.

Lack of exclusive breastfeeding, nutritional deficiency and indoor air pollution are risk factors for pneumonia, including pneumococcal pneumonia, in infants and young children.[29] In addition to the high incidence of

De nombreux sérotypes différents peuvent provoquer des affections non invasives, comme l'otite moyenne ou la sinusite, mais les maladies invasives sont causées par un nombre plus restreint de sérotypes. Les sérotypes 1, 5, 6A, 6B, 14, 19F et 23F sont le plus souvent responsables des PI observées chez l'enfant de <5 ans à l'échelle mondiale. Avant que les VPC ne soient utilisés à grande échelle, les sérotypes 1, 5 et 14 étaient à l'origine de 28-43% des cas de PI parmi les enfants de <5 ans à l'échelle mondiale et d'environ 30% des cas dans 20 des pays les plus pauvres de la planète; les sérotypes 19F et 23F étaient responsables de 9-18% des cas dans le monde. Le sérotype 18C était fréquemment observé dans les régions comptant une plus forte proportion de pays à revenu élevé (Europe, Amérique du Nord et Océanie).[2] Certains sérotypes, tels que 6B, 9V, 14, 19A, 19F et 23 F, sont plus susceptibles que les autres de présenter une résistance aux antimicrobiens.[27]

Maladie

L'infection pneumococcique et la maladie qui en résulte peuvent toucher divers systèmes de l'organisme. Lorsque la bactérie envahit la circulation sanguine, elle provoque une bactériémie pouvant occasionnellement s'étendre à des sites secondaires, comme les méninges, les articulations et le péritoine. Dans d'autres cas, une propagation contiguë à partir du rhinopharynx peut entraîner des affections telles qu'une otite moyenne ou une sinusite. La pneumonie résulte souvent de l'aspiration des pneumocoques présents dans le rhinopharynx, mais elle peut aussi être imputable à une propagation par voie sanguine. Lorsqu'elle est associée à une bactériémie, la pneumonie est catégorisée comme une PI.[22] Comme le diagnostic microbiologique de la PI est dépourvu d'ambiguïté, on utilise souvent l'incidence de cette maladie comme mesure de l'incidence des pneumococcies graves en général.

Le taux de létalité de la PI peut être élevé chez les enfants, allant jusqu'à 20% pour la septicémie et 50% pour la méningite dans les pays à revenu faible ou intermédiaire. Des séquelles neurologiques de longue durée, telles qu'une perte auditive, un retard mental, des troubles moteurs et des convulsions, ont été observés chez 24,7% (intervalle interquartile: 16,2-35,3%) des sujets ayant survécu à une méningite pneumococcique pendant l'enfance; le risque de séquelles chez les survivants est 3 fois plus important en Afrique et en Asie qu'en Europe.[28] L'otite moyenne et la sinusite pneumococciques présentent des manifestations cliniques moins graves, mais sont des problèmes de santé publique beaucoup plus répandus à l'échelle mondiale, qui représentent une lourde charge économique, en particulier dans les pays où les frais payés directement par les patients constituent une large proportion des dépenses de santé. Elles entraînent en outre une consommation considérable d'antimicrobiens.

Chez le nourrisson et le jeune enfant, l'absence d'un allaitement au sein exclusif, les carences nutritionnelles et la pollution intérieure sont des facteurs de risque de pneumonie, y compris de pneumonie à pneumocoques.[29] Outre la forte incidence observée

[27] Kyaw MH, et al. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. N Engl J Med. 2006;354:1455–63.

[28] Edmond K, et al. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. Lancet Infect Dis. 2010;10(5):317–28.

[29] Global action plan for prevention and control of pneumonia (GAPP): report of an informal consultation. Geneva: World Health Organization, 2008 (http://www.who.int/maternal_child_adolescent/documents/9789241596336/en/, accessed May 2018).

[27] Kyaw MH, et al. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. N Engl J Med. 2006;354:1455–63.

[28] Edmond K, et al. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. Lancet Infect Dis. 2010;10(5):317–28.

[29] Global action plan for prevention and control of pneumonia (GAPP): report of an informal consultation. Genève, Organisation mondiale de la Santé, 2008 (http://www.who.int/maternal_child_adolescent/documents/9789241596336/en/, consulté en mai 2018).

pneumococcal disease in children <2 years of age, the risk is also increased in individuals with chronic medical conditions such as heart disease, lung disease, diabetes, sickle-cell anaemia, asplenia or other conditions that suppress the immune system, such as advanced HIV infection. Development of pneumococcal resistance to commonly used antimicrobials such as penicillins, macrolides, cephalosporins and co-trimoxazole is a serious problem in some parts of the world. Since large-scale introduction of pneumococcal vaccination, however, a reduction in the circulation of antimicrobial-resistant strains has been observed; among children under 2 years of age, disease caused by strains that are not susceptible to penicillins decreased from 70.3 to 13.1 cases per 100 000 (a decrease of 81%).[27]

Diagnosis

While clinical diagnosis of pneumonia or meningitis is based on symptoms, signs and radiological tests, diagnosis of pneumococcal disease requires laboratory confirmation. A definitive diagnosis of pneumococcal infection is made by isolating the bacterium from blood or other normally sterile body sites, such as cerebrospinal fluid; however, etiological diagnosis is usually not possible in cases of non-bacteraemic pneumococcal disease, such as pneumonia and otitis media, as biological specimens are usually not available for testing. Rapid diagnostic tests, such as for antigens, and polymerase chain reaction assays are increasingly used, especially for the diagnosis of pneumococcal meningitis; these tests are more sensitive than bacterial culture, especially in patients pretreated with antimicrobials.

Treatment

Pneumococcal disease can be treated with antimicrobials. The choice of antimicrobial and the duration of treatment depend on the site of infection and the pattern of susceptibility to antimicrobials; the outcome depends on age, disease syndrome, severity, duration of illness before initiation of treatment and susceptibility to the antimicrobials used.

Naturally acquired immunity

The risk of pneumococcal disease decreases after early childhood and increases again in old age, suggesting acquisition of natural immunity and loss of immunity in older adults due to immunosenescence and increased susceptibility due to other diseases. The mechanisms of natural immunity are not fully understood, although antibodies to capsular polysaccharide, protein antigens and cell-mediated immune responses are thought to contribute.[30, 31]

chez l'enfant de <2 ans, le risque de pneumococcie est également plus élevé chez les sujets présentant une affection médicale chronique, comme une cardiopathie, une pneumopathie, un diabète, une anémie falciforme, une asplénie ou d'autres pathologies qui provoquent une dépression du système immunitaire, telles que l'infection à VIH à un stade avancé. L'acquisition par les pneumocoques d'une résistance aux antibiotiques d'usage courant, comme les pénicillines, les macrolides, les céphalosporines et le cotrimoxazole, représente un grave problème dans certaines parties du monde. Toutefois, depuis que la vaccination antipneumococcique a été mise en place à grande échelle, on a observé une baisse de la circulation des souches résistantes aux antimicrobiens; parmi les enfants de <2 ans, le nombre de cas de maladies dues à des souches non sensibles aux pénicillines a régressé de 81%, passant de 70,3 à 13,1 cas pour 100 000.[27]

Diagnostic

Le diagnostic clinique de la pneumonie ou de la méningite repose sur l'observation des symptômes et sur des tests radiologiques, mais une confirmation en laboratoire est nécessaire pour établir le diagnostic de la pneumococcie. Les infections à pneumocoques peuvent être diagnostiquées avec certitude en isolant la bactérie à partir du sang ou d'un autre site normalement stérile de l'organisme, comme le liquide céphalorachidien; cependant, dans le cas des pneumococcies non bactériémiques, telles que la pneumonie ou l'otite moyenne, le diagnostic étiologique n'est souvent pas possible car les échantillons biologiques ne sont généralement pas disponibles pour l'analyse. Les tests de diagnostic rapide, reposant par exemple sur la détection des antigènes, et les essais d'amplification en chaîne par polymérase sont de plus en plus souvent employés, en particulier pour le diagnostic de la méningite pneumococcique. Ces tests sont plus sensibles que la culture bactérienne, surtout chez les patients préalablement traités par des antimicrobiens.

Traitement

La pneumococcie peut être traitée au moyen d'antimicrobiens. Le choix de l'antimicrobien et la durée du traitement dépendent du site d'infection et du profil de sensibilité aux antimicrobiens. L'issue du traitement dépend de l'âge, du syndrome pathologique, de la gravité de la maladie, du temps écoulé entre son apparition et le début du traitement et de la sensibilité de l'agent pathogène aux antimicrobiens utilisés.

Immunité acquise naturellement

Le risque de pneumococcie diminue après la petite enfance mais recommence à augmenter chez les personnes âgées, ce qui laisse supposer qu'une immunité naturelle est acquise et que cette immunité décline chez les personnes âgées en raison de l'immunosénescence et d'une sensibilité accrue liée à d'autres maladies. Les mécanismes de l'immunité naturelle ne sont pas entièrement connus, mais on pense que les anticorps dirigés contre les polyosides capsulaires, les antigènes protéiques et les réponses immunitaires à médiation cellulaire contribuent à l'acquisition de cette immunité.[30, 31]

[30] Malley R. Antibody and cell-mediated immunity to *Streptococcus pneumoniae*: implications for vaccine development. J Mol Med (Berl) 2010; 88(2): 135-142.

[31] Francis JP, et al. A longitudinal study of natural antibody development to pneumococcal surface protein A families 1 and 2 in Papua New Guinean Highland children: a cohort study. Pneumonia (Nathan Qld). 2016;8:12.

[30] Malley R. Antibody and cell-mediated immunity to *Streptococcus pneumoniae*: implications for vaccine development. J Mol Med (Berl) 2010; 88(2): 135-142.

[31] Francis JP, et al. A longitudinal study of natural antibody development to pneumococcal surface protein A families 1 and 2 in Papua New Guinean Highland children: a cohort study. Pneumonia (Nathan Qld). 2016;8:12.

Pneumococcal conjugate vaccines

Two polysaccharide-protein conjugate vaccines have been on the market since 2009: the 10-valent (PCV10) and the 13-valent (PCV13) vaccines. Previously, a 7-valent pneumococcal conjugate vaccine (PCV7) was available, and at least 9 other pneumococcal conjugate vaccines containing 10–20 serotypes are undergoing trials in humans. WHO has developed a set of principles to ensure the quality, safety and efficacy of these vaccines.[32] This position paper pertains to the currently licensed PCV10 and PCV13 used in children <5 years of age. The recommendations in this paper do not necessarily apply to products that become available in the future. Data on other PCV formulations, including the previously licensed PCV7 and the 9- and 11-valent conjugate vaccines that were evaluated in phase-3 clinical trials in Africa and Asia but were not licensed, are referred to where relevant to the use of PCV10 and PCV13.

Vaccine characteristics, content, dosage, administration and storage

PCV10 is composed of capsular polysaccharides purified from 10 serotypes: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. Each capsular polysaccharide is conjugated to a carrier protein, either protein D (an outer membrane protein from non-typable *Haemophilus influenzae*), tetanus toxoid or diphtheria toxoid. Protein D is used as the carrier protein for 8 of the 10 serotypes (1, 4, 5, 6B, 7F, 9V, 14 and 23F); 19F is conjugated to diphtheria toxoid and serotype 18C to tetanus toxoid.[33]

PCV10 contains the adjuvant aluminium phosphate and is presented in a single-dose syringe, a single-dose vial without preservative or a 4-dose vial that contains 2-phenoxyethanol as the preservative. The volume per dose is 0.5 mL. Each vaccine dose contains 1 µg each of the polysaccharide of serotypes 1, 5, 6B, 7F, 9V, 14 and 23F and 3 µg each of the serotype-specific polysaccharide of serotypes 4, 18C and 19F.

PCV13 contains the capsular polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, individually conjugated to a nontoxic diphtheria cross-reactive material (CRM197) carrier protein. A 0.5-mL PCV13 dose contains approximately 2.2 µg of polysaccharide from each of 12 serotypes and approximately 4.4 µg of polysaccharide from serotype 6B. The vaccine contains aluminium phosphate as an adjuvant. PCV13 is available as a single-dose pre-filled syringe, in a single-

[32] Recommendations to assure the quality, safety and efficacy of pneumococcal conjugate vaccines (WHO Technical Report Series, No. 977, Annex 3). Geneva: World Health Organization; 2013

[33] Synflorix: pneumococcal polysaccharide conjugate vaccine (adsorbed). London: European Medicines Agency; undated (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000973/WC500054346.pdf, accessed May 2018).

Vaccins antipneumococciques conjugués

Deux vaccins conjugués polyoside-protéine sont commercialisés depuis 2009: un vaccin 10-valent (VPC10) et un vaccin 13-valent (VPC13). Auparavant, un vaccin antipneumococcique conjugué 7-valent (VPC7) était également disponible et actuellement, au moins 9 autres vaccins antipneumococciques conjugués contenant 10 à 20 sérotypes font l'objet d'essais chez l'homme. L'OMS a défini une série de principes pour garantir la qualité, l'innocuité et l'efficacité de ces vaccins.[32] La présente note de synthèse traite des vaccins VPC10 et VPC13 actuellement homologués pour une utilisation chez les enfants de <5 ans. Les recommandations formulées dans cette note ne s'appliquent pas nécessairement aux produits futurs. Dans la mesure où elles sont pertinentes pour le VPC10 et VPC13, la présente note mentionne certaines données relatives à d'autres formulations du VPC, y compris le VPC7 précédemment homologué et les vaccins conjugués 9-valent et 11-valent qui ont été évalués dans le cadre d'essais cliniques de phase 3 en Afrique et en Asie mais qui n'ont pas été homologués.

Propriétés, contenu, dosage, administration et conservation des vaccins

Le VPC10 est constitué de polyosides capsulaires purifiés provenant de 10 sérotypes, à savoir 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F et 23F. Chaque polyoside capsulaire est conjugué à une protéine porteuse, qui peut être soit la protéine D (une protéine de la membrane externe d'*Haemophilus influenzae* non typable), soit l'anatoxine tétanique, soit encore l'anatoxine diphtérique. La protéine D est utilisée comme protéine porteuse pour 8 des 10 sérotypes (1, 4, 5, 6B, 7F, 9V, 14 et 23F); le sérotype 19F est conjugué à l'anatoxine diphtérique et le sérotype 18C à l'anatoxine tétanique.[33]

Le VPC10 est adjuvanté avec du phosphate d'aluminium et se présente sous forme d'une seringue à dose unique, d'un flacon à dose unique sans agent conservateur ou d'un flacon à 4 doses contenant du 2-phénoxyéthanol comme conservateur. Le volume d'une dose est de 0,5 ml. Chaque dose de vaccin contient 1 µg de polyoside de chacun des sérotypes 1, 5, 6B, 7F, 9V, 14 et 23F et 3 µg de polyoside de chacun des sérotypes 4, 18C et 19F.

Le VPC13 contient les polyosides capsulaires des sérotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F et 23F, chacun étant conjugué à la protéine diphtérique CRM197 non toxique (CRM=substance à réactivité croisée), qui sert de protéine porteuse. Une dose de 0,5 ml de VPC13 contient environ 2,2 µg de polyoside par sérotype pour 12 des sérotypes et environ 4,4 µg de polyoside pour le sérotype 6B. Le vaccin est adjuvanté avec du phosphate d'aluminium. Le VPC13 est disponible sous forme de seringue préremplie à dose unique, de flacon à dose

[32] Recommendations to assure the quality, safety and efficacy of pneumococcal conjugate vaccines (WHO Technical Report Series, No. 977, Annex 3). Genève, Organisation mondiale de la Santé; 2013

[33] Synflorix: pneumococcal polysaccharide conjugate vaccine (adsorbed). London: European Medicines Agency; undated (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000973/WC500054346.pdf, consulté en mai 2018).

dose vial without preservative or in a 4-dose vial that contains 2-phenoxyethanol as the preservative.[34, 35, 36]

The storage temperature for both PCV10 and PCV13 recommended by the manufacturers is 2–8 °C, and the vaccines must not be frozen. The 1- and 4-dose vials of both vaccines come with a Vaccine Vial Monitor 30.

A systematic review and meta-analysis of data on IPD serotypes from children <5 years during the period 1980–2007 (i.e. before national introduction of PCV in the country of the study) showed that the serotypes in PCV10 and PCV13 cover ≥70% of IPD in each geographical region (range, 70–84% for PCV10 and 74–88% for PCV13).[2]

Although the details of labelling may differ by country, both PCV10 and PCV13 are prequalified by WHO and licensed for active vaccination for the prevention of IPD, pneumonia and acute otitis media caused by the respective vaccine serotypes of *S. pneumoniae* in infants and children aged from 6 weeks to 5 years.[36, 37] The vaccines are given by injection into the anterolateral aspect of the thigh of infants and into the deltoid from the second year of life onwards. For PCV10 and PCV13, the manufacturers recommend 3 primary doses at an interval of at least 4 weeks, plus a booster dose at least 6 months after the third dose (3p+1 schedule). The first dose can be given as early as 6 weeks of age; the booster dose is given preferably between 9 and 15 months of age. An alternative schedule consists of 2 primary doses given 2 months apart, starting at 2 months of age (6 weeks for PCV10), followed by a booster dose at least 6 months after the second dose (2p+1 schedule) for PCV10 and at 11–15 months of age for PCV13.

The manufacturers further recommend that previously unvaccinated infants aged 7–11 months should receive 2 doses, the second dose at least 4 weeks after the first, followed by a third dose in the second year of life at an interval of at least 2 months after the last primary dose. For PCV10, it is recommended that unvaccinated children aged 12 months to 5 years receive 2 doses, with an interval of at least 2 months between the first and second dose. For PCV13, unvaccinated children aged 12–23 months should receive 2 doses at an interval of at least 2 months, and children aged 2–5 years should receive a single dose.

unique sans agent conservateur ou de flacon à 4 doses contenant du 2-phénoxyéthanol comme conservateur.[34, 35, 36]

Pour le VPC10 comme pour le VPC13, la température de stockage recommandée par les fabricants est de 2-8 °C et les vaccins ne doivent pas être congelés. Les flacons à dose unique et les flacons à 4 doses des deux vaccins sont munis d'une pastille de contrôle des vaccins VVM30.

Une revue systématique et une méta-analyse des données relatives aux sérotypes responsables de la PI recueillies chez des enfants de <5 ans dans la période 1980-2007 (c'est-à-dire avant l'introduction nationale des VPC dans les pays étudiés) ont montré que les sérotypes contenus dans le VPC10 et le VPC13 étaient à l'origine de ≥70% des cas de PI dans chaque région géographique (plages de valeurs: 70-84% pour le VPC10 et 74-88% pour le VPC13).[2]

Bien que certains détails de l'étiquetage puissent varier d'un pays à l'autre, le VPC10 et le VPC13 sont tous deux préqualifiés par l'OMS et homologués pour une vaccination active aux fins de la prévention de la PI, de la pneumonie et de l'otite moyenne aiguë provoquées par les sérotypes correspondants de *S. pneumoniae* chez les nourrissons et les jeunes enfants âgés de 6 semaines à 5 ans.[36, 37] Les vaccins sont administrés par injection dans la face antérolatérale de la cuisse chez le nourrisson et dans le muscle deltoïde à partir de la deuxième année de vie. Pour le VPC10 et le VPC13, les fabricants recommandent d'administrer 3 doses de primovaccination espacées d'au moins 4 semaines, suivies d'un rappel au moins 6 mois après la troisième dose (schéma 3p+1). La première dose peut être administrée dès l'âge de 6 semaines, la dose de rappel étant injectée de préférence entre les âges de 9 et 15 mois. Un autre schéma possible consiste à administrer 2 doses de primovaccination espacées de 2 mois à partir de l'âge de 2 mois (6 semaines pour le VPC10), suivies d'une dose de rappel au moins 6 mois après la deuxième dose pour le VPC10 (schéma 2p+1) et à l'âge de 11-15 mois pour le VPC13.

En outre, chez les nourrissons de 7 à 11 mois qui n'ont pas encore été vaccinés, les fabricants recommandent l'administration de 2 doses espacées d'au moins 4 semaines, suivies d'une troisième dose au cours de la deuxième année de vie, au moins 2 mois après la dernière dose de primovaccination. Pour le VPC10, il est recommandé que les enfants non vaccinés âgés de 12 mois à 5 ans reçoivent 2 doses, avec un intervalle d'au moins 2 mois entre la première et la seconde dose. Pour le VPC13, les enfants non vaccinés âgés de 12 à 23 mois doivent recevoir 2 doses espacées d'au moins 2 mois, et ceux qui ont entre 2 et 5 ans ne doivent recevoir qu'une seule dose.

[34] Approved products: Prevnar 13: pneumococcal 13-valent conjugate vaccine (diphtheria CRM 197 protein). Washington DC: Food and Drug Administration; 2018 (https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM574852.pdf, accessed May 2018).

[35] Prevenar 13: Annex 1: Summary of product characteristics. London: European Medicines Agency; undated (https://www.ema.europa.eu/documents/product-information/prevenar-13-epar-product-information_en.pdf, accessed December 2018)

[36] WHO prequalified vaccines. Pneumococcal (conjugate) Prevenar 13 multidose vial. Geneva: World Health Organization (https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID =317, accessed May 2018).

[37] WHO prequalified vaccines. Pneumococcal (conjugate) Synflorix multidose vial. Geneva: World Health Organization (https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID =341, accessed January 2019).

[34] Approved products: Prevnar 13: pneumococcal 13-valent conjugate vaccine (diphtheria CRM 197 protein). Washington DC: Food and Drug Administration; 2018 (https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM574852.pdf, consulté en mai 2018).

[35] Prevenar 13: Annex 1: Summary of product characteristics. London: European Medicines Agency; undated (https://www.ema.europa.eu/documents/product-information/prevenar-13-epar-product-information_en.pdf, consulté en décembre 2018)

[36] WHO prequalified vaccines. Pneumococcal (conjugate) Prevenar 13 multidose vial. Genève, Organisation mondiale de la Santé (https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID =317, consulté en mai 2018).

[37] WHO prequalified vaccines. Pneumococcal (conjugate) Synflorix multidose vial. Genève, Organisation mondiale de la Santé (https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID =341, consulté en janvier 2019).

Serological criteria for evaluation of immunological responses to pneumococcal conjugate vaccines

WHO has defined serological criteria for non-inferiority that should be used in the primary analysis of studies of immunological responses to PCV.[32] The criteria are: (i) the percentage of PCV recipients with serotype-specific immunoglobulin G ≥0.35 µg/mL (hereafter referred to as "percentage of responders") in a WHO reference assay (or an alternative, well-justified threshold based on a specific in-house assay) and (ii) the serotype-specific immunoglobulin G geometric mean concentration (GMC) measured 4 weeks after completion of the primary infant vaccination series. In view of the efficacy of PCV7 and the experimental PCV9 against IPD, it is reasonable to use the proportion of infants with an antibody concentration ≥0.35 µg/mL as a marker of efficacy. It is unknown whether a lower serotype-specific GMC of antibody indicates less efficacy for those serotypes. The threshold is meant to be used to establish non-inferiority against the reference PCV in aggregate, and no serotype-specific thresholds have been defined.

Immunogenicity, efficacy and effectiveness

The recommendations in this position paper are based on a systematic review of primary evidence from the literature on the immunogenicity and effectiveness against clinical disease (IPD and pneumonia) and NP carriage (which provides an indication of potential indirect effects of vaccination) of the 2 available PCV products used either as 3 primary doses with no booster (3p+0) or a 2p+1 schedule; studies that included schedules of 2 primary doses with no booster (2p+0) and 3p+1 were included when technically relevant.[38]

Both PCV10 and PCV13 have been shown to be safe and effective and to have both direct (in vaccinated individuals) and indirect (in unvaccinated individuals living in communities with vaccinated children) effects against pneumococcal disease caused by vaccine serotypes when used in a 3-dose schedule (either 2p+1 or 3p+0) or in a 4-dose schedule (3p+1). There is substantial evidence of the impact of each schedule on disease in various routine use settings. There are "head-to-head" studies[39] of effects on immunogenicity and NP carriage but not on the effects of products or schedules on disease outcomes.

The results of the analysis of choice of schedules and of products are briefly summarized here.

Choice of schedule

In head-to-head studies on immunogenicity, after the primary series, the 2p+1 schedule resulted in lower

[38] Pneumococcal conjugate vaccine review of impact evidence (PRIME): summary of findings from systematic review, October 2017. Geneva: World Health Organization; 2017 (http://www.who.int/immunization/sage/meetings/2017/october/3_FULL_PRIME_REPORT_2017Sep26.pdf?ua=1, accessed July 2018).

[39] In "head-to-head" studies, 2 drug or treatment schedules are compared directly.

Critères sérologiques pour l'évaluation de la réponse immunologique aux vaccins antipneumococciques conjugués

L'OMS a défini des critères sérologiques de non-infériorité qu'il convient d'utiliser lors de l'analyse primaire des études de la réponse immunologique aux VPC.[32] Ces critères sont les suivants: i) le pourcentage de sujets vaccinés par les VPC qui présentent un taux ≥0,35 µg/ml d'immunoglobulines G spécifiques aux sérotypes concernés (ci-après «pourcentage de sujets répondant à la vaccination») dans le cadre d'un test de référence de l'OMS (ou une autre valeur seuil justifiée sur la base d'un test effectué en interne) et b) la moyenne géométrique des titres d'immunoglobulines G spécifiques aux sérotypes concernés, mesurée 4 semaines après la fin de la série de primovaccination chez le nourrisson. Compte tenu de l'efficacité du VPC7 et du VPC9 expérimental contre la PI, il est raisonnable d'utiliser la proportion de nourrissons présentant un taux d'anticorps ≥0,35 µg/ml comme indicateur de l'efficacité. On ne sait pas si une moyenne géométrique plus faible des titres d'anticorps pour un sérotype donné est révélatrice d'une efficacité réduite contre ce sérotype. La valeur seuil sert à établir la non-infériorité globale d'un vaccin par rapport au VPC de référence et aucun seuil propre à chaque sérotype n'a été défini.

Immunogénicité et efficacité

Les recommandations formulées dans la présente note de synthèse reposent sur une revue systématique des données primaires issues de la littérature concernant l'immunogénicité et l'efficacité vaccinale contre les pathologies cliniques (PI et pneumonie) et le portage rhinopharyngé (qui fournit une indication des effets indirects potentiels de la vaccination) pour les 2 produits vaccinaux disponibles, administrés soit sous forme de 3 doses de primovaccination sans dose de rappel (3p+0), soit selon un schéma 2p+1. Lorsqu'elles étaient pertinentes sur le plan technique, les études portant sur des schémas à 2 doses de primovaccination sans rappel (2p+0) et 3p+1 ont été prises en compte.[38]

Il a été démontré que le VPC10 et le VPC13 sont tous deux efficaces et sans danger et qu'ils ont des effets à la fois directs (chez les personnes vaccinées) et indirects (chez les sujets non vaccinés vivant dans des communautés comptant des enfants vaccinés) contre les pneumococcies provoquées par les sérotypes vaccinaux lorsqu'ils sont administrés selon un schéma à 3 doses (soit 2p+1, soit 3p+0) ou à 4 doses (3p+1). De nombreuses données démontrent l'impact de chacun de ces schémas d'administration sur la maladie dans différents contextes d'administration systématique. Il existe des études de comparaison directe[39] concernant les effets des produits ou des schémas d'administration sur l'immunogénicité et le portage rhinopharyngé, mais pas sur les issues de la maladie.

Les conclusions relatives au choix du schéma d'administration et du produit sont brièvement résumées ci-après.

Choix du schéma d'administration

Dans les études de comparaison directe de l'immunogénicité, après la série de primovaccination, le schéma 2p+1 a donné

[38] Pneumococcal conjugate vaccine review of impact evidence (PRIME): summary of findings from systematic review, October 2017. Genève, Organisation mondiale de la Santé; 2017 (http://www.who.int/immunization/sage/meetings/2017/october/3_FULL_PRIME_REPORT_2017Sep26.pdf?ua=1, consulté en juillet 2018).

[39] In "head-to-head" studies, 2 drug or treatment schedules are compared directly.

GMCs of antibody than the 3p+0 schedule but a similar percentage of responders for most serotypes, except serotypes 6A and 6B, for which a 3p+0 schedule resulted in both higher GMCs and a higher percentage of responders than with the 2 primary doses in the 2p+1 schedule. After the third dose of each schedule (post-booster for 2p+1 and post-primary for 3p+0), the 2p+1 schedule resulted in higher GMCs but a similar percentage of responders as compared with a 3p+0 schedule for most serotypes, except for serotype 6B, for which the percentage of responders was higher with the 2p+1 schedule.

une moyenne géométrique des titres d'anticorps plus faible que le schéma 3p+0, mais une proportion semblable de sujets ayant répondu à la vaccination pour la plupart des sérotypes, à l'exception des sérotypes 6A et 6B, pour lesquels le schéma 3p+0 s'est soldé par une moyenne géométrique des titres plus élevée ainsi qu'un pourcentage plus important de sujets répondant à la vaccination par rapport aux 2 doses de primovaccination du schéma 2p+1. Après l'administration de la troisième dose de chaque schéma (post-rappel pour 2p+1 et post-primovaccination pour 3p+0), le schéma 2p+1 a donné une moyenne géométrique des titres plus élevée, mais un pourcentage comparable de sujets répondant à la vaccination, par rapport au schéma 3p+0 pour la majorité des sérotypes, à l'exception du sérotype 6B, pour lequel le pourcentage de personnes répondant à la vaccination était plus important avec le schéma 2p+1.

Evidence from ecological and case–control studies indicates that both schedules reduce the burden of IPD due to vaccine serotypes in both vaccinated (direct effects) and unvaccinated (indirect effects) members of the population. Evaluation of which schedule is better is, however, confounded by factors such as previous population exposure to PCV7 and differences in baseline IPD incidence. Data on the impact on IPD of the 2p+1 schedule are available mainly from high-income countries in which PCV13 is used, PCV7 was used previously, and there is a low baseline incidence of IPD, whereas data on the impact of the 3p+0 schedule are mainly from LMICs in which PCV10 is used, PCV7 was not used previously and there is a high baseline IPD incidence. Because of the booster dose in the 2p+1 schedule and the older age at which it is given, this schedule may provide longer protection and have greater indirect effects than the 3p+0 schedule.

Les données issues d'études écologiques et d'études cas-témoins indiquent que les deux schémas entraînent une diminution de la charge des PI imputables aux sérotypes vaccinaux, à fois chez les sujets vaccinés (effets directs) et chez les personnes non vaccinées (effets indirects) appartenant à la population concernée. Il est toutefois difficile de déterminer quel schéma est le meilleur car cette évaluation est sujette à plusieurs facteurs de confusion, notamment l'exposition antérieure de la population au VPC7 ou des incidences de départ différentes de la PI. Les données dont on dispose concernant l'impact du schéma 2p+1 sur la PI proviennent essentiellement de pays à revenu élevé qui utilisent le VPC13, où le VPC7 avait déjà été administré et où l'incidence de départ de la PI est faible, tandis que les données relatives à l'impact du schéma 3p+0 viennent principalement de pays à revenu faible ou intermédiaire qui utilisent le VPC10, où le VPC7 n'a jamais été administré et où l'incidence de départ de la PI est forte. Étant donné que le schéma 2p+1 contient une dose de rappel et qu'il est administré à un âge plus avancé, il pourrait conférer une protection de plus longue durée et avoir des effets indirects plus marqués que le schéma 3p+0.

The evidence for an impact on pneumonia of each schedule depends on the pneumonia outcome studied (radiologically confirmed pneumonia, empyema or pneumococcal pneumonia), and more data were available for the 2p+1 than for the 3p+0 schedule. The evidence does not indicate an advantage of one schedule over the other in preventing pneumonia.

Les données dont on dispose concernant l'impact de chacun de ces schémas sur la pneumonie dépendent de l'affection pneumonique étudiée (pneumonie confirmée par examen radiologique, empyème ou pneumonie à pneumocoques) et sont plus nombreuses pour le schéma 2p+1 que pour le schéma 3p+0. Les données disponibles ne permettent pas de conclure à la supériorité d'un schéma par rapport à l'autre en termes de prévention de la pneumonie.

Few data were available on the association between different schedules and mortality, and no conclusions could be drawn.

Pour ce qui est du lien entre les différents schémas et la mortalité, les données disponibles sont insuffisantes pour tirer une conclusion.

Evidence for the impact of different schedules on NP carriage in different settings was inconclusive, as it is confounded by factors including use of PCV7 before the introduction of PCV10/13, the PCV product used and differences in the baseline prevalence of carriage. Nevertheless, 2 studies in which PCV10 was used in the 2p+1 or 3p+0 schedules showed that both were effective in reducing vaccine-type NP carriage, with no significant difference; both studies were small and conducted in low-carriage settings.

Les données relatives à l'effet des différents schémas sur le portage rhinopharyngé dans divers contextes n'étaient pas concluantes, car elles sont sujettes à des facteurs de confusion, comme l'utilisation du VPC7 avant l'introduction du VPC10 ou du VPC13, le produit VPC employé et les différences en termes de prévalence de départ du portage. Toutefois, 2 études dans lesquelles le VPC10 a été administré selon les schémas 2p+1 et 3p+0 ont montré l'efficacité des deux approches pour réduire le portage rhinopharyngé des sérotypes vaccinaux, sans différence majeure entre les deux; ces 2 études ont été menées à petite échelle et dans des contextes de faible portage.

Product choice

Both PCV10 and PCV13 induce antibodies against the serotypes common to both vaccines (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F). Although the mean antibody response to the common serotypes differed with the 2 products, in general, they induced comparable immunogenicity, as assessed by the proportion of children with protective antibody levels; however, no head-to-head studies of protective levels were available. The clinical implications, if any, of the relatively small differences in immunogenicity against the common serotypes have not been established.

PCV13 has 3 additional serotypes, 3, 6A and 19A. PCV13 induces an immune response to serotype 3; PCV10 contains neither serotype 3 nor any cross-reactive serotype, and immunogenicity against serotype 3 is not measured in studies of this vaccine. Both PCV10 and PCV13 induce an antibody response to serotype 6A, which is included in PCV13 but not in PCV10; in PCV10, this is thought to be due to cross-reactivity with serotype 6B. Evidence indicates that PCV13 induces higher serotype 6A GMCs and a higher percentage of responders than PCV10. Both PCV10 and PCV13 induce an antibody response against serotype 19A, although PCV13 induces higher serotype 19A GMCs and a higher percentage of responders than PCV10; for PCV10, the antibody response against serotype 19A is thought to be due to cross-reactivity with serotype 19F.

Although no head-to-head studies of the impact or effectiveness of the 2 products on IPD outcomes have been reported, the available evidence indicates that both products are effective in reducing overall vaccine-type IPD in both vaccinated and unvaccinated individuals. Although PCV13 contains 3 additional serotypes, there is currently insufficient evidence to determine whether they change the impact on overall IPD burden (vaccine-type and non-vaccine-type disease combined).

PCV10 use did not reduce IPD due to serotype 3 in either vaccine-eligible or non-eligible age groups, as it does not contain serotype 3. Despite immunogenicity data, evidence for a direct or indirect reduction in IPD due to serotype 3 after administration of PCV13 was inconclusive, although most studies showed no effect.

Few data are available on the impact of PCV10 on IPD due to serotype 6A, but they generally indicate a direct effect. Most assessments of the effects of PCV13 on IPD due to serotype 6A were conducted in settings in which there had been prior use of PCV7, with a residual low burden of serotype 6A IPD remaining after use of PCV7 in both vaccine-eligible and non-eligible cohorts. In the only reported case-control study, effectiveness against serotype 6A was observed.

Four case–control studies and an indirect cohort study of the effectiveness of PCV10 indicate a protective effect against serotype 19A IPD in vaccinated children, although not all the results reached statistical signifi-

Choix du produit

Le VPC10 et le VPC13 induisent tous deux une production d'anticorps dirigés contre les sérotypes communs aux deux vaccins (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F et 23F). Bien que la réponse moyenne en anticorps contre ces sérotypes communs soit différente entre les 2 produits, l'immunogénicité induite, mesurée par la proportion d'enfants présentant des titres protecteurs d'anticorps, est généralement comparable entre les 2 produits; cependant, il n'existe aucune étude de comparaison directe des titres protecteurs. Les conséquences cliniques, s'il y en a, des différences relativement faibles de l'immunogénicité contre les sérotypes communs n'ont pas été déterminées.

Le VPC13 contient 3 sérotypes supplémentaires, 3, 6A et 19A. Le VPC13 induit une réponse immunitaire au sérotype 3; le VPC10 ne contient ni de sérotype 3, ni de sérotype à réactivité croisée, et l'immunogénicité contre le sérotype 3 n'est pas mesurée dans les études portant sur ce vaccin. Le VPC10 et le VPC13 induisent tous deux une réponse en anticorps contre le sérotype 6A, qui est contenu dans le VPC13 mais pas le VPC10; dans le cas du VPC10, on pense que cette réponse est imputable à une réactivité croisée avec le sérotype 6B. Les données indiquent qu'avec le VPC13, la moyenne géométrique des titres d'anticorps contre le sérotype 6A et le pourcentage de sujets répondant à la vaccination sont plus élevés qu'avec le VPC10. Le VPC10 et le VPC13 entraînent tous deux une réponse en anticorps contre le sérotype 19A, la moyenne géométrique des titres contre ce sérotype et le pourcentage de personnes répondant au vaccin étant toutefois supérieurs avec le VPC13 qu'avec le VPC10; dans le cas du VPC10, on pense que cette réponse contre le sérotype 19A est due à une réactivité croisée avec le sérotype 19F.

Bien qu'aucune étude de comparaison directe de l'impact ou de l'efficacité des 2 produits sur les issues de la PI n'ait été publiée, les données disponibles indiquent que les deux produits sont efficaces pour réduire la charge globale de la PI due aux sérotypes vaccinaux, tant chez les personnes vaccinées que non vaccinées. Bien que le VPC13 contienne 3 sérotypes supplémentaires, les données actuellement disponibles sont insuffisantes pour déterminer si cela modifie l'impact du vaccin sur la charge globale de PI (sérotypes vaccinaux et non vaccinaux confondus).

L'utilisation du VPC10 n'a pas entraîné de réduction de la charge de la PI imputable au sérotype 3, que ce soit parmi les groupes d'âge éligibles à la vaccination ou non, car ce vaccin ne contient pas le sérotype 3. Malgré les données d'immunogénicité disponibles, les éléments de preuve d'une réduction directe ou indirecte de la charge de la PI due au sérotype 3 après l'administration de VPC13 ne sont pas concluants, bien que la plupart des études aient indiqué une absence d'effet.

Concernant l'effet du VPC10 sur la PI imputable au sérotype 6A, les données disponibles sont limitées, mais indiquent généralement un effet direct. La plupart des évaluations de l'effet du VPC13 sur la PI due au sérotype 6A ont été menées dans des contextes où le VPC7 avait été préalablement utilisé, laissant une faible charge résiduelle de PI due au sérotype 6A, que ce soit dans les cohortes éligibles à la vaccination ou non. Dans la seule étude cas-témoins signalée à ce jour, une efficacité contre le sérotype 6A a été observée.

Quatre études cas-témoins et une étude de cohorte indirecte de l'efficacité du VPC10 ont mis en évidence un effet protecteur de ce vaccin contre la PI imputable au sérotype 19A chez les enfants vaccinés, bien que les résultats n'aient pas tous été

cance; 2 population-based incidence studies were less conclusive, neither demonstrating an impact. Among cohorts not eligible for the vaccine, those living in communities where PCV10 was used showed increases or no change in serotype 19A IPD rates; therefore, there is no evidence that PCV10 induces indirect protection against serotype 19A. PCV13 was effective against serotype 19A IPD, with both direct and indirect effects. Very few data are available on the impact of PCV10 against serotype 6C IPD. Some studies showed a significant impact of PCV13 on serotype 6C IPD.

Both PCV10 and PCV13 had direct and indirect effects against pneumonia; however, as there are no comparative studies, there is no evidence of a difference in impact. No conclusions could be drawn about a differential impact on mortality by product.

Limited evidence was available from head-to-head studies on the differential impact or effectiveness of PCV10 and PCV13 on NP carriage. Both products reduced carriage of the serotypes common to both vaccines, but studies of individual products could not be compared quantitatively because of substantial confounding by schedule, local epidemiology and prior PCV7 use in the community.

With respect to the 3 additional serotypes in PCV13, no significant direct or indirect effects were found for PCV10 on serotype 3 carriage, and evidence for an effect of PCV13 on serotype 3 NP carriage was mixed. Direct effects of both products on serotype 6A carriage were observed, but there was insufficient evidence to conclude whether the magnitude of the impact differed. Possible indirect effects against serotype 6A carriage were found for PCV10 in studies in communities with no prior use of PCV7. No evidence is available on indirect effects of PCV13 because serotype 6A carriage had already been substantially reduced by PCV7 use where this was studied. PCV10 use was associated with statistically significant increases in serotype 19A carriage in some studies and nonsignificant increases or reductions in other studies with low pre-study carriage; in settings with high baseline carriage, statistically significant reductions in carriage were observed. Studies of PCV13 demonstrated consistent reductions in serotype 19A carriage in children age-eligible for routine vaccination. No analyses of indirect effects of PCV13 on serotype 19A carriage are available.

Results of the impact of vaccination on serotype 6C carriage were limited for both products, and the studies were generally underpowered. The 2 studies of PCV10 showed increased serotype 6C carriage, and the results of 1 study were statistically significant. Conversely, all 4 studies of PCV13 showed decreased serotype 6C carriage, and the 1 with sufficient power showed a statistically significant reduction in carriage.

significatifs sur le plan statistique; 2 études de l'incidence en population ont été moins concluantes, aucune d'entre elles ne démontrant un impact. Parmi les cohortes non éligibles à la vaccination, celles qui vivent dans des communautés où le VPC10 a été administré présentaient des taux accrus ou inchangés de PI imputable au sérotype 19A; rien n'indique donc que le VPC10 confère une protection indirecte contre le sérotype 19A. Le VPC13 était efficace contre la PI due au sérotype 19A, avec des effets à la fois directs et indirects. Pour ce qui est de la PI due au sérotype 6C, les données relatives à l'effet du VPC10 sont très limitées, mais certaines études indiquent un effet considérable du VPC13.

Le VPC10 et le VPC13 ont tous deux des effets directs et indirects contre la pneumonie. Toutefois, aucune étude comparative n'ayant été réalisée, on ne dispose d'aucune donnée sur les différences éventuelles de leur impact. Aucune conclusion relative à l'effet différentiel de chaque produit sur la mortalité n'a pu être tirée.

On dispose de données limitées provenant d'études de comparaison directe de l'efficacité ou de l'impact différentiels du VPC10 et du VPC13 sur le portage rhinopharyngé. Les deux produits réduisent le portage des sérotypes commun aux deux vaccins, mais les résultats d'études portant sur les produits individuels n'ont pas pu être comparés de manière quantitative car ils sont sujets à des facteurs de confusion importants, tels que le schéma d'administration, l'épidémiologie locale et l'utilisation antérieure du VPC7 dans la communauté.

En ce qui concerne les 3 sérotypes supplémentaires contenus dans le VPC13, aucun effet direct ou indirect significatif du VPC10 sur le portage du sérotype 3 n'a été observé, et les données relatives à l'effet du VPC13 sur le portage rhinopharyngé du sérotype 3 étaient contradictoires. Des effets directs sur le portage du sérotype 6A ont été constatés pour les deux produits, mais les données n'étaient pas suffisantes pour déterminer si l'ampleur de cet impact était différente d'un produit à l'autre. D'éventuels effets indirects sur le portage du sérotype 6A ont été observés pour le VPC10 dans des études menées au sein de communautés où le VPC7 n'avait jamais été administré. Aucune information n'est disponible concernant les effets indirects du VPC13 car, dans les communautés où ces effets ont été étudiés, le portage du sérotype 6A était déjà fortement réduit par suite de l'administration du VPC7. L'utilisation du VPC10 était associée à une augmentation statistiquement significative du portage du sérotype 19A dans certaines études et à une augmentation non significative, voire un déclin, dans d'autres études lorsque le taux de portage initial était faible; dans les contextes où le portage de départ était élevé, une réduction statistiquement significative a été observée. Pour le VPC13, les études indiquent toutes une baisse du portage du sérotype 19A chez les enfants répondant aux critères d'âge de la vaccination systématique. Aucune analyse des effets indirects du VPC13 sur le portage du sérotype 19A n'a été réalisée.

Concernant l'impact de la vaccination sur le portage du sérotype 6C, on ne dispose que de résultats limités pour les deux produits, provenant d'études dont la puissance statistique était généralement insuffisante. Les 2 études portant sur le VPC10 indiquaient un portage accru du sérotype 6C, seule l'une d'entre elles donnant des résultats statistiquement significatifs. Inversement, les 4 études sur le VPC13 faisaient état d'une diminution du portage du sérotype 6C; seule l'une d'entre elles avait une puissance suffisante, indiquant une baisse statistiquement significative du portage.

In summary, PCV10 and PCV13 have comparable immunogenicity and impact on IPD, pneumonia and NP carriage due to shared vaccine serotypes. While differences were found in their immunogenicity and impact on the 3 serotypes included in PCV13 and not PCV10 and on serotype 6C, there is currently insufficient evidence that the 2 vaccines differ in their impact on overall pneumococcal disease burden.

Catch-up vaccination

Empirical evidence of the impact of catch-up PCV vaccination at the time of its introduction among children in older birth cohorts is limited. Results from modelling studies of catch-up vaccination with PCV on disease impact in Kenya[40] and Viet Nam[41] were reviewed, which suggest that catch-up vaccination of children <5 years in older birth cohorts at the time of national PCV introduction accelerated both direct and indirect protection and thereby hastened the impact of PCV. Modelling of NP carriage and IPD data from a study in Kenya indicated that, at the time of PCV introduction, a catch-up campaign for children <5 years of age had a greater benefit per dose administered than catch-up campaigns for more narrow age strata or routine infant vaccination alone.[40] Limited evidence is available to determine whether a single dose is sufficient or whether 2 doses are required for catch-up vaccination after infancy. For children aged 12–23 months of age, some programmes have used 2 PCV doses separated by at least 8 weeks, while others have used a single dose. The benefits of a catch-up campaign are mitigated if the resources used divert resources from wider PCV coverage in the birth cohort, delay introduction or if those in the catch-up age cohort have only moderate vaccine serotype carriage and disease.

Vaccination in pneumococcal disease outbreaks

Limited evidence exists on the effectiveness of PCV as a response to pneumococcal disease outbreaks. Serotype 1 has been associated with disease outbreaks.[3, 4, 5] Recent data from an outbreak of serotype 1 disease in Ghana, where PCV is used in the routine infant immunization programme in a 3p+0 schedule, showed lower rates of disease in the vaccinated cohort of children <5 years than in serotype 1 outbreaks before introduction of vaccination.[4] This suggests direct protection against serotype 1 disease in vaccinated children but no indirect effects.[4, 5]

En résumé, le VPC10 et le VPC13 présentent une immunogénicité et des effets comparables sur la PI, la pneumonie et le portage rhinopharyngé associés aux sérotypes communs aux deux vaccins. Bien que des différences d'immunogénicité et d'impact aient été constatées pour les 3 sérotypes qui sont contenus dans le VPC13 mais pas dans le VPC10, ainsi que pour le sérotype 6C, les données actuelles sont insuffisantes pour conclure à une différence de l'impact des 2 vaccins sur la charge globale de la pneumococcie.

Vaccination de rattrapage

On ne dispose que de données empiriques limitées sur les effets de la vaccination de rattrapage par les VPC chez les enfants appartenant à des cohortes de naissance plus âgées lors de l'introduction du vaccin. Les résultats d'études de modélisation de l'impact de la vaccination de rattrapage par les VPC menées au Kenya[40] et au Viet Nam[41] ont été examinés. Ils laissent supposer que la vaccination de rattrapage des enfants de <5 ans parmi les cohortes de naissance plus âgées au moment de l'introduction nationale des VPC permet d'établir plus rapidement une protection à la fois directe et indirecte, accélérant ainsi l'impact des VPC. La modélisation des données sur le portage rhinopharyngé et la PI issues d'une étude réalisée au Kenya a montré qu'au moment de l'introduction des VPC, les campagnes de rattrapage visant les enfants de <5 ans produisaient des effets bénéfiques plus importants par dose administrée que les campagnes de rattrapage ciblant une tranche d'âge plus étroite ou que la seule vaccination systématique des nourrissons.[40] On ne dispose que de données limitées pour déterminer si une dose unique est suffisante ou si 2 doses sont nécessaires pour la vaccination de rattrapage après la petite enfance. Pour les enfants âgés de 12 à 23 mois, certains programmes ont administré 2 doses de VPC espacées d'au moins 8 semaines, tandis que d'autres ont utilisé une dose unique. Les campagnes de rattrapage ne présentent que des avantages mitigés si elles détournent les ressources nécessaires à la couverture générale par les VPC dans la cohorte de naissance, si elles retardent l'introduction du vaccin ou si les sujets appartenant à la cohorte d'âge ciblée par la vaccination de rattrapage ne présentent que des taux modérés de portage ou de maladie imputables aux sérotypes vaccinaux.

Vaccination lors de flambées de pneumococcies

Les données relatives à l'efficacité des VPC dans le cadre des activités de riposte aux flambées de pneumococcies sont limitées. Le sérotype 1 a été associé à des flambées de maladie.[3, 4, 5] De récentes données recueillies dans le cadre d'une flambée de pneumococcie due au sérotype 1 au Ghana, où le VPC est utilisé dans le programme de vaccination systématique du nourrisson selon un schéma 3p+0, ont indiqué que les taux de maladie dans la cohorte vaccinée d'enfants de <5 ans étaient plus faibles que lors des flambées de sérotype 1 survenues avant l'introduction de la vaccination.[4] Cela laisse supposer que le vaccin confère une protection directe contre la pneumococcie due au sérotype 1 chez les enfants vaccinés, mais n'a pas d'effets indirects.[4, 5]

[40] Flasche S, et al. Assessing the efficiency of catch-up campaigns for the introduction of pneumococcal conjugate vaccine: a modelling study based on data from PCV10 introduction in Kilifi, Kenya. BMC Med. 2017;15:113.

[41] Le Polain de Waroux O, et al. Predicting the impact of pneumococcal conjugate vaccine programme options in Vietnam. Hum Vaccin Immunother. 2018;14(8):1939–47.

Serotype replacement following PCV use

An increase in the incidence of non-vaccine-type disease after use of PCV, a phenomenon referred to as "serotype replacement", has been described with PCV7 in many settings. A review of data from 21 eligible surveillance datasets showed that the overall IPD incidence in children had decreased by year 1 after vaccine introduction (relative risk [RR] 0.55, 95% CI 0.46–0.65) and remained stable through year 7 (RR 0.49, 95% CI 0.35–0.68), as compared with the pre-vaccine era. The incidence of vaccine-type IPD decreased annually through year 7 (RR 0.03; 95% CI, 0.01–0-10); the incidence of non-vaccine-type IPD increased by year 7 (RR 2.81; 95% CI, 2.12–3.71), and a single serotype, 19A, was responsible for most of the replacement.[42] Limited data were available from LMICs in the above analysis, and no data on PCV10 or PCV13 were available for inclusion at the time of the analysis. A systematic review is being conducted of data on serotype replacement that includes data after use of PCV10 and PCV13 and from LMICs.

Non-vaccine factors may influence the recorded rates of serotype-specific disease and thereby confound interpretation of the relation between introduction of PCV and changes in serotype distribution. Such factors include variation in the proportion of isolates serotyped before and after vaccine introduction, changes in blood culture practice, secular trends and outbreaks of pneumococcal disease. These factors should be considered in interpreting surveillance data on pneumococcal disease.[42]

Safety of PCVs

The safety profiles of PCV10 and PCV13 are as favourable as that of PCV7 when they are administered to infants and young children.[43–46] The most common adverse reactions observed after administration of PCV10 to infants were redness at the injection site and irritability, which occurred after approximately 41% and 55% of all doses, respectively. These adverse reactions were more common after booster vaccination. Fever was reported in 30–40% of infants with solicited adverse events, although grade 3 fever (>40 °C) occurred after no more than 3.9% of primary doses, 2.9% of booster doses and 2.2% of catch-up doses.[33] Similarly, redness

Remplacement des sérotypes après l'administration des VPC

Avec le VPC7, on a constaté dans de nombreux contextes un phénomène de «remplacement des sérotypes», à savoir une augmentation de l'incidence des pneumococcies imputables à des sérotypes non vaccinaux après l'administration du VPC. Une analyse de 21 séries de données de surveillance pertinentes a révélé que l'incidence globale de la PI chez les enfants avait reculé 1 an après l'introduction du vaccin (risque relatif [RR]: 0,55, IC à 95%: 0,46-0,65), et était ensuite restée stable jusqu'à 7 ans après l'introduction du vaccin (RR: 0,49, IC à 95%: 0,35-0,68), par rapport à la période antérieure à la vaccination. L'incidence de la PI due aux sérotypes vaccinaux avait régressé chaque année jusqu'à la 7e année (RR: 0,03; IC à 95%: 0,01-0,10). À la 7e année, on avait observé une augmentation de l'incidence de la PI due aux sérotypes non vaccinaux (RR: 2,81; IC à 95%: 2,12-3,71), ce phénomène de remplacement étant principalement attribuable à un sérotype unique, le 19A.[42] Dans cette analyse, les données provenant des pays à revenu faible ou intermédiaire étaient limitées et aucune donnée sur le VPC10 ou le VPC13 n'était disponible. Une revue systématique sur le remplacement des sérotypes, intégrant les données consécutives à l'utilisation du VPC10 et du VPC13 et les données des pays à revenu faible ou intermédiaire, est en cours.

Des facteurs non vaccinaux peuvent influer sur les taux de maladie observés pour chaque sérotype et donc biaiser l'interprétation de la relation entre l'introduction des VPC et l'évolution de la distribution des sérotypes. Parmi ces facteurs figurent les variations de la proportion d'isolats sérotypés avant et après l'introduction du vaccin, l'évolution des pratiques d'hémoculture, les tendances séculaires et les flambées de pneumococcie. L'interprétation des données de surveillance de la pneumococcie doit donc tenir compte de ces facteurs.[42]

Innocuité des VPC

Le VPC10 et le VPC13 ont des profils d'innocuité aussi favorables que le VPC7 lorsqu'ils sont administrés aux nourrissons et aux jeunes enfants.[43-46] Après l'administration du VPC10 aux nourrissons, les réactions indésirables les plus fréquentes étaient une rougeur au point d'injection (environ 41% de toutes les doses administrées) et une irritabilité (environ 55% des doses). Ces réactions étaient plus fréquemment observées après la vaccination de rappel. La fièvre représentait 30-40% des réactions indésirables signalées sur demande chez le nourrisson. Toutefois, une fièvre de grade 3 (>40 °C) n'a été observée que pour 3,9% des doses de primovaccination, 2,9% des doses de rappel et 2,2% des doses de rattrapage.[33] De même pour le

[42] Feikin DR, et al. Serotype-specific changes in invasive pneumococcal disease after pneumococcal conjugate vaccine introduction: a pooled analysis of multiple surveillance sites. PLoS Med. 2013 10(9):e1001517.

[43] Tseng HF, et al. Postlicensure surveillance for pre-specified adverse events following the 13-valent pneumococcal conjugate vaccine in children. Vaccine. 2013;31:2578–83.

[44] Silfverdal SA, et al. Safety profile of the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV). Expert Rev Vaccines. 2017;16 (2):109–21.

[45] Artama M, et al. Register-based ecologic evaluation of safety signals related to pneumococcal conjugate vaccine in children. Curr Drug Saf. 2018;13(2):107–12.

[46] Littlejohn ES, et al. Surveillance of adverse events following the introduction of 13-valent pneumococcal conjugate vaccine in infants, and comparison with adverse events following 7-valent pneumococcal conjugate vaccine, in Victoria, Australia. Hum Vaccin Immunother. 2015;11(7):1828–35.

[42] Feikin DR, et al. Serotype-specific changes in invasive pneumococcal disease after pneumococcal conjugate vaccine introduction: a pooled analysis of multiple surveillance sites. PLoS Med. 2013 10(9):e1001517.

[43] Tseng HF, et al. Postlicensure surveillance for pre-specified adverse events following the 13-valent pneumococcal conjugate vaccine in children. Vaccine. 2013;31:2578–83.

[44] Silfverdal SA, et al. Safety profile of the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV). Expert Rev Vaccines. 2017;16 (2):109–21.

[45] Artama M, et al. Register-based ecologic evaluation of safety signals related to pneumococcal conjugate vaccine in children. Curr Drug Saf. 2018;13(2):107–12.

[46] Littlejohn ES, et al. Surveillance of adverse events following the introduction of 13-valent pneumococcal conjugate vaccine in infants, and comparison with adverse events following 7-valent pneumococcal conjugate vaccine, in Victoria, Australia. Hum Vaccin Immunother. 2015;11(7):1828–35.

(24–42%) and swelling (20–32%) were the most common local adverse events observed after PCV13, with higher rates of local reactions after the booster dose. Irritability, observed in up to 85.6% of infants, was the most common systemic adverse event. Fever was reported in 24–36% of recipients of PCV13, although severe fever was reported in only 0.1–0.3%.[34]

There was a trend towards more Kawasaki disease 0–28 days after vaccination with PCV13 as compared with PCV7 (RR, 1.94; 95% CI, 0.79–4.86).[43] Kawasaki disease was also observed more commonly in PCV10-vaccinated groups than in controls, although it was rare (<1/10 000 children), and the incidence was below or within the expected population background range.[44]

Concurrent administration with diphtheria, tetanus and pertussis vaccine resulted in rates of fever among recipients of PCV13 of 15–34%, with higher rates after the second dose. Administration of trivalent inactivated influenza vaccines on the same day as PCV13 was associated with a higher risk of febrile seizures than when they were given on a separate day (incidence rate ratio, 3.5; 95% CI, 1.13–10.85); however, the absolute risk of post-vaccination febrile seizures was small.[47]

Vaccination of special risk groups, contraindications and precautions

Children with impaired immune responsiveness may have a reduced antibody response to vaccination with PCV. The available data suggest that the safety profiles of the 2 vaccines are similar in these risk groups and in healthy children.[44]

Vaccine co-administration

The immunogenicity and reactogenicity of PCVs are not significantly altered when they are given concomitantly with monovalent or combination vaccines against diphtheria, tetanus, pertussis (acellular and whole-cell vaccines), hepatitis B, polio (inactivated and live oral vaccines), *H. influenzae* type b, measles, mumps, rubella, varicella, meningococcus serogroup C (conjugate vaccine) or rotavirus.[33, 34] Co-administration with yellow fever vaccine has not been studied.

Cost–effectiveness

The cost–effectiveness of PCV use depends on many factors, including the burden of disease, vaccine effectiveness, indirect effects, vaccination coverage, vaccine price, delivery costs and schedule.[48]

An analysis of data from 22 studies in LMICs showed that vaccination with PCV10 and PCV13 is cost-effective from the perspective of both health care providers and

VPC13, les rougeurs (24-42%) et les œdèmes (20-32%) étaient les réactions indésirables locales les plus couramment observées et elles étaient plus fréquentes après la dose de rappel. L'irritabilité, signalée chez près de 85,6% des nourrissons, était la réaction indésirable systémique la plus fréquente. L'apparition de fièvre a été signalée chez 24-36% des sujets vaccinés par le VPC13, mais seulement 0,1-0,3% présentaient une fièvre sévère.[34]

Il a été constaté que dans les 28 jours suivant la vaccination, le taux de maladie de Kawasaki tendait à être plus élevé avec le VPC13 qu'avec le VPC7 (RR: 1,94; IC à 95%: 0,79-4,86).[43] La maladie de Kawasaki a aussi été plus souvent observée dans les groupes vaccinés par le VPC10 que dans les groupes témoins; elle était toutefois rare (<1/10 000 enfants), avec une incidence se situant en dessous ou à l'intérieur de la plage de valeurs attendue pour l'incidence de fond dans la population.[44]

Lorsque le VPC13 était administré en même temps que le vaccin antidiphtérique-antitétanique-anticoquelucheux, les taux de fièvre observés étaient de 15-34%, avec un taux plus élevé après la seconde dose. L'administration de vaccins antigrippaux trivalents inactivés le même jour que le VPC13 était associée à un risque plus élevé de convulsions fébriles que si les deux vaccins étaient administrés des jours différents (rapport des taux d'incidence: 3,5; IC à 95%: 1,13-10,85); cependant, le risque absolu de convulsions fébriles postvaccinales était faible.[47]

Vaccination de groupes à risque particuliers, contre-indications et précautions

Les enfants dont la réactivité immunitaire est affaiblie peuvent avoir une réponse en anticorps réduite à la vaccination par les VPC. Les données disponibles semblent indiquer que pour les 2 vaccins, les profils d'innocuité sont comparables entre ces groupes à risque et les enfants sains.[44]

Coadministration avec d'autres vaccins

Aucune modification notable de l'immunogénicité et de la réactogénicité des VPC n'est observée lorsque ces vaccins sont administrés en même temps que les vaccins monovalents ou combinés contre la diphtérie, le tétanos, la coqueluche (vaccins acellulaires et à germes entiers), l'hépatite B, la poliomyélite (vaccin inactivé et vaccin oral vivant), *H. influenzae* type b, la rougeole, les oreillons, la rubéole, la varicelle, les méningocoques du sérogroupe C (vaccin conjugué) ou les rotavirus.[33, 34] La coadministration avec le vaccin antiamaril n'a pas été étudiée.

Rapport coût/efficacité

Le rapport coût/efficacité des VPC dépend de nombreux facteurs, notamment de la charge de morbidité, de l'efficacité du vaccin, des effets indirects de la vaccination, de la couverture vaccinale, du prix des vaccins, des coûts de distribution et du schéma d'administration.[48]

Une analyse des données tirées de 22 études menées dans les pays à revenu faible ou intermédiaire a montré que la vaccination par le VPC10 et le VPC13 présentait un bon rapport coût/

[47] Duffy J, et al. Febrile seizure risk after vaccination in children 6 to 23 months. Pediatrics. 2016;138(1):e20160320.

[48] Chaiyakunapruk N, et al. Cost effectiveness of pediatric pneumococcal conjugate vaccines: a comparative assessment of decision-making tools. BMC Med. 2011;9:53.

[47] Duffy J, et al. Febrile seizure risk after vaccination in children 6 to 23 months. Pediatrics. 2016;138(1):e20160320.

[48] Chaiyakunapruk N, et al. Cost effectiveness of pediatric pneumococcal conjugate vaccines: a comparative assessment of decision-making tools. BMC Med. 2011;9:53.

society.[49] The cost-effectiveness according to product choice will depend on country characteristics, including local serotype prevalence and coverage rates achieved with different schedules.

WHO position

Currently available PCVs are safe and effective, and the increase in the number of serotypes in these vaccines as compared with the first licensed PCV7 represents significant progress in the fight against pneumococcal disease-related morbidity and mortality, particularly for developing countries.

WHO recommends the inclusion of PCVs in childhood immunization programmes worldwide.

Use of pneumococcal vaccine should be complementary to other disease prevention and control measures, such as appropriate case management, promotion of exclusive breastfeeding for the first 6 months of life and reducing known risk factors such as indoor air pollution and tobacco smoke.

Schedule

For administration of PCV to infants, WHO recommends a 3-dose schedule administered either as 2p+1 or as 3p+0, starting as early as 6 weeks of age.[50] In choosing between the 2p+1 and 3p+0 schedules, countries should consider programmatic factors, including timeliness of vaccination and expected coverage. The 2p+1 schedule has potential benefits over the 3p+0 schedule, when programmatically feasible, as higher antibody levels are induced in the second year of life, which may be important in maintaining herd immunity, although no high-quality evidence is available.

If the 2p+1 schedule is selected, an interval of ≥8 weeks is recommended between the 2 primary doses, but the interval may be shortened if there is a compelling reason to do so, such as timeliness of receipt of the second dose and/or achieving higher coverage when a 4-week interval is used. For the 2p+1 schedule, the booster dose should be given at 9–18 months of age, according to programmatic considerations; there is no defined minimum or maximum interval between the primary series and the booster dose. If the 3p+0 schedule is used, a minimum interval of 4 weeks should be maintained between doses.

Previously unvaccinated or incompletely vaccinated children who recover from IPD should be vaccinated according to the recommended age-appropriate regimens. Interrupted schedules should be resumed without repeating the previous dose.

efficacité, tant du point de vue des prestataires de soins que sur le plan sociétal.[49] Le rapport coût/efficacité selon le produit choisi dépendra des caractéristiques du pays, notamment de la prévalence locale des sérotypes et des taux de couverture atteints avec les différents schémas d'administration.

Position de l'OMS

Les VPC actuellement disponibles sont efficaces et sans danger et le fait qu'ils contiennent un plus grand nombre de sérotypes par rapport au VPC7, le premier VPC à avoir été homologué, représente une avancée majeure dans la lutte contre la morbidité et la mortalité liées aux pneumococcies, en particulier dans les pays en développement.

L'OMS recommande que les VPC soient intégrés aux programmes de vaccination de l'enfant dans le monde entier.

La vaccination antipneumococcique devrait s'inscrire en complément d'autres mesures de prévention et de lutte contre la maladie: prise en charge appropriée des cas, encouragement d'un allaitement exclusif au sein pendant les 6 premiers mois de vie et réduction des facteurs de risque connus, comme la pollution intérieure et la fumée de tabac.

Schéma

L'OMS recommande d'administrer les VPC aux nourrissons selon un calendrier à 3 doses, pouvant être appliqué sous forme de schéma 2p+1 ou 3p+0, dès l'âge de 6 semaines.[50] Pour choisir entre les schémas 2p+1 et 3p+0, les pays devront tenir compte des facteurs programmatiques, notamment des délais de vaccination et de la couverture escomptée. Le schéma 2p+1, s'il est réalisable sur le plan programmatique, pourrait présenter certains avantages par rapport au schéma 3p+0 car des titres d'anticorps plus élevés sont induits au cours de la deuxième année de vie, ce qui peut jouer un rôle important dans le maintien de l'immunité collective, bien qu'on ne dispose pas de données de qualité à ce sujet.

Si le schéma 2p+1 est choisi, un écart de ≥8 semaines est recommandé entre les 2 doses de primovaccination, mais cet intervalle peut être raccourci si une raison impérieuse le justifie, par exemple l'administration en temps utile de la deuxième dose et/ou l'obtention d'une meilleure couverture vaccinale en espaçant les doses de 4 semaines. Dans le schéma 2p+1, la dose de rappel doit être administrée entre les âges de 9 et 18 mois, en tenant compte des considérations programmatiques; il n'y a pas d'intervalle minimal ou maximal à respecter entre la série de primovaccination et la dose de rappel. Si le schéma 3p+0 est employé, un intervalle d'au moins 4 semaines doit être respecté entre les doses.

Les enfants non vaccinés ou partiellement vaccinés qui se sont rétablis à la suite d'une PI doivent être vaccinés selon les schémas recommandés pour leur âge. Si un calendrier de vaccination est interrompu, il convient de le reprendre sans réadministrer la dose précédente.

[49] Saokaew S, et al. Cost effectiveness of pneumococcal vaccination in children in low- and middle-income countries: a systematic review. Pharmacoeconomics. 2016;34(12):1211–25.

[50] Evidence to recommendations table: pneumococcal conjugate vaccine (PCV), Table 1: Dosing schedule impact. Geneva: World Health Organization; 2018 (http://www.who.int/immunization/policy/position_papers/recommendation_table_PCV_dosing_schedule_impact.pdf, accessed February 2019).

[49] Saokaew S, et al. Cost effectiveness of pneumococcal vaccination in children in low- and middle-income countries: a systematic review. Pharmacoeconomics. 2016;34(12):1211–25.

[50] Evidence to recommendations table: pneumococcal conjugate vaccine (PCV), Table 1: Dosing schedule impact. Genève, Organisation mondiale de la Santé; 2018 (http://www.who.int/immunization/policy/position_papers/recommendation_table_PCV_dosing_schedule_impact.pdf, consulté en février 2019).

Product choice

Both PCV10 and PCV13 have substantial impacts against pneumonia, vaccine-type IPD and NP carriage. There is at present insufficient evidence of a difference in the net impact of the 2 products on overall disease burden.[51] PCV13 may have an additional benefit in settings where disease attributable to serotype 19A or serotype 6C is significant. The choice of product to be used in a country should be based on programmatic characteristics, vaccine supply, vaccine price, the local and regional prevalence of vaccine serotypes and antimicrobial resistance patterns.

Interchangeability

Once a PCV vaccination programme has been initiated, product switching is not recommended unless there are substantial changes in the epidemiological or programmatic factors that determined the original choice of product, e.g. an increasing burden of serotype 19A. If a series cannot be completed with the same type of vaccine, the available PCV product should be used. Restarting a series is not recommended, even for the primary series.

Catch-up vaccination

Wherever possible, catch-up vaccination at the time of introduction of PCV should be used to accelerate its impact on disease in children aged 1–5 years, particularly in settings with a high disease burden and mortality. If there is limited availability of vaccine or of financial resources for catch-up vaccination, the youngest children (e.g. <2 years of age) should be prioritized to receive catch-up doses of PCV because of their higher risk for pneumococcal disease.

Catch-up vaccination can be done with a single dose of vaccine for children ≥24 months. Current data are insufficient for a firm recommendation on the optimal number of doses (1 or 2) required in 12–23-month-olds as part of catch-up vaccination, so countries choosing to use 1 dose might wish to monitor for impact and vaccine failures.

Unvaccinated children aged 1–5 years who are at high risk for pneumococcal infection because of underlying medical conditions, such as HIV infection or sickle-cell disease, should receive at least 2 doses separated by at least 8 weeks.

In humanitarian or other emergency situations, age-appropriate schedules of PCV vaccination should be

[51] Evidence to recommendations table: pneumococcal conjugate vaccine (PCV), Table 2: Product choice impact. Geneva: World Health Organization; 2018 (http://www.who.int/immunization/policy/position_papers/recommendation_table_PCV_product_choice_impact.pdf, accessed February 2019).

Choix du produit

Le VPC10 et le VPC13 ont tous deux un impact considérable contre la pneumonie, la PI imputable aux sérotypes vaccinaux et le portage rhinopharyngé. Les données actuellement disponibles sont insuffisantes pour mettre en évidence une différence entre les effets nets des 2 produits sur la charge de morbidité globale.[51] Le VPC13 pourrait présenter un avantage supplémentaire dans les contextes où la morbidité attribuable aux sérotypes 19A ou 6C est importante. Le choix du produit dans un pays donné devra se fonder sur les caractéristiques programmatiques, l'approvisionnement en vaccins, le prix des vaccins, la prévalence locale et régionale des sérotypes vaccinaux et les profils de résistance aux antimicrobiens.

Interchangeabilité des vaccins

Une fois qu'un programme de vaccination par les VPC a été mis en place, il est déconseillé de passer d'un produit à l'autre à moins d'une évolution majeure des facteurs épidémiologiques ou programmatiques sur lesquels s'est fondé le choix initial du produit, par exemple en cas d'augmentation de la charge du sérotype 19A. Si une série ne peut être menée à terme avec le même type de vaccin, on utilisera le VPC qui est disponible. Il est déconseillé de recommencer une série, même s'il s'agit de la série de primovaccination.

Vaccination de rattrapage

Dans la mesure du possible, on procèdera à une vaccination de rattrapage lors de l'introduction des VPC afin d'accélérer les effets de la vaccination sur la maladie parmi les enfants âgés de 1 à 5 ans, en particulier dans les zones où la charge de morbidité et la mortalité liées à la maladie sont élevées. Si la quantité de vaccins disponibles ou les ressources financières sont insuffisantes pour mettre pleinement en œuvre la vaccination de rattrapage, les doses de rattrapage de VPC devront être administrées en priorité aux enfants les plus jeunes (par exemple de <2 ans) en raison du risque plus élevé de pneumococcie dans cette population.

Chez les enfants de ≥24 mois, on pourra administrer une dose unique de vaccin aux fins de la vaccination de rattrapage. Pour les enfants de 12 à 23 mois, on ne dispose actuellement pas de données suffisantes pour formuler une recommandation ferme quant au nombre optimal de doses (1 ou 2) à administrer dans le cadre de la vaccination de rattrapage; dans les pays ayant décidé d'utiliser 1 dose, il pourrait donc être utile de surveiller l'impact de la vaccination et les échecs vaccinaux.

Les enfants âgés de 1 à 5 ans qui n'ont pas été vaccinés et qui présentent un risque élevé d'infection pneumococcique en raison d'affections médicales sous-jacentes, comme une infection à VIH ou une drépanocytose, doivent recevoir au moins 2 doses espacées d'au moins 8 semaines.

Dans les situations d'urgence humanitaires ou autres, l'administration de VPC, selon un schéma adapté à l'âge, devra être

[51] Evidence to recommendations table: pneumococcal conjugate vaccine (PCV), Table 2: Product choice impact. Genève, Organisation mondiale de la Santé; 2018 (http://www.who.int/immunization/policy/position_papers/recommendation_table_PCV_product_choice_impact.pdf, consulté en février 2019).

used for children <1 year of age and considered for children ≤5 years of age, as indicated by the situation.[52]

Catch-up vaccination may also be an important means to prevent outbreaks. Vaccine campaigns in response to outbreaks of confirmed vaccine-type pneumococcal disease are under consideration, but experience is currently lacking.

Vaccination of special populations

PCVs should not be given to individuals with a history of anaphylactic reactions or severe allergic reactions to any component of the vaccine. HIV-positive infants and pre-term neonates who have received their 3 primary vaccine doses before 12 months of age may benefit from a booster dose in the second year of life.

Vaccination of travelling children

Travelling children are generally not at special risk of pneumococcal disease, unless they travel to an outbreak setting. They should follow the vaccine recommendations for the general population and ensure they are up to date with their vaccinations before travelling.

Co-administration

Despite the lack of comprehensive data on the immunogenicity, effectiveness and safety of all possible combinations of PCV and other routine vaccines, co-administration for programmatic reasons appears to be acceptable.

Surveillance

While a comprehensive surveillance system for pneumococcal disease is recommended, countries without such a system in place should not wait to introduce PCV vaccines. WHO recommends that the epidemiological impact of PCV be carefully monitored in sustained, high-quality sentinel and population-based surveillance for pneumococcal disease and in periodic NP carriage surveys.[53, 54] Such surveillance and surveys should be conducted to monitor changes in disease and the circulation of pneumococcal serotypes in the community after use of different PCV products at different dosing schedules and in different geographical and epidemiological settings with different pneumococcal disease burdens and transmission. Ideally, surveillance should be started at least 1–2 years before introduction of PCV and be continued indefinitely but at least for 5 years

assurée chez les enfants de <1 an et envisagée chez les enfants de ≤5 ans, selon la situation.[52]

La vaccination de rattrapage peut également jouer un rôle important dans la prévention des flambées. La possibilité de mener des campagnes vaccinales en riposte aux flambées de pneumococcies confirmées dues aux sérotypes vaccinaux est à l'étude, mais on manque actuellement de données empiriques à ce sujet.

Vaccination de populations particulières

Les VPC ne doivent pas être administrés à des personnes ayant des antécédents de réaction anaphylactique ou de réaction allergique sévère à l'un quelconque des constituants du vaccin. Chez les nourrissons positifs pour le VIH et les prématurés qui ont reçu leurs 3 doses de primovaccination avant d'atteindre l'âge de 12 mois, un rappel au cours de la deuxième année de vie peut être bénéfique.

Vaccination des enfants lors des voyages

Les enfants qui partent en voyage ne sont généralement pas exposés à un risque particulier de pneumococcie, sauf s'ils se rendent dans une zone touchée par une flambée. Il convient de respecter les recommandations vaccinales applicables à la population générale et de vérifier que leurs vaccinations sont à jour avant le voyage.

Coadministration

Bien qu'on ne dispose pas de données exhaustives sur l'immunogénicité, l'efficacité et l'innocuité de toutes les associations possibles des VPC avec d'autres vaccins du programme de vaccination systématique, la coadministration motivée par des raisons programmatiques semble acceptable.

Surveillance

Le recours à un système complet de surveillance de la pneumococcie est recommandé. Toutefois, les pays qui ne possèdent pas de tel système ne doivent pas attendre avant d'introduire les vaccins VPC. L'OMS recommande de suivre attentivement l'impact épidémiologique des VPC en assurant une surveillance durable et de qualité de la pneumococcie, sur des sites sentinelles et en population, et en menant des enquêtes périodiques sur le portage rhinopharyngé.[53, 54] Cette surveillance et ces enquêtes viseront à suivre l'évolution de la maladie et la circulation des sérotypes pneumococciques dans la communauté après l'administration de différents VPC selon des schémas différents et dans différents contextes géographiques et épidémiologiques, présentant des charges de morbidité et des profils de transmission de la pneumococcie différents. Dans l'idéal, les activités de surveillance devraient commencer au moins 1 à 2 ans avant l'introduction des VPC et se poursuivre indéfini-

[52] Vaccination in humanitarian emergencies: implementation guide. Geneva: World Health Organization; 2017 (http://www.who.int/immunization/documents/general/who_ivb_17.13/en/, accessed October 2018).

[53] Surveillance standards for vaccine-preventable diseases, second edition. Chapter 17: Pneumococcus. Geneva: World Health Organization; 2018 (https://www.who.int/immunization/monitoring_surveillance/burden/vpd/WHO_SurveillanceVaccinePreventable_17_Pneumococcus_R2.pdf?ua=1, accessed January 2019).

[54] Measuring impact of *Streptococcus pneumoniae* and *Haemophilus influnzae* type b conjugate vaccination. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/handle/10665/75835/WHO_IVB_12.08_eng.pdf?sequence=1, accessed January 2019)

[52] Vaccination in humanitarian emergencies: implementation guide. Genève, Organisation mondiale de la Santé; 2017 (http://www.who.int/immunization/documents/general/who_ivb_17.13/en/, consulté en octobre 2018).

[53] Surveillance standards for vaccine-preventable diseases, second edition. Chapter 17: Pneumococcus. Genève, Organisation mondiale de la Santé; 2018 (https://www.who.int/immunization/monitoring_surveillance/burden/vpd/WHO_SurveillanceVaccinePreventable_17_Pneumococcus_R2.pdf?ua=1, consulté en janvier 2019).

[54] Measuring impact of *Streptococcus pneumoniae* and *Haemophilus influnzae* type b conjugate vaccination. Genève, Organisation mondiale de la Santé; 2012 (http://apps.who.int/iris/bitstream/handle/10665/75835/WHO_IVB_12.08_eng.pdf?sequence=1, consulté en janvier 2019)

after introduction. While population-based surveillance is required to document impact on disease incidence and serotype replacement, IPD surveillance at sentinel sites in hospitals without a defined catchment population provides useful information on the distribution of serotypes in routine use of PCV. A qualitative estimate of its impact can be made by comparing the proportions of disease due to different pneumococcal serotypes over time. Periodic cross-sectional studies of NP carriage could offer insight into the roles of cases and carriers in continuing circulation of vaccine serotypes. In countries with no surveillance in place, data from neighbouring countries with similar disease burden, socioeconomic and demographic patterns can be used, but WHO encourages countries to conduct high-quality surveillance to monitor their immunization programmes, with the goal of strengthening overall disease surveillance and laboratory capacity.

Research priorities

Additional research should be conducted on: (1) further assessment of vaccine impact, duration of protection and indirect effects of different dosing schedules; (2) serotype replacement; (3) further establishment of serotype-specific immune correlates of protection against IPD in different transmission settings; (4) the epidemiology of pneumococcal outbreaks, particularly epidemics of serotype 1 disease, including use of PCV to prevent or respond to outbreaks; (5) the impact of PCV on antimicrobial use and resistance; and (6) comparison of a 1-dose versus a 2-dose catch-up schedule for children >12 months of age. ■

ment, ou du moins pendant au moins 5 ans après l'introduction. La surveillance en population est nécessaire pour observer l'impact de la vaccination sur l'incidence de la maladie et le remplacement des sérotypes, mais la surveillance de la PI sur des sites sentinelles qui sont situés dans des hôpitaux ne desservant pas une population spécifiquement définie fournit également des informations utiles sur la distribution des sérotypes dans le cadre de la vaccination systématique par les VPC. Une estimation qualitative de l'impact de la vaccination peut être obtenue en comparant la proportion de cas imputables aux différents sérotypes pneumococciques au cours du temps. Des études transversales périodiques du portage rhinopharyngé peuvent fournir des renseignements sur le rôle que jouent les cas et les sujets porteurs dans la circulation persistante des sérotypes vaccinaux. Dans les pays dépourvus de système de surveillance, on pourra utiliser les données provenant de pays voisins, dans la mesure où leur charge de morbidité et leur profil socioéconomique et démographique sont comparables. Toutefois, l'OMS encourage les pays à assurer une surveillance de qualité de leurs programmes de vaccination en vue de renforcer la surveillance globale des maladies et les capacités des laboratoires.

Priorités pour la recherche

Des travaux de recherche supplémentaires devraient être menés dans les domaines suivants: 1) évaluation approfondie de l'impact des vaccins, de la durée de protection et des effets indirects des différents schémas d'administration; 2) remplacement des sérotypes; 3) définition détaillée, selon le sérotype, d'indicateurs immunitaires de la protection contre la PI dans différents contextes de transmission; 4) épidémiologie des flambées de pneumococcie, en particulier des épidémies de maladies dues au sérotype 1, et utilisation des VPC aux fins de la prévention ou de la riposte aux flambées; 5) effets des VPC sur le recours aux antimicrobiens et la résistance aux antimicrobiens; et 6) comparaison des schémas à 1 dose et à 2 doses pour la vaccination de rattrapage des enfants âgés de >12 mois. ■

How to obtain the WER through the Internet

(1) WHO WWW server: Use WWW navigation software to connect to the WER pages at the following address: **http://www.who.int/wer/**

(2) An e-mail subscription service exists, which provides by electronic mail the table of contents of the WER, together with other short epidemiological bulletins. To subscribe, send a message to **listserv@who.int**. The subject field should be left blank and the body of the message should contain only the line subscribe wer-reh. A request for confirmation will be sent in reply.

Comment accéder au REH sur Internet?

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@who.int** en laissant vide le champ du sujet. Le texte lui même ne devra contenir que la phrase suivante: subscribe wer-reh.

www.who.int/wer
Email • send message **subscribe wer-reh** to **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@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

Avian influenza	**http://www.who.int/csr/disease/avian_influenza/en/**	Grippe aviaire
Buruli ulcer	**http://www.who.int/buruli/en/**	Ulcère de Buruli
Child and adolescent health and development	**http://www.who.int/child_adolescent_health/en/**	Santé et développement des enfants et des adolescents
Cholera	**http://www.who.int/cholera/en/**	Choléra
Deliberate use of biological and chemical agents	**http://www.who.int/csr/delibepidemics/informationresources/en/**	Usage délibéré d'agents chimiques et biologiques
Dengue	**http://www.who.int/denguecontrol/en/**	Dengue
Epidemic and pandemic surveillance and response	**http://www.who.int/csr/en/**	Alerte et action en cas d'épidémie et de pandémie
Eradication/elimination programmes	**http://www.who.int/topics/infectious_diseases/en/**	Programmes d'éradication/élimination
Fact sheets on infectious diseases	**http://www.who.int/topics/infectious_diseases/factsheets/en/**	Aide-mémoires sur les maladies infectieuses
Filariasis	**http://www.filariasis.org**	Filariose
Geographical information systems (GIS)	**http://gamapserver.who.int/mapLibrary/**	Systèmes d'information géographique
Global atlas of infectious diseases	**http://apps.who.int/globalatlas/InteractiveMap/HowTo/HowTo.htm**	Atlas mondial des maladies infectieuses
Global Outbreak Alert and Response Network (GOARN)	**http://www.who.int/csr/outbreaknetwork/en/**	Réseau mondial d'alerte et d'action en cas d'épidémie (GOARN)
Health topics	**http://www.who.int/topics/en**	La santé de A à Z
Human African trypanosomiasis	**http://www.who.int/trypanosomiasis_african/en/**	Trypanosomiase humaine africaine
Influenza	**http://www.who.int/csr/disease/influenza/en/**	Grippe
Influenza network (FluNet)	**http://who.int/flunet**	Réseau grippe (FluNet)
International Health Regulations	**http://www.who.int/ihr/en/**	Règlement sanitaire international
International travel and health	**http://www.who.int/ith/en/**	Voyages internationaux et santé
Leishmaniasis	**http://www.who.int/leishmaniasis/en**	Leishmaniose
Leprosy	**http://www.who.int/lep/en**	Lèpre
Lymphatic filariasis	**http://www.who.int/lymphatic_filariasis/en/**	Filiariose lymphatique
Malaria	**http://www.who.int/malaria/en**	Paludisme
Neglected tropical diseases	**http://www.who.int/neglected_diseases/en/**	Maladies tropicales négligées
Onchocerciasis	**http://www.who.int/onchocerciasis/en/**	Onchocercose
Outbreak news	**http://www.who.int/csr/don/en**	Flambées d'épidémies
Poliomyelitis	**http://www.polioeradication.org**	Poliomyélite
Rabies	**http://www.who.int/rabies/en**	Rage
Global Foodborne Infections Network (GFN)	**http://www.who.int/gfn/en**	Réseau mondial d'infections d'origine alimentaire
Smallpox	**http://www.who.int/csr/disease/smallpox/en**	Variole
Schistosomiasis	**http://www.who.int/schistosomiasis/en/**	Schistosomiase
Soil-transmitted helminthiases	**http://www.who.int/intestinal_worms/en/**	Géohelminthiases
Trachoma	**http://www.who.int/trachoma/en/**	Trachome
Tropical disease research	**http://www.who.int/tdr/**	Recherche sur les maladies tropicales
Tuberculosis	**http://www.who.int/tb/en** and/et **http://www.stoptb.org**	Tuberculose
Immunization, Vaccines and Biologicals	**http://www.who.int/immunization/en/**	Vaccination, Vaccins et Biologiques
Weekly Epidemiological Record	**http://www.who.int/wer/**	Relevé épidémiologique hebdomadaire
WHO Lyon Office for National Epidemic Preparedness and Response	**http://www.who.int/ihr/lyon/en/index.html**	Bureau OMS de Lyon pour la préparation et la réponse des pays aux épidémies
WHO Pesticide Evaluation Scheme (WHOPES)	**https://www.who.int/whopes/resources/en/**	Schéma OMS d'évaluation des pesticides (WHOPES)
WHO Mediterranean Centre for Vulnerability Reduction, Tunis	**http://wmc.who.int/**	Centre Méditerranéen de l'OMS pour la Réduction de la Vulnérabilité à Tunis (WMC)
Yellow fever	**http://www.who.int/csr/disease/yellowfev/en/**	Fièvre jaune

Pneumococcal vaccines: WHO position paper on their use in community outbreak settings

Addendum to Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019

Introduction

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes. They summarize essential background information on diseases and vaccines and conclude with the current WHO position on the use of vaccines worldwide.

The papers are reviewed by external experts and WHO staff, and reviewed and endorsed by the WHO Strategic Advisory Group of Experts (SAGE) on Immunization (www.who.int/immunization/sage/en). A description of the processes followed for the development of vaccine position papers is available at: www.who.int/immunization/position_papers/position_paper_process.pdf .

The position papers are intended for use mainly by national public health officials and managers of immunization programmes. They may also be of interest to international funding agencies, vaccine advisory groups, vaccine manufacturers, the medical community, the scientific media, and the general public.

The current WHO position on the use of pneumococcal vaccine is set out in the 2019 WHO position paper: *Pneumococcal conjugate vaccines in infants and children*

Utilisation des vaccins antipneumococciques dans le cadre de flambées épidémiques communautaires: note de synthèse de l'OMS

Addendum au document Vaccins antipneumococciques conjugués chez les nourrissons et les enfants de moins de 5 ans: note de synthèse de l'OMS – février 2019

Introduction

Conformément à son mandat, qui prévoit qu'elle conseille les États Membres en matière de politique sanitaire, l'OMS publie une série de notes de synthèse régulièrement mises à jour sur les vaccins et les associations vaccinales contre les maladies ayant une incidence sur la santé publique internationale. Ces notes, qui portent principalement sur l'utilisation des vaccins dans les programmes de vaccination à grande échelle, résument les informations essentielles sur les maladies et les vaccins correspondants et présentent en conclusion la position actuelle de l'OMS concernant l'utilisation de ces vaccins à l'échelle mondiale.

Ces notes sont examinées par des experts externes et des membres du personnel de l'OMS, puis évaluées et approuvées par le Groupe stratégique consultatif d'experts sur la vaccination (SAGE) de l'OMS (www.who.int/immunization/sage/fr). La procédure suivie pour élaborer les notes de synthèse sur les vaccins est décrite dans le document: www.who.int/immunization/position_papers/position_paper_process.pdf.

Les notes de synthèse s'adressent avant tout aux responsables nationaux de la santé publique et aux administrateurs des programmes de vaccination, mais elles peuvent également présenter un intérêt pour les organismes internationaux de financement, les groupes consultatifs sur la vaccination, les fabricants de vaccins, le corps médical, les médias scientifiques et le grand public.

La position actuelle de l'OMS sur l'utilisation des vaccins antipneumococciques est exposée dans la note de synthèse de 2019 de l'OMS, intitulée *Vaccins antipneumococciques conjugués*

under 5 years of age.[1] Those recommendations are unchanged. This addendum to the 2019 position paper pertains specifically to use of pneumococcal vaccine to prevent or respond to community outbreaks. Recommendations on the use of pneumococcal vaccine in community outbreak settings were discussed by SAGE in October 2020.[2] The evidence presented at the meeting can be accessed here: www.who.int/immunization/sage/meetings/2020/october/SAGE_eYB_Oct2020final.pdf?ua=1.

Background

While pneumococcal meningitis is generally an endemic disease, it has the potential to cause large community outbreaks, similar to those caused by *Neisseria meningitidis*. In 2016, WHO provisionally defined an outbreak as occurring in a district or subdistrict with a weekly incidence of ≥5 suspected cases/100 000 population with at least 60% of confirmed meningitis cases due to *Streptococcus pneumoniae* and ≥10 confirmed cases of pneumococcal meningitis.[3] Pneumococcal outbreaks have been reported in communities in Africa within the meningitis belt and in areas contiguous to this region. Between 2000 and 2018, a total of 10 outbreaks of pneumococcal meningitis were identified in Africa through a systematic review of the literature and review of surveillance data.[4] Occasional outbreaks of invasive pneumococcal disease and pneumonia have also been reported in mostly indigenous populations in Australia.[5]

The 10 identified outbreaks of pneumococcal meningitis in Africa were reported in the following countries: Burkina Faso, Central African Republic, Chad and Ghana. These outbreaks showed up to a tenfold higher incidence of pneumococcal meningitis than the local baseline. They ranged in size from 71 to 1733 suspected cases (maximum weekly incidence from 13 to 350 cases per 100 000), among which 37–92% of cases were laboratory-confirmed as pneumococcal meningitis. In 6 outbreaks with data on annual cumulative incidence, this ranged from 78 to 504 per 100 000 (median 107 per 100 000). The case–fatality ratio (CFR) for suspected cases ranged from 4% to 18% and for confirmed pneumococcal cases from 10% to 46%. Three of the outbreaks lasted for more than a year and were considered recur-

chez les nourrissons et les enfants de moins de 5 ans.[1] Ces recommandations restent inchangées. Le présent addendum à la note de synthèse de 2019 traite spécifiquement de l'utilisation des vaccins antipneumococciques pour prévenir ou combattre une flambée épidémique communautaire. Les recommandations relatives à l'utilisation des vaccins antipneumococciques en situation de flambée communautaire ont été examinées par le SAGE en octobre 2020.[2] Les éléments présentés lors de cette réunion peuvent être consultés à l'adresse: www.who.int/immunization/sage/meetings/2020/october/SAGE_eYB_Oct2020final.pdf?ua=1.

Contexte

Bien que la méningite pneumococcique soit généralement une maladie endémique, elle est susceptible de donner lieu à de larges flambées communautaires, comparables à celles provoquées par *Neisseria meningitidis*. En 2016, l'OMS a formulé une définition provisoire selon laquelle il existe une flambée dès lors qu'un district ou sous-district enregistre une incidence hebdomadaire ≥5 cas suspects pour 100 000 habitants, avec au moins 60% des cas confirmés de méningite imputables à *Streptococcus pneumoniae* et ≥10 cas confirmés de méningite pneumococcique.[3] Des flambées de pneumococcie ont été signalées dans certaines communautés d'Afrique, à l'intérieur ou à la périphérie de la région appelée «ceinture de la méningite». Une revue systématique de la littérature et l'examen des données de surveillance ont mis en évidence 10 flambées de méningite pneumococcique survenues en Afrique entre 2000 et 2018.[4] Des flambées occasionnelles de pneumococcie invasive et de pneumonie ont également été signalées en Australie, principalement parmi des populations autochtones.[5]

Les 10 flambées de méningite pneumococcique identifiées en Afrique concernaient les pays suivants: Burkina Faso, Ghana, République centrafricaine et Tchad. L'incidence de la méningite pneumococcique enregistrée lors de ces flambées était jusqu'à dix fois supérieure à l'incidence de base locale. Le nombre de cas suspects variait entre 71 et 1733 selon la flambée (incidence hebdomadaire maximale comprise entre 13 et 350 cas pour 100 000 habitants), dont 37-92% ont été confirmés en laboratoire comme étant des cas de méningite pneumococcique. Dans les 6 flambées pour lesquelles on dispose de données sur l'incidence annuelle cumulée, cette dernière variait entre 78 et 504 pour 100 000 habitants (valeur médiane 107 pour 100 000). Le taux de létalité (TL) variait entre 4% et 18% parmi les cas suspects, et entre 10% et 46% chez les cas confirmés de pneumococcie. Trois de ces flambées ont duré plus d'un an et étaient

[1] Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. Weekly Epidemiological Record. 2019;94:85-104 (https://apps.who.int/iris/bitstream/handle/10665/310968/WER9408.pdf?ua=1; accessed February 2021).

[2] Highlights from the Meeting of the 5–7 October 2020 (www.who.int/publications/m/item/highlights-from-the-meeting-of-the-5-7-october-2020, accessed March 2021).

[3] Pneumococcal meningitis outbreaks in sub-Saharan Africa. Weekly Epidemiological Record. 2016; 91(23):298–302.

[4] Franklin K, Kwambana-Adams B, Lessa FC, Soeters H, Cooper L, Coldiron ME et al. Pneumococcal meningitis outbreaks in Africa, 2000–2018: Systematic literature review and meningitis surveillance database analyses (in press).

[5] Cook HM, Giele CM, Jayasinghe SH, Wakefield A, Krause VL for the Enhanced Invasive Pneumococcal Disease Surveillance Working Group. An outbreak of serotype-1 sequence type 306 invasive pneumococcal disease in an Australian Indigenous population. Commun Dis Intell (2018). 2020;44 (https://doi.org/10.33321/cdi.2020.44.66) Epub 15/09/2020

[1] Vaccins antipneumococciques conjugués chez les nourrissons et les enfants de moins de 5 ans: note de synthèse de l'OMS – février 2019. Relevé épidémiologique hebdomadaire. 2019;94:85-104 (https://apps.who.int/iris/bitstream/handle/10665/310968/WER9408.pdf?ua=1; consulté en février 2021).

[2] Highlights from the Meeting of the 5–7 October 2020 (www.who.int/publications/m/item/highlights-from-the-meeting-of-the-5-7-october-2020, consulté en mars 2021).

[3] Flambées de méningite à pneumocoque en Afrique subsaharienne. Relevé épidémiologique hebdomadaire. 2016; 91(23):298–302.

[4] Franklin K, Kwambana-Adams B, Lessa FC, Soeters H, Cooper L, Coldiron ME et al. Pneumococcal meningitis outbreaks in Africa, 2000–2018: Systematic literature review and meningitis surveillance database analyses (sous presse).

[5] Cook HM, Giele CM, Jayasinghe SH, Wakefield A, Krause VL for the Enhanced Invasive Pneumococcal Disease Surveillance Working Group. An outbreak of serotype-1 sequence type 306 invasive pneumococcal disease in an Australian Indigenous population. Commun Dis Intell (2018). 2020;44 (https://doi.org/10.33321/cdi.2020.44.66) Epub 15/09/2020

rent. Half (5) of the outbreaks were mixed outbreaks caused by meningococcus and pneumococcus; in 7 of the 10 outbreaks, pneumococcus accounted for more than 50% of cases.[6]

Seven of the 10 outbreaks occurred prior to the introduction of pneumococcal conjugate vaccine (PCV) into the infant immunization programme. The age group most affected in these outbreaks was children under 5 years of age. For the 3 outbreaks that occurred after introduction of PCV, individuals over the age of 5 years were most affected. Serotype 1 (ST1) was the predominant pneumococcal serotype (43–75% of isolates) identified in the 4 outbreaks where serotyping of isolates was done. Two of these 4 outbreaks occurred prior to the introduction of PCV and 2 occurred less than 5 years after introduction of PCV (which included ST1) into the childhood immunization programme. This evidence suggests that routine immunization programmes have provided direct protection against ST1 pneumococcal meningitis; however, indirect protection in older children and adults was not observed in the first few years after PCV introduction.

Many challenges have been faced in identifying and responding to outbreaks of pneumococcal meningitis in African countries. These challenges include: case identification; laboratory confirmation, especially when lumbar puncture and testing of cerebral spinal fluid (CSF) samples are not routinely collected; inadequate data capture and reporting within national surveillance systems; poor microbiological capacity; and low public awareness of the disease. Additional programme issues include ensuring appropriate case management.

A number of strategies have been proposed to prevent or mitigate these outbreaks.[7] They include: reactive immunization campaigns, improving routine immunization coverage in children; catch-up campaigns for those under 5 years of age at the time of vaccine introduction; and using an immunization schedule with a booster dose, e.g. a schedule with 2 primary doses followed by a booster dose (2p+1) for infant vaccination (rather than 3 primary doses (3p+0)).

To estimate the impact of reactive vaccination campaigns at different time points after identification of an outbreak, mathematical modeling was conducted using data from vaccinated individuals aged 5 to 29 years in the 2015–16 pneumococcal outbreak in the Brong-Ahafo region of Ghana. Modelling estimates indicate that if a vaccination campaign is implemented at the time an epidemic is declared, 35% of cases of pneumococcal meningitis could be prevented; if vaccination is started within 2 weeks of declaration of the outbreak, 21% of

considérées comme récurrentes. La moitié (5) des flambées étaient de nature mixte, imputables à la fois aux méningocoques et aux pneumocoques; dans 7 des 10 flambées, les pneumocoques étaient responsables de plus de 50% des cas.[6]

Sur les 10 flambées, 7 se sont produites avant que le vaccin antipneumococcique conjugué (VPC) ne soit introduit dans le programme de vaccination du nourrisson. Les enfants de moins de 5 ans constituaient la tranche d'âge la plus touchée par ces flambées. Dans les 3 flambées survenues après l'introduction du VPC, les sujets de plus de 5 ans étaient les plus touchés. Dans les 4 flambées pour lesquelles un sérotypage des isolats a été effectué, le sérotype 1 était le sérotype pneumococcique prédominant (43-75% des isolats). Deux de ces 4 flambées se sont produites avant l'introduction du VPC et les 2 autres sont apparues moins de 5 ans après l'introduction du VPC (comprenant le sérotype 1) dans le programme de vaccination de l'enfant. Ces données laissent supposer que les programmes de vaccination systématique ont conféré une protection directe contre la méningite à pneumocoques de sérotype 1; cependant, aucune protection indirecte des enfants plus âgés ou des adultes n'a été observée dans les premières années suivant l'introduction du VPC.

La détection et l'endiguement des flambées de méningite pneumococcique dans les pays africains se sont heurtés à de nombreux obstacles, notamment dans les domaines suivants: identification des cas; confirmation en laboratoire, en particulier lorsque les ponctions lombaires et les analyses du liquide céphalorachidien (LCR) ne sont pas collectées de manière systématique; collecte et notification inadéquates des données dans le cadre des systèmes de surveillance nationaux; faibles capacités de microbiologie; et connaissance insuffisante de la maladie par le public. D'autres difficultés se posent au niveau programmatique, notamment en matière de prise en charge des cas.

Plusieurs stratégies ont été proposées pour prévenir ou atténuer ces flambées.[7] Elles reposent notamment sur les axes suivants: campagnes de vaccination réactive; amélioration de la couverture vaccinale systématique chez l'enfant; campagnes de rattrapage chez les sujets de moins de 5 ans au moment de l'introduction du vaccin; et application d'un calendrier vaccinal comprenant une dose de rappel, par exemple selon un schéma à 2 doses de primovaccination suivies d'une dose de rappel (2p+1) chez les nourrissons (plutôt que 3 doses de primovaccination (3p+0)).

Pour estimer l'impact que peuvent avoir les campagnes de vaccination réactive selon le moment où elles sont menées après la détection d'une flambée, une modélisation mathématique a été effectuée à partir des données recueillies sur les personnes âgées de 5 à 29 ans qui ont été vaccinées lors de la flambée de pneumococcie de 2015-2016 dans la région de Brong-Ahafo au Ghana. Les estimations issues de cette modélisation indiquent que si une campagne de vaccination est mise en œuvre dès que l'épidémie est déclarée, 35% des cas de méningite pneumococcique pourraient être évités, contre 21%

[6] SAGE meeting of October 2020 (www.who.int/immunization/sage/meetings/2020/october/presentations_background_docs/en/, accessed March 2021).

[7] Stuart J. Can infant vaccination prevent pneumococcal meningitis outbreaks in sub-Saharan Africa? European Journal of Tropical Medicine and International Health. 2017;22(5):514-5 (https://onlinelibrary.wiley.com/doi/full/10.1111/tmi.12860).

[6] Réunion d'octobre 2020 du SAGE (www.who.int/immunization/sage/meetings/2020/october/presentations_background_docs/en/, consulté en mars 2021).

[7] Stuart J. Can infant vaccination prevent pneumococcal meningitis outbreaks in sub-Saharan Africa? European Journal of Tropical Medicine and International Health. 2017;22(5):514-5 (https://onlinelibrary.wiley.com/doi/full/10.1111/tmi.12860).

cases could be prevented; with a 4-week delay, only 11% of cases could be prevented. The number needed to vaccinate (NNV) to prevent one case was estimated to be between 9100 and 27 800, a higher range than previous estimates for reactive meningococcal vaccination campaigns (3700–11 600 for a 2–4-week delay). However, the NNV to prevent death may be comparable to that for reactive meningococcal vaccination, since pneumococcal meningitis has a higher case–fatality ratio. Since vaccination is conducted in response to outbreaks of meningococcal meningitis, countries may view a similar response to pneumococcal meningitis outbreaks as fair or equitable for affected communities, despite limited evidence of impact.

The Pneumococcal Serotype Replacement and Distribution Estimation (PSERENADE) project analysed data from 44 surveillance sites (Europe (21), North America (7), Africa (7), Latin America (2), Asia (4), and Oceania (3)) to examine the direct and indirect effects of routine use in childhood programmes of PCV10 and PCV13 on the incidence of ST1 invasive pneumococcal disease (IPD).[6] Implementation of routine infant PCV immunization led to an 85% decrease in ST1 IPD in children and adults of all ages 6 years after introduction. No difference was observed by region, by PCV product, by schedule (3p+0 or 2p+1) or by under-5 mortality strata, although some subgroups included few countries. In the 5 African countries that provided data for PSERENADE, including one in the meningitis belt, 3 of which used a 3p+0 schedule, the direct and indirect effects of PCV in children and adults were similar to those in other countries (using a 2p+1 schedule) by year 5 after vaccine introduction. In the 5 African countries, ST1 IPD was virtually eliminated by year 5 in children up to 17 years of age (and also in one site among adults ≥18 years, where data were available for this age group). However, 4 of the 5 African countries were outside the meningitis belt or were non-contiguous to areas where outbreaks were reported, so that data were insufficient to compare the impact of different PCV schedules in the meningitis belt.

Three of the 5 African sites with 3p+0 schedules that provided data to the PSERENADE project used a catch-up campaign to immunize older children as well as infants who were age-eligible for routine vaccination at the time of PCV10/13 introduction: in 2 sites, children under the age of 1 year were vaccinated (Kilifi, Kenya and Blantyre District, Malawi) and in one site, those under 5 years were vaccinated (Asembo, Kenya). Although these sites showed a faster decline in ST1 IPD incidence in the first 2 years of PCV10/13 use compared with a 4th 3p+0 African site (Basse, Gambia), results after 4 years of use were similar. The data are too limited to allow any differences to be attributed solely

des cas si la vaccination est démarrée dans les 2 semaines et 11% si ce délai est de 4 semaines. Il a été estimé que le nombre de personnes à vacciner pour prévenir un cas s'établissait entre 9100 et 27 800, ce qui est plus élevé que les estimations précédemment obtenues pour les campagnes de vaccination réactive contre les méningocoques (3700-11 600 pour un délai de 2 à 4 semaines). Toutefois, le nombre de personnes à vacciner pour prévenir un décès pourrait être comparable à celui de la vaccination antiméningococcique réactive compte tenu du taux de létalité plus élevé de la méningite pneumococcique. Étant donné qu'une vaccination est mise en œuvre en riposte aux flambées de méningite à méningocoques, les pays pourraient considérer qu'une riposte similaire aux flambées de méningite à pneumocoques est juste ou équitable pour les communautés touchées, malgré les preuves limitées de leur impact.

Dans le cadre du projet PSERENADE (estimation de la distribution et du remplacement des sérotypes pneumococciques), les données provenant de 44 sites de surveillance (Europe (21), Amérique du Nord (7), Afrique (7), Amérique latine (2), Asie (4) et Océanie (3)) ont été analysées pour examiner les effets directs et indirects de l'utilisation du VPC10 et du VPC13 dans les programmes de vaccination systématique de l'enfant sur l'incidence de la pneumococcie invasive due au sérotype 1.[6] La mise en œuvre de la vaccination systématique par le VPC chez les nourrissons s'est soldée, 6 ans après son introduction, par une baisse de 85% des cas de pneumococcie invasive attribuables au sérotype 1 chez les enfants et les adultes de tous les âges. Aucune différence n'a été observée entre les régions, les types de VPC, les schémas de vaccination (3p+0 ou 2p+1) ou les strates de mortalité chez les enfants de moins de 5 ans, bien qu'il faille noter que certains sous-groupes ne comprenaient que peu de pays. Parmi les 5 pays africains ayant fourni des données pour le projet PSERENADE, dont 1 se situait dans la ceinture de la méningite, on a observé que dans les 3 pays qui appliquaient un schéma 3p+0, les effets directs et indirects de l'administration du VPC chez les enfants et les adultes étaient comparables à ceux constatés dans les autres pays (appliquant un schéma 2p+1) 5 ans après l'introduction du vaccin. Dans ces 5 pays africains, la pneumococcie invasive imputable au sérotype 1 avait pratiquement été éliminée au bout de 5 ans chez les enfants âgés de 17 ans ou moins (et, sur un site, chez les adultes de ≥18 ans, lorsque les données sur cette tranche d'âge étaient disponibles). Cependant, 4 des 5 pays africains étudiés ne se situaient ni à l'intérieur de la ceinture de la méningite, ni à proximité immédiate de zones où des flambées avaient été notifiées, de sorte que les données étaient insuffisantes pour comparer l'impact de différents schémas d'administration du VPC dans la ceinture de la méningite.

Trois des 5 sites africains utilisant un schéma d'administration 3p+0 qui ont fourni des données au projet PSERENADE avaient mené une campagne de rattrapage pour vacciner les enfants plus âgés, ainsi que les nourrissons répondant aux critères d'âge pour la vaccination systématique au moment de l'introduction du VPC10/13: le vaccin a été administré aux enfants de moins de 1 an sur 2 sites (Kilifi, Kenya, et Blantyre District, Malawi) et aux enfants de moins de 5 ans sur un site (Asembo, Kenya). Bien que ces sites aient enregistré un déclin plus rapide de l'incidence de la pneumococcie invasive due au sérotype 1 au cours des 2 premières années d'utilisation du VPC10/13 par rapport au 4e site africain appliquant le schéma 3p+0 (Basse, Gambie), les résultats obtenus au bout de 4 ans étaient compa-

to the impact of catch-up campaigns over temporal-related events at the time of PCV10/13 introduction.

Data from Burkina Faso, which were not included in the PSERENADE analysis, showed that, following introduction of PCV13, the incidence of meningitis caused by the PCV13-serotypes decreased by 32%. The greatest decline was seen among children aged <1 year (76% decrease). Direct protection and herd protection assessed 3 years after introduction were less pronounced for ST1 than for the other PCV13 serotype, and ST1 was still the most common PCV13 type causing meningitis.[8]

Among pneumococcal carriers aged <1 year in Burkina Faso, vaccine type (VT) carriage declined from 55.8% to 36.9 % 3 years after introduction (difference: 18.9%, 95% confidence interval (CI): 1.9–35.9%, P=0.03); among carriers aged 1–4 years, VT carriage declined from 55.3% to 31.8% (difference: 23.5%, 95% CI: 6.8–40.2%, P=0.004). No change in VT carriage prevalence was observed among older children and young adults. There were insufficient data on ST1 carriage to draw any conclusions.[9]

WHO Position

All countries, including those prone to outbreaks, should include PCV in their infant immunization programmes and should maximize coverage. The data reviewed indicate that high coverage with 3 doses of PCV in children will provide protection against endemic pneumococcal meningitis, and is likely to reduce the risk and scale of epidemic outbreaks. Wherever possible, catch-up vaccination at the time that PCV is introduced should be used to accelerate its impact on disease in children aged 1–5 years, particularly in settings with a high disease burden and mortality. For outbreak-prone countries introducing PCV in childhood programmes, a 2p+1 schedule has potential benefits over the 3p+0 schedule, as the former induces higher antibody levels in the second year of life. The impact of this benefit is unknown and must be weighed against programme feasibility and the coverage expected to be achieved with either schedule. In countries where PCV has been given to children for 5 or more years, there is insufficient evidence to recommend a preferred schedule for outbreak-prone areas (i.e. 2p+1 or 3p+0).

rables. Les données disponibles sont trop limitées pour permettre d'imputer les différences observées au seul impact des campagnes de rattrapage par rapport à d'autres événements présentant un lien temporel avec l'introduction du VPC10/13.

Les données provenant du Burkina Faso, qui n'ont pas été incluses dans l'analyse PSERENADE, montrent qu'après l'introduction du VPC13, l'incidence de la méningite due aux sérotypes contenus dans le VPC13 a régressé de 32%. Le déclin le plus important a été observé chez les enfants de <1 an (réduction de 76%). La protection directe et collective induite par la vaccination, évaluée 3 ans après l'introduction du vaccin, était moins prononcée pour le sérotype 1 que pour l'autre sérotype contenu dans le VPC13, et le sérotype 1 était encore le sérotype du VPC13 le plus souvent responsable des cas de méningite.[8]

Parmi les porteurs de pneumocoques âgés de <1 an au Burkina Faso, le portage des sérotypes vaccinaux a diminué, passant de 55,8% à 36,9% 3 ans après l'introduction (différence: 18,9%, intervalle de confiance (IC) à 95%: 1,9–35,9%, P=0,03); parmi les porteurs âgés de 1 à 4 ans, le portage des sérotypes vaccinaux est passé de 55,3% à 31,8% (différence: 23,5%, IC à 95%: 6,8–40,2%, P=0,004). Aucun changement de la prévalence du portage des sérotypes vaccinaux n'a été observé chez les enfants d'un âge plus avancé et chez les jeunes adultes. Les données sur le portage du sérotype 1 étaient insuffisantes pour tirer des conclusions.[9]

Position de l'OMS

Tous les pays, y compris ceux qui sont sujets aux flambées épidémiques, devraient inclure le VPC dans leur programme de vaccination du nourrisson et œuvrer à l'obtention d'une couverture maximale. Les données examinées montrent que la vaccination par 3 doses de VPC chez l'enfant, avec une couverture élevée, confère une protection contre la méningite pneumococcique endémique et réduit probablement le risque et l'ampleur des flambées épidémiques. Dans la mesure du possible, on procèdera à une vaccination de rattrapage lors de l'introduction du VPC afin d'accélérer les effets de la vaccination sur la maladie parmi les enfants âgés de 1 à 5 ans, en particulier dans les zones où la charge de morbidité et la mortalité liées à la maladie sont élevées. Pour les pays sujets aux flambées qui introduisent le VPC dans leur programme de vaccination de l'enfant, le schéma d'administration 2p+1 pourrait présenter des avantages par rapport au schéma 3p+0 car il induit des taux d'anticorps plus élevés au cours de la deuxième année de vie. L'impact de cet avantage n'est pas connu et doit être évalué au regard de la faisabilité programmatique et de la couverture que l'on peut espérer atteindre avec chacun des deux schémas. Dans les pays où le VPC est administré aux enfants depuis au moins 5 ans, les données sont insuffisantes pour recommander un schéma préférentiel (2p+1 ou 3p+0) pour les zones sujettes aux flambées.

[8] Kambiré D, Soeters HM, Ouédrago-Traoré R, Medah I, Sangaré L, Yaméogo G et al. Early impact of 13-valent pneumococcal conjugate vaccine on pneumococcal meningitis – Burkina Faso, 2014-2015. Journal of Infection. 2018;76(3):270-279.

[9] Kabore L, Adebanjoc T, Njanpop-Lafourcadea BM, Ouangraouad S, Tarbangdoe FT, Méda B et al. Pneumococcal carriage in Burkina Faso after 13-valent pneumococcal conjugate vaccine introduction: results from two cross-sectional population-based surveys. BMC infectious diseases, in press.

[8] Kambiré D, Soeters HM, Ouédrago-Traoré R, Medah I, Sangaré L, Yaméogo G et al. Early impact of 13-valent pneumococcal conjugate vaccine on pneumococcal meningitis – Burkina Faso, 2014-2015. Journal of Infection. 2018;76(3):270-279.

[9] Kabore L, Adebanjoc T, Njanpop-Lafourcadea BM, Ouangraouad S, Tarbangdoe FT, Méda B et al. Pneumococcal carriage in Burkina Faso after 13-valent pneumococcal conjugate vaccine introduction: results from two cross-sectional population-based surveys. BMC infectious diseases, in press.

Countries with existing PCV programmes should strengthen service delivery to achieve high and equitable coverage. Subnational variations in immunization coverage will need to be monitored and specific strategies should be implemented to address areas of low coverage.[10]

At this time, the available evidence does not support recommending reactive campaigns against pneumococcal meningitis outbreaks.

High priority should be given to conducting research in outbreak-prone areas to examine the direct and indirect effects on disease and carriage outcomes following administration of PCV to children. Research is needed to better understand the direct and indirect effects of the recommended childhood vaccination schedules on disease and pneumococcal carriage at different coverage levels and various time points after vaccine introduction in countries prone to community outbreaks of pneumococcal meningitis. Strategies to prevent and respond to outbreaks should be studied. Technical assistance and financial support for these endeavours should be provided to encourage and facilitate this work. Surveillance and laboratory capacity should be strengthened to facilitate timely detection of outbreaks and confirmation of the causative agent. This should include training, mentoring, and support to improve lumbar puncture practices and CSF specimen examination and management. ■

Dans les pays déjà dotés de programmes de vaccination par le VPC, il convient de renforcer la prestation des services afin de parvenir à une couverture élevée et équitable. Les variations infranationales de la couverture vaccinale devront être surveillées et des stratégies spécifiques devront être mises en œuvre pour combler les lacunes dans les zones de faible couverture.[10]

À ce jour, les données disponibles ne permettent pas de recommander la tenue de campagnes réactives contre les flambées de méningite pneumococcique.

La priorité doit être accordée à la réalisation de travaux de recherche dans les zones sujettes aux flambées pour examiner les effets directs et indirects de l'administration du VPC aux enfants sur la maladie et le portage. Des études sont nécessaires afin de mieux comprendre les effets directs et indirects des schémas de vaccination recommandés chez l'enfant sur la maladie et sur le portage pneumococcique à différents niveaux de couverture et à différents moments après l'introduction du vaccin dans les pays sujets aux flambées communautaires de méningite pneumococcique. Il convient en outre d'examiner les stratégies de prévention et de riposte aux flambées. Un soutien technique et financier devrait être fourni pour encourager et faciliter ces travaux. Les capacités de surveillance et les moyens des laboratoires devraient être renforcés afin de favoriser la détection en temps utile des flambées et la confirmation rapide de l'agent étiologique. Cela suppose notamment d'offrir des possibilités de formation, un encadrement et un appui pour améliorer les pratiques de ponction lombaire et l'analyse et la gestion des échantillons de liquide céphalorachidien. ■

[10] The RED strategy. Geneva: World Health Organization (https://www.who.int/immunization/programmes_systems/service_delivery/red/en/, accessed March 2021).

[10] The RED strategy. Genève: Organisation mondiale de la santé (https://www.who.int/immunization/programmes_systems/service_delivery/red/en/, consulté en mars 2021).

World Health Organization

Session 5

Measles Case Fatality Ratio estimation

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

13 September 2022

Alyssa Sbarra[1,2], Jon Mosser[2,3], Mark Jit[1], Allison Portnoy[4]

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

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Outline

- Motivation
- Modelling and data updates
- Future work and discussion

Following the March 2022 meeting, IVIR-AC:

- Reinforced previous recommendations to make **resources available** to support model development, literature and data reviews, and the generation of CFRs, predictions, and projections
- **Recommended clearer language and descriptions** of statistical criteria used for:
    - selecting **the final list of indicators** in each mechanistic modelling group to ensure transparency
    - the **metrics included in decomposition analysis** used to quantify changes
    - the **inclusion of indicators**, or proxy indicators, with no prior evidence of an association to measles CFR versus those for which an association is supported by evidence in the literature
    - the **collinearity of proxy indicators** that fall within more than one mechanistic modelling group
- Suggested considering information on **study quality and case definitions** in the meta-regression modelling framework
- Asked for **validation** of predicted CFRs against **unpublished data sources**
- Recommended creation of a **website** to document project resources
- Suggested that **future iterations** of this work should:
    - periodically reassess indicators and update the list of indicators selected, as needed, with a particular focus on the **potential availability of new data**
    - **expand** the literature searches to **databases**

Following the March 2022 meeting, IVIR-AC:

- Reinforced previous recommendations to make **resources available** to support model development, literature and data reviews, and the generation of CFRs, predictions, and projections
- **Recommended clearer language and descriptions** of statistical criteria used for:
    - selecting **the final list of indicators** in each mechanistic modelling group to ensure transparency
    - the **metrics included in decomposition analysis** used to quantify changes
    - the **inclusion of indicators**, or proxy indicators, with no prior evidence of an association to measles CFR versus those for which an association is supported by evidence in the literature
    - the **collinearity of proxy indicators** that fall within more than one mechanistic modelling group
- Suggested considering information on **study quality and case definitions** in the meta-regression modelling framework
- Asked for **validation** of predicted CFRs against **unpublished data sources**
- Recommended creation of a **website** to document project resources
- Suggested that **future iterations** of this work should:
    - periodically reassess indicators and update the list of indicators selected, as needed, with a particular focus on the **potential availability of new data**
    - **expand** the literature searches to **databases**

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
- Modelling and data updates
    - Step 1: updates to modeling framework
    - Step 2: updates to covariates
    - Step 3: updates to data (and age)
    - Results
    - Validation and sensitivity analyses
- Future work and discussion

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

Step 1: updates to modelling framework

Former (Lancet paper)	Updated
Log-linear regression	Fixed-effects meta-regression (with option for mixed-effects)
Uses cases as weights	Uses standard error as weights
Model in log-linear space	Model uses logit(CFR) as outcome

Step 1: 5-fold cross validation metrics

IS	Former model	Updated model
Correlation	0.29	0.3415
RMSE	0.0616	0.0598
Mean Error	0.0104	0.0075
Mean Abs. Error	0.0356	0.0354

OOS	Former model	Updated model
Correlation	0.2897	0.3376
RMSE	0.0624	0.0608
Mean Error	0.0100	0.0052
Mean Abs. Error	0.0357	0.0364

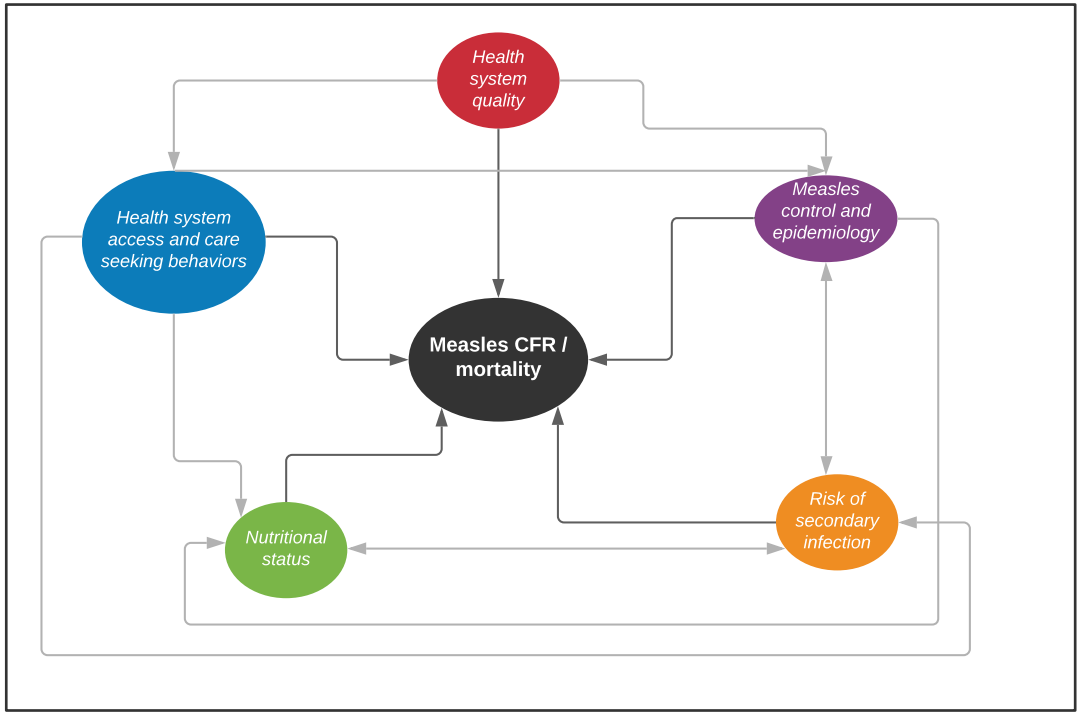
Step 2: covariate updates

I. Finalized list of new indicators from systematic review
II. Identified covariate sets to represent indicators
III. Data analysis to remove collinear covariates and those without likely ability to be informative in predictions of CFR
IV. Interpolated and projected missing covariate values
V. Transformed and standardized for each covariate set
VI. Applied to updated modeling framework with validation

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
    - **Determined from expert working group review, not statistical criteria**
- Created a conceptual framework relating mechanistic groups to CFR
- Conducted a systematic literature review to assess strength evidence of relationships between indicators and CFR
    - **Revised to include both significant and non-significant relationships**
- 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



List of covariates with significant evidence and passed data analysis

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

GDP per capita (as proxy for general equity indicator)

HIV prevalence

Maternal education (covariate set for educational attainment)

MCV1 coverage

Prop urban (as proxy for travel time to nearest health care facility)

TFR (as proxy for average household size)

Under-5 mortality rate

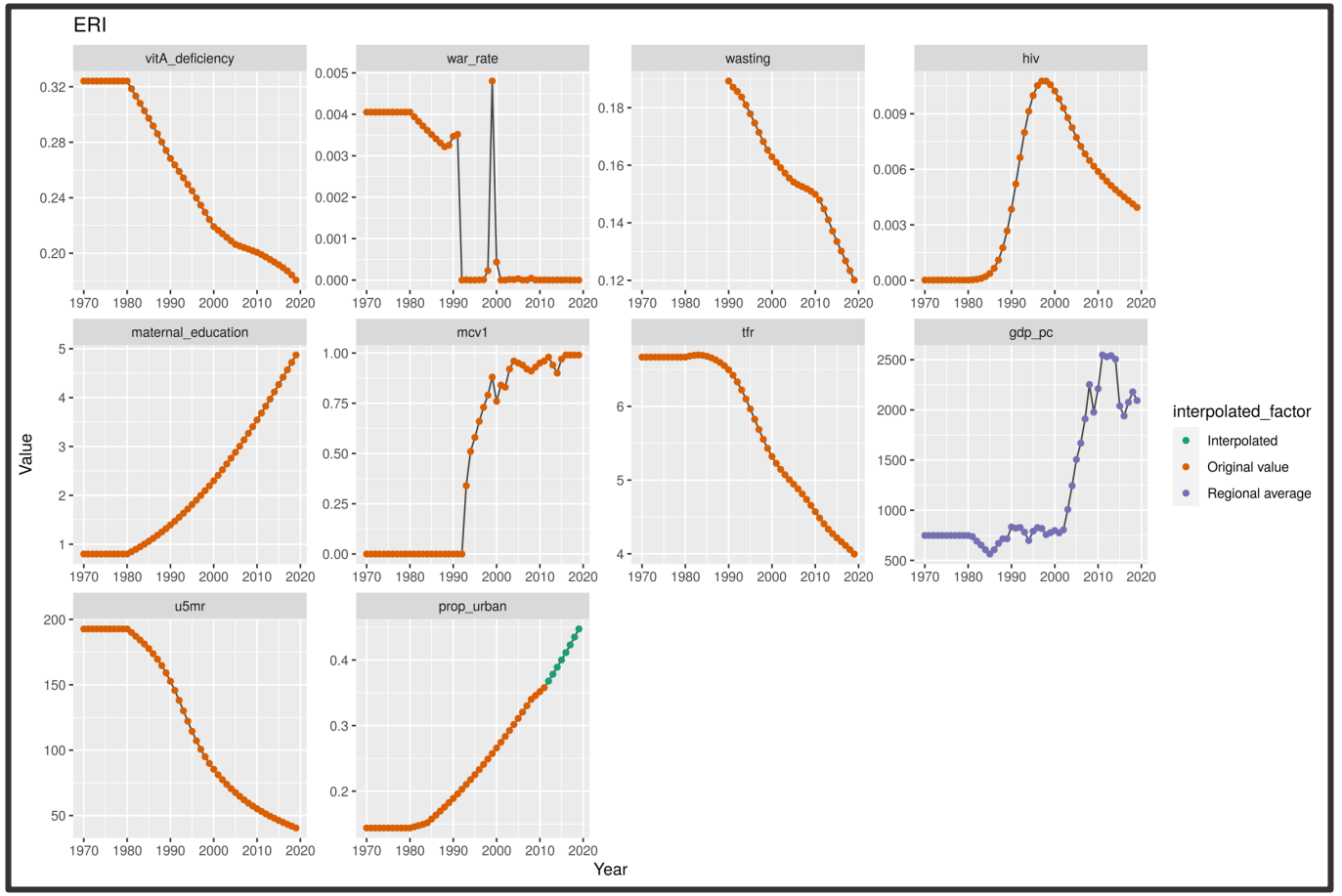
Vitamin A deficiency prevalence

War and terrorism mortality rate (covariate set for surrounding conflict)

Wasting prevalence

Interpolation

- If missing < 25% of data:
  - End of time series: forwards projections using annualized rate of change, with exponential weights
  - Beginning of time series: backwards projections using annualized rate of change, with exponential weights
    - Except wasting prevalence – sensitivity analysis
  - Middle of time series: linear interpolation between latest years of data available
- If missing >= 25% of data: used regional covariate average for entire time series



Transformation and standardization

- Compare transformed covariate options (untransformed, log, logit) to CFR data observations
- Compare overall distribution of covariate observations to those in observed data and full prediction set
- Perform regression and select transformation via model with lowest AIC score

$$logit(CFR) = \beta_0 + \beta_1(transformed\ covariate)$$

- Standardized covariates per:

$$standardized\ covariate = \frac{transformed\ covariate - mean}{SD}$$

In- and out-of-sample validation

IS	Former model	Step 1	Step 2
Correlation	0.29	0.3415	0.3929
RMSE	0.0616	0.0598	0.0591
ME	0.0104	0.0075	-0.0010
MAE	0.0356	0.0354	0.0349

OOS	Former model	Step 1	Step 2
Correlation	0.2897	0.3376	0.3833
RMSE	0.0624	0.0608	0.0616
ME	0.0100	0.0052	-0.0022
MAE	0.0357	0.0364	0.0362

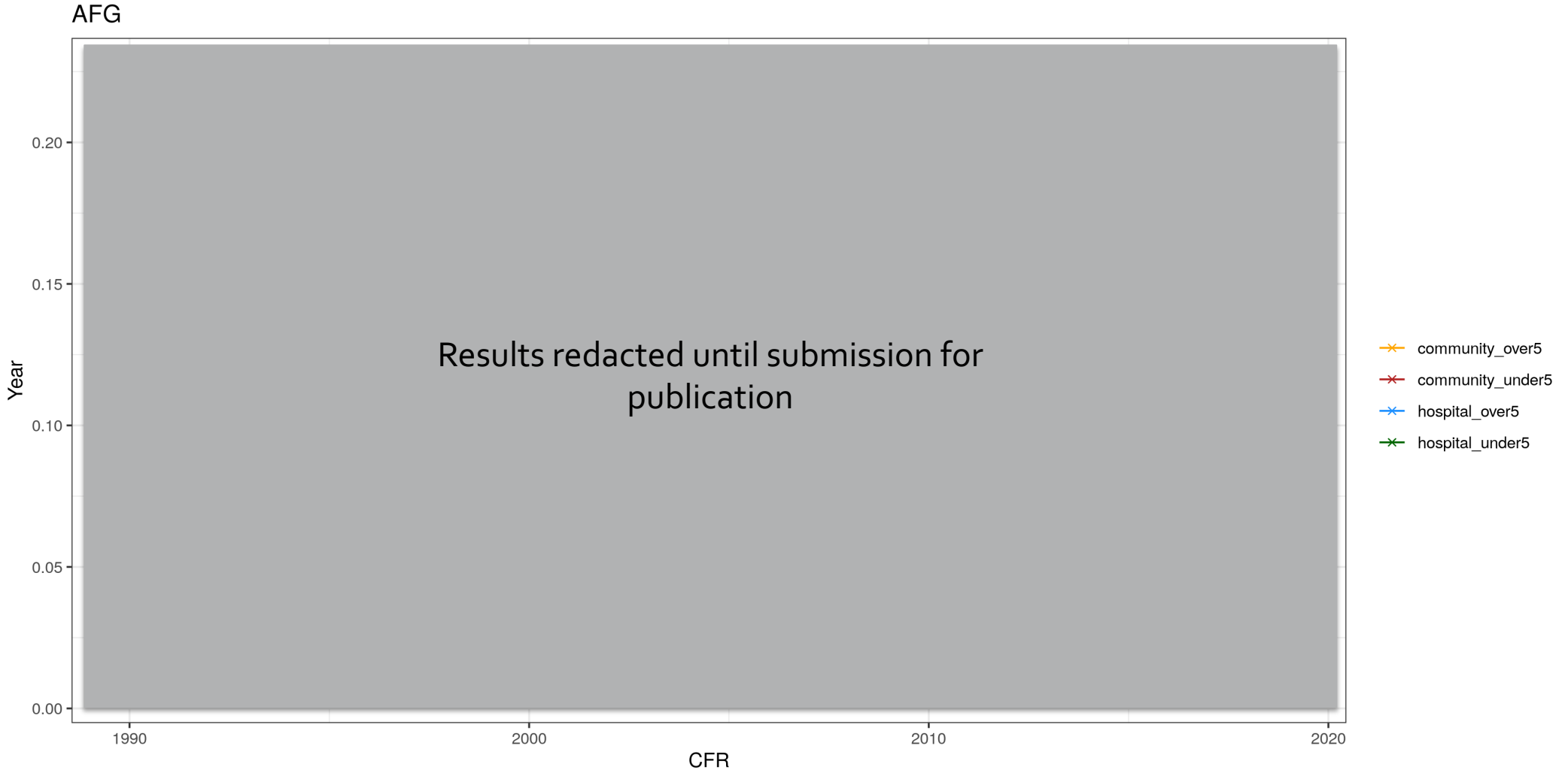
Step 3: Data updates

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

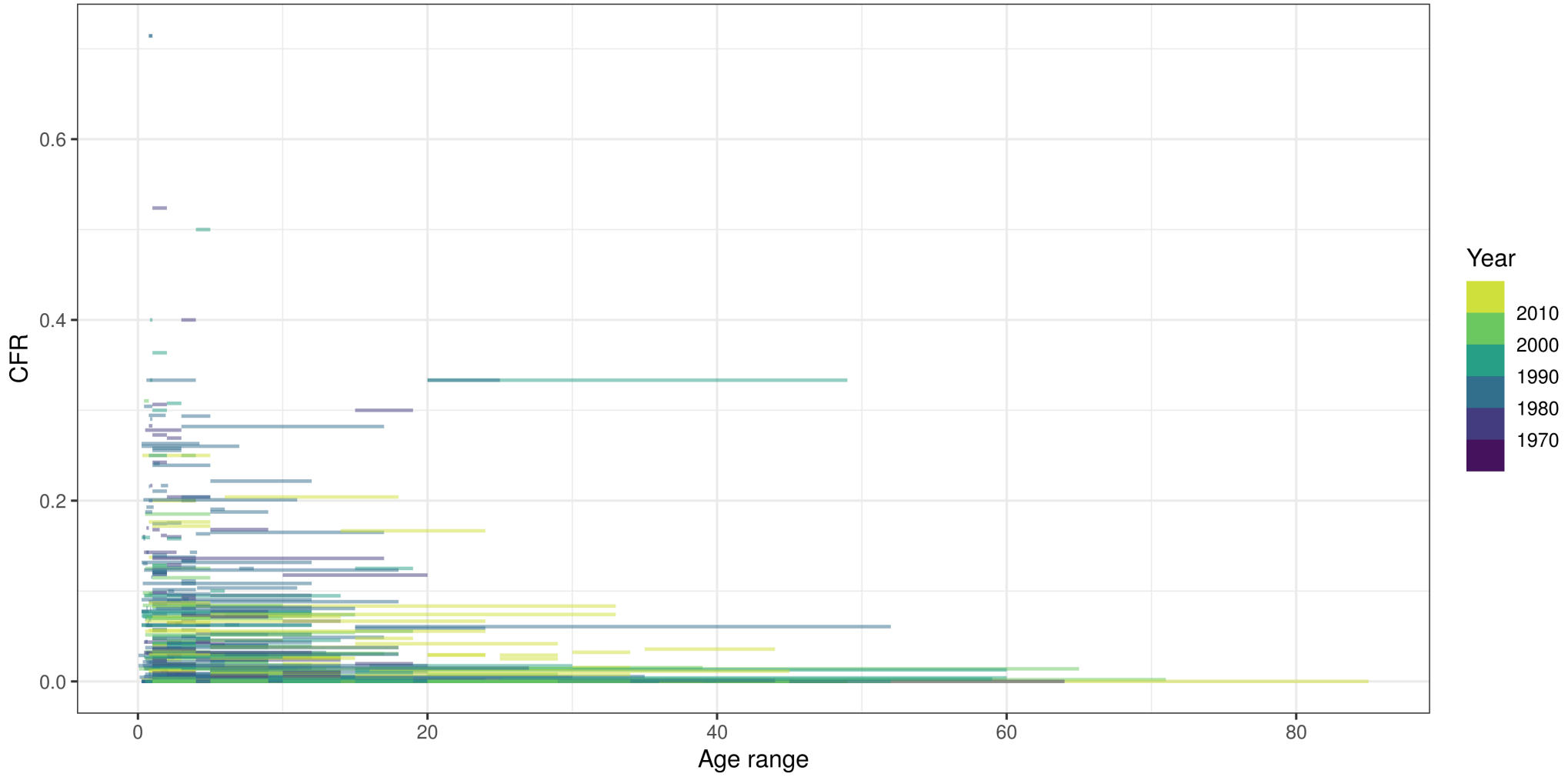
- High-income countries:
  - 1980 – present: updated literature review

- Other: non-English studies

Results without additional age modifications



Age granularity in updated data set

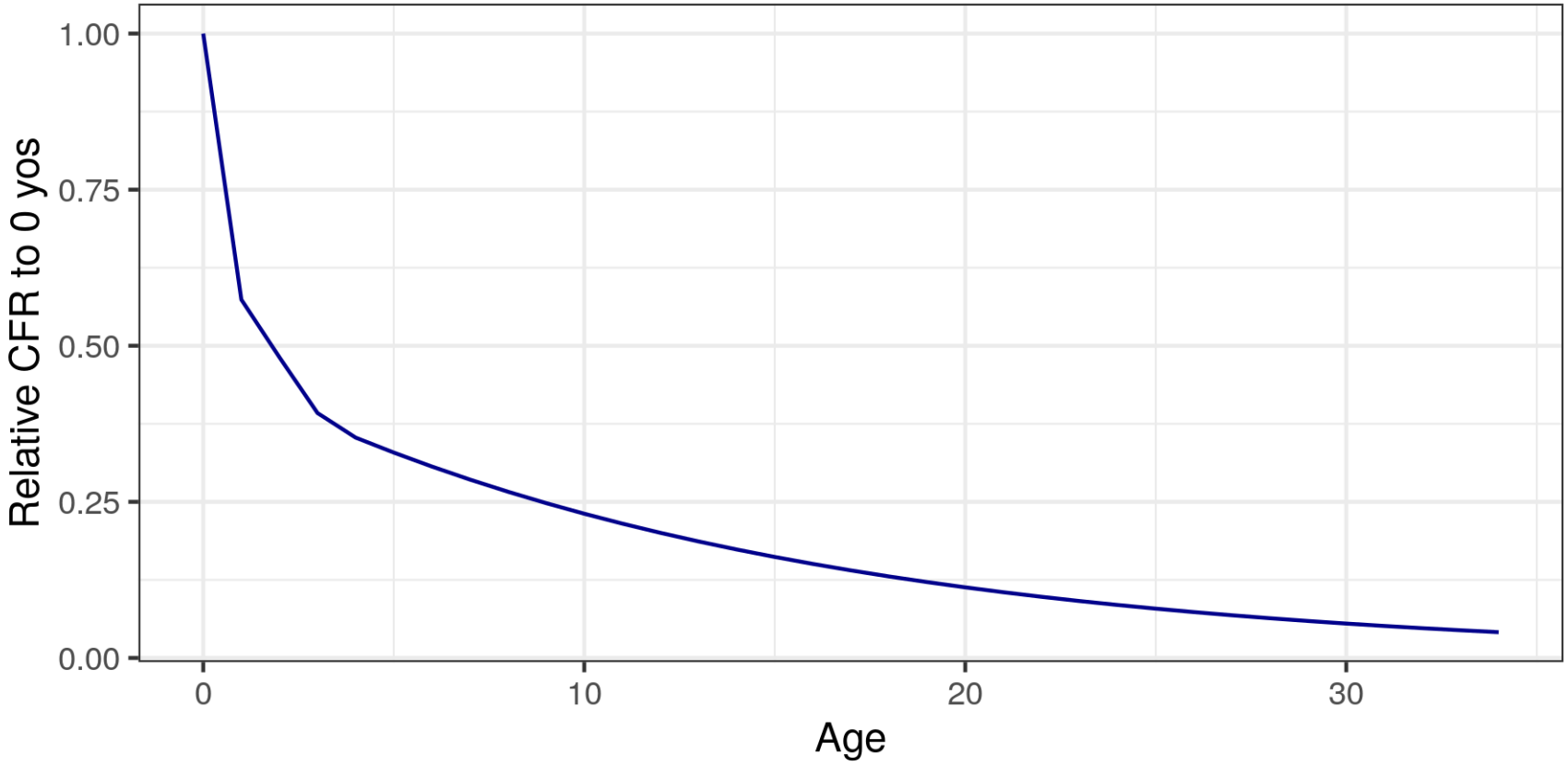


Adapted age methodology

- **Step 1:** To avoid bias among sources with wide age ranges, we have differentially split cases and deaths based on:
  - Cases: modelled age-specific incidence
    - **Only available for low- and middle-income countries**
  - Deaths: a preliminary modeled CFR age curve
    - Only including data in 5yr bins or smaller
    - Meta-regression with spline for age, allowing inclusion of full age range as input

- **Step 2:** "Integration model" in meta-regression framework

Age-splitting CFR curve

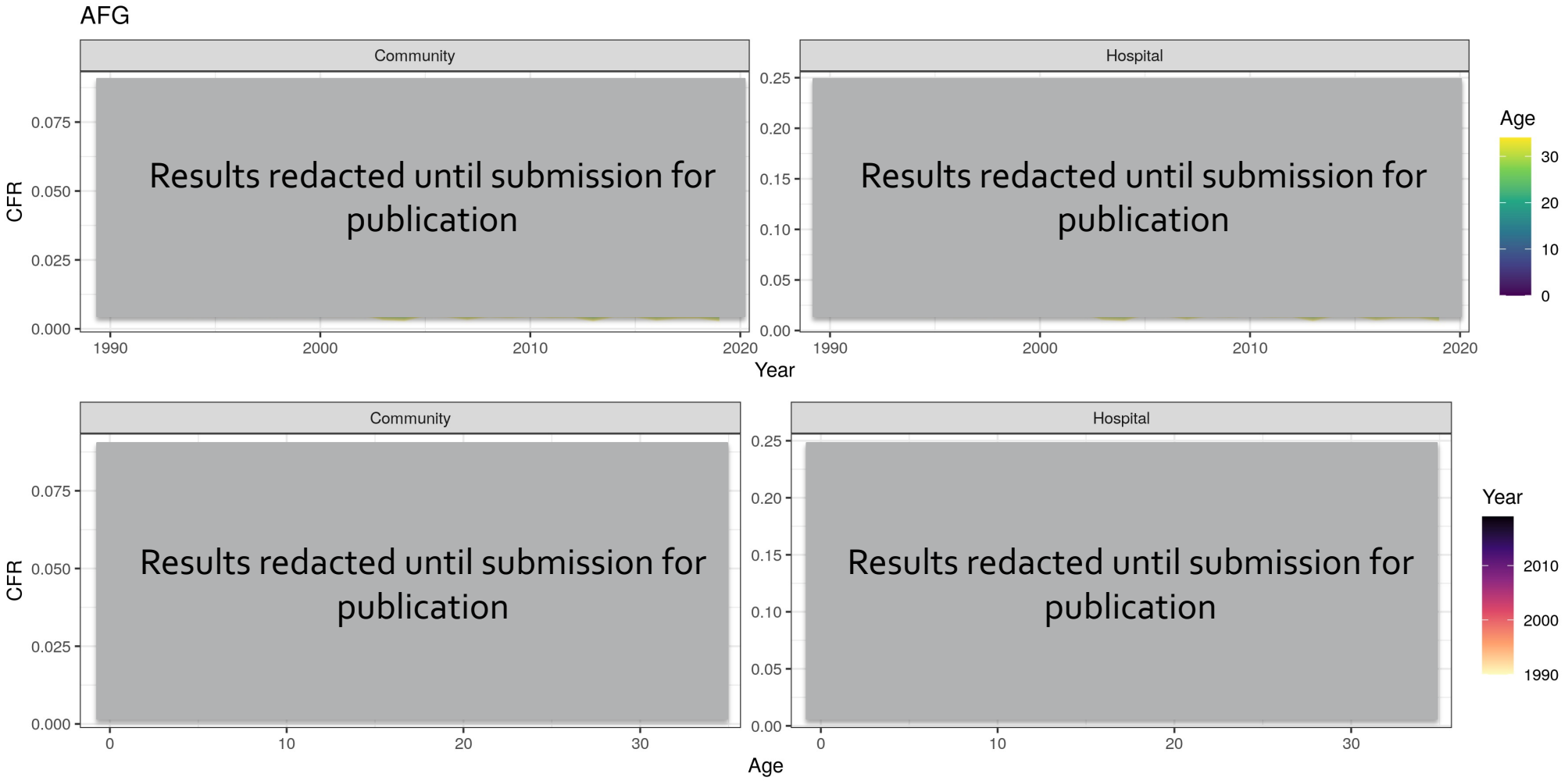


Adapted age methodology

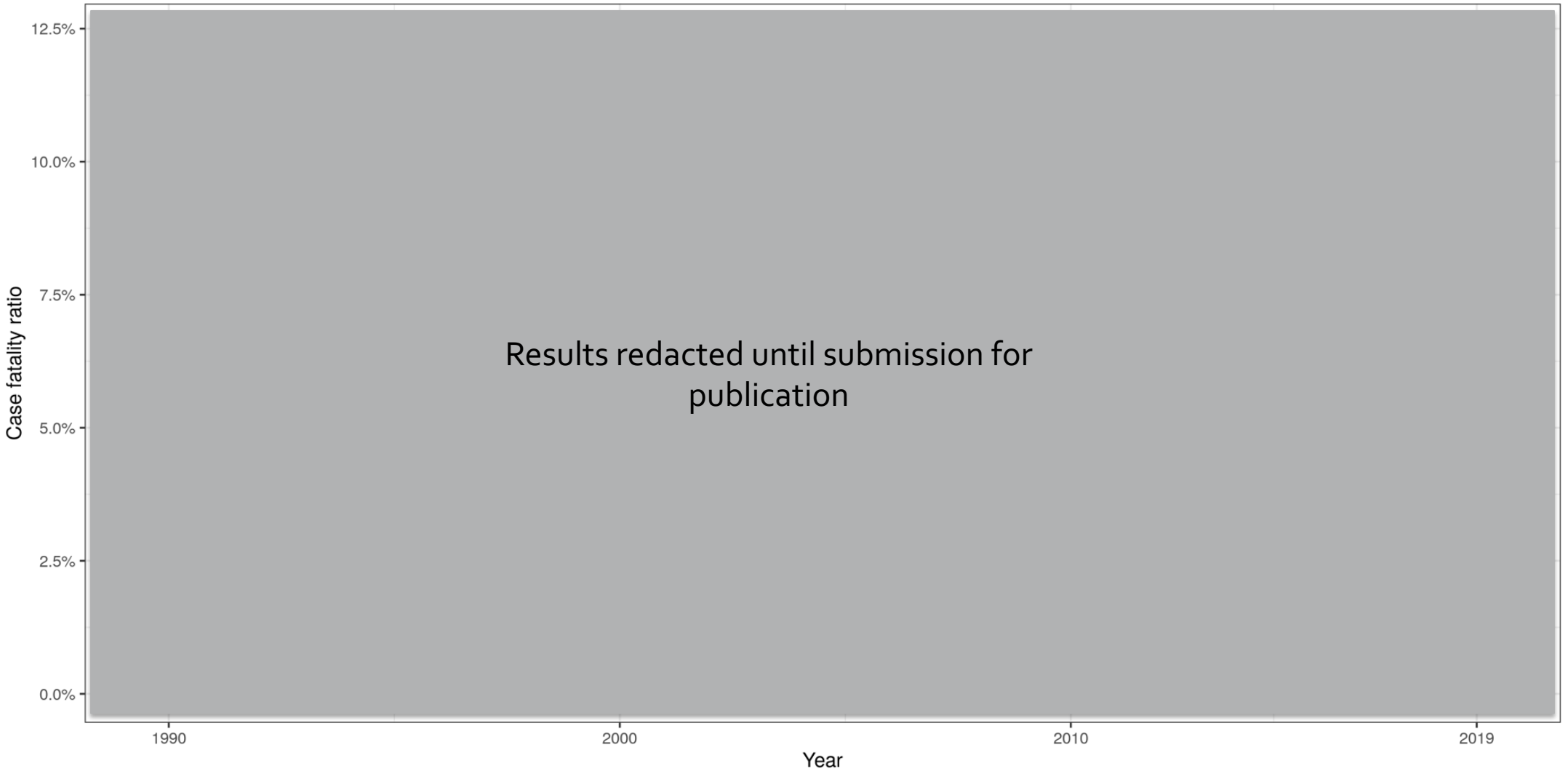
- **Step 1:** To avoid bias among sources with wide age ranges, we have differentially split cases and deaths

- **Step 2:** "Integration model" in meta-regression framework
  - Use full suite of covariates
  - Age start and end input as continuous variable range from data
    - In fitting and prediction, integrate over spline
    - Will yield predictions at any specified age range
  - Various options for knot placement and spline degree
    - AIC score used for best model selection

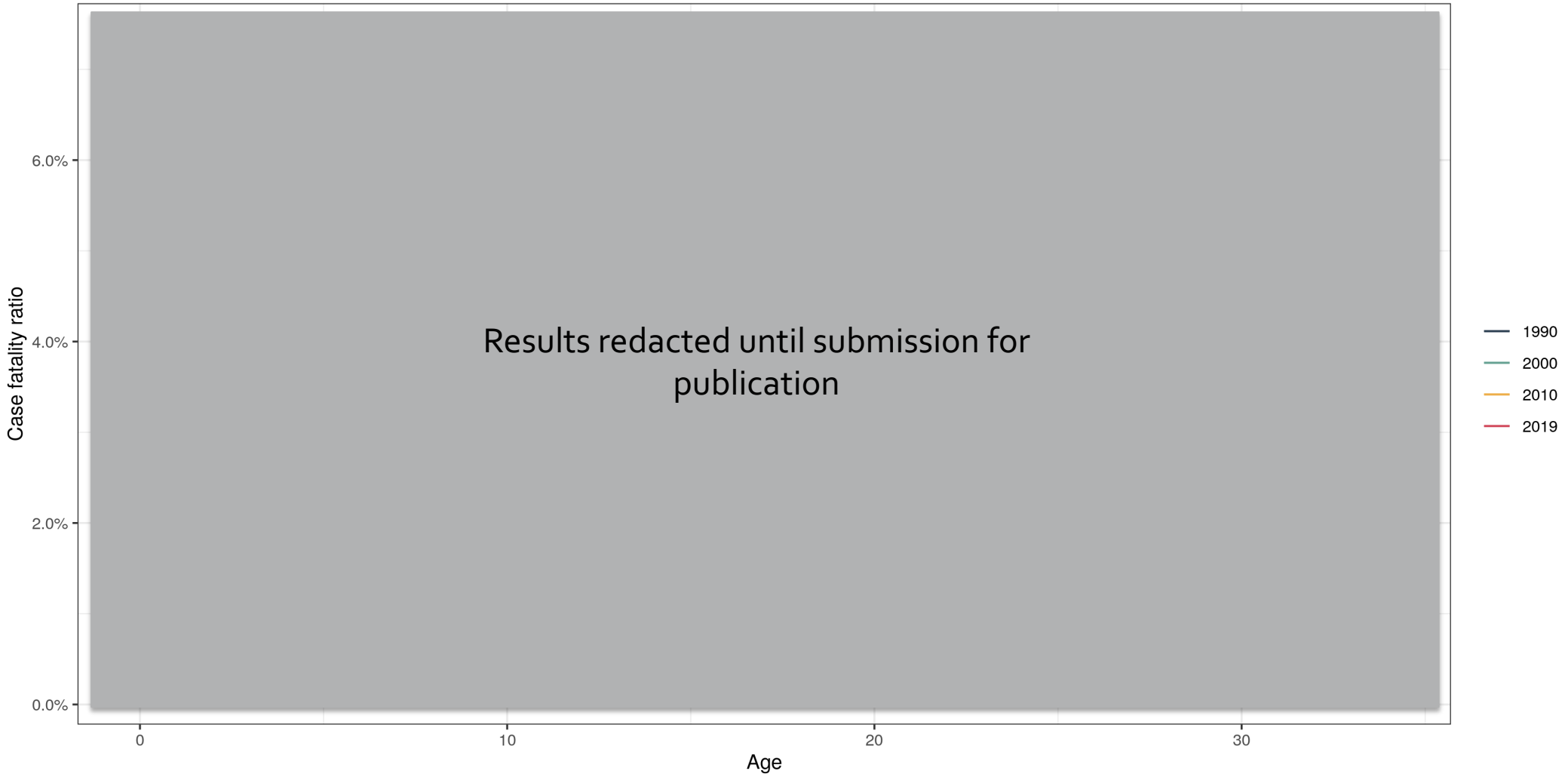
Results


AFG
Community
Hospital
Results redacted until submission for publication
Results redacted until submission for publication
CFR
0.000
0.025
0.050
0.075
0.00
0.05
0.10
0.15
0.20
0.25
1990
2000
2010
2020
Year
Age
30
20
10
0
Community
Hospital
Results redacted until submission for publication
Results redacted until submission for publication
0
10
20
30
Age
Year
2010
2000
1990

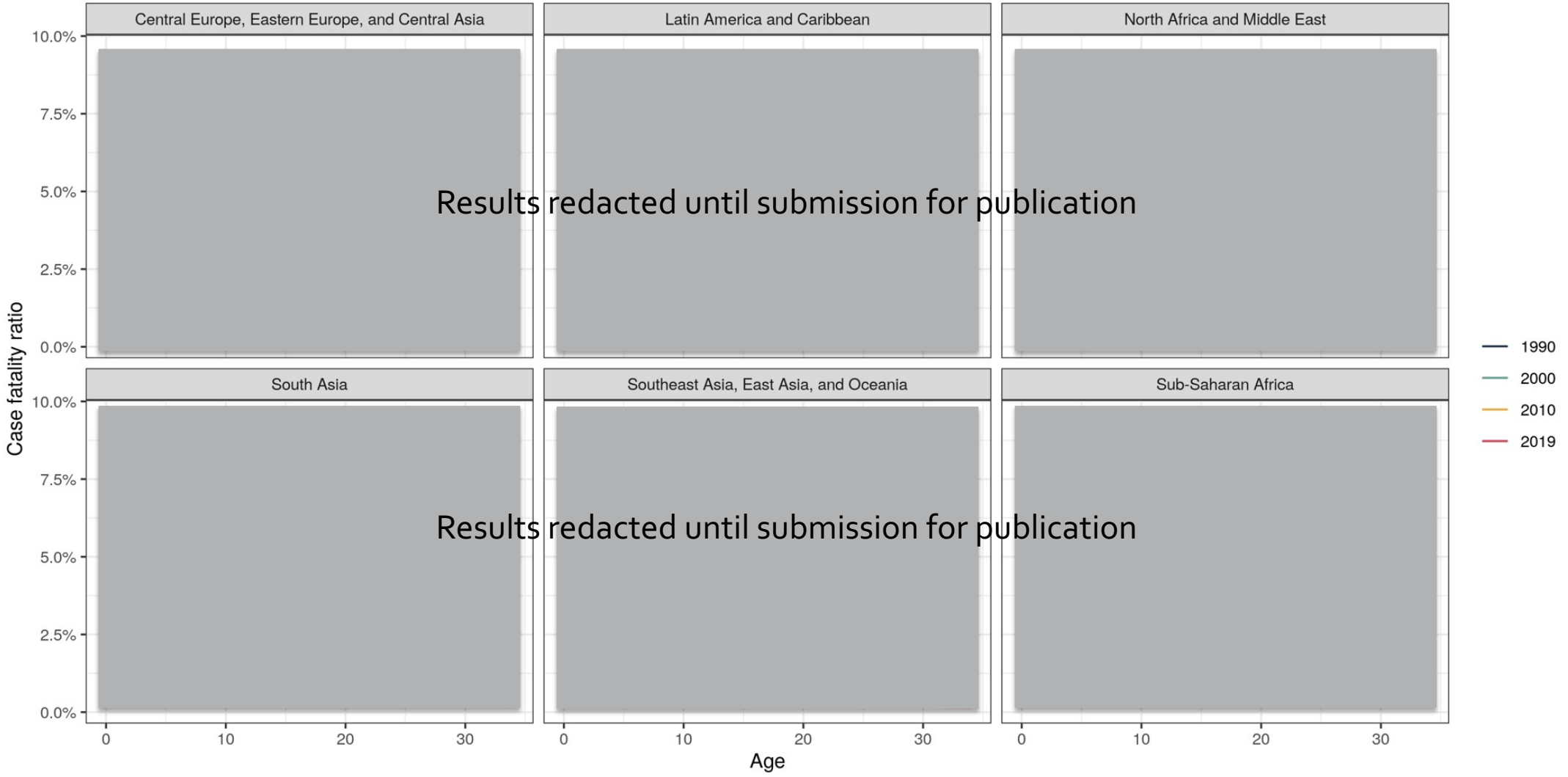
Results


Results redacted until submission for publication
Case fatality ratio
12.5%
10.0%
7.5%
5.0%
2.5%
0.0%
1990
2000
2010
2019
Year

Results


Results redacted until submission for publication
Case fatality ratio
6.0%
4.0%
2.0%
0.0%
0
10
20
30
Age
1990
2000
2010
2019

Results


Central Europe, Eastern Europe, and Central Asia
Latin America and Caribbean
North Africa and Middle East
South Asia
Southeast Asia, East Asia, and Oceania
Sub-Saharan Africa
Case fatality ratio
10.0%
7.5%
5.0%
2.5%
0.0%
0
10
20
30
Age
1990
2000
2010
2019
Results redacted until submission for publication
Results redacted until submission for publication

In- and out-of-sample validation

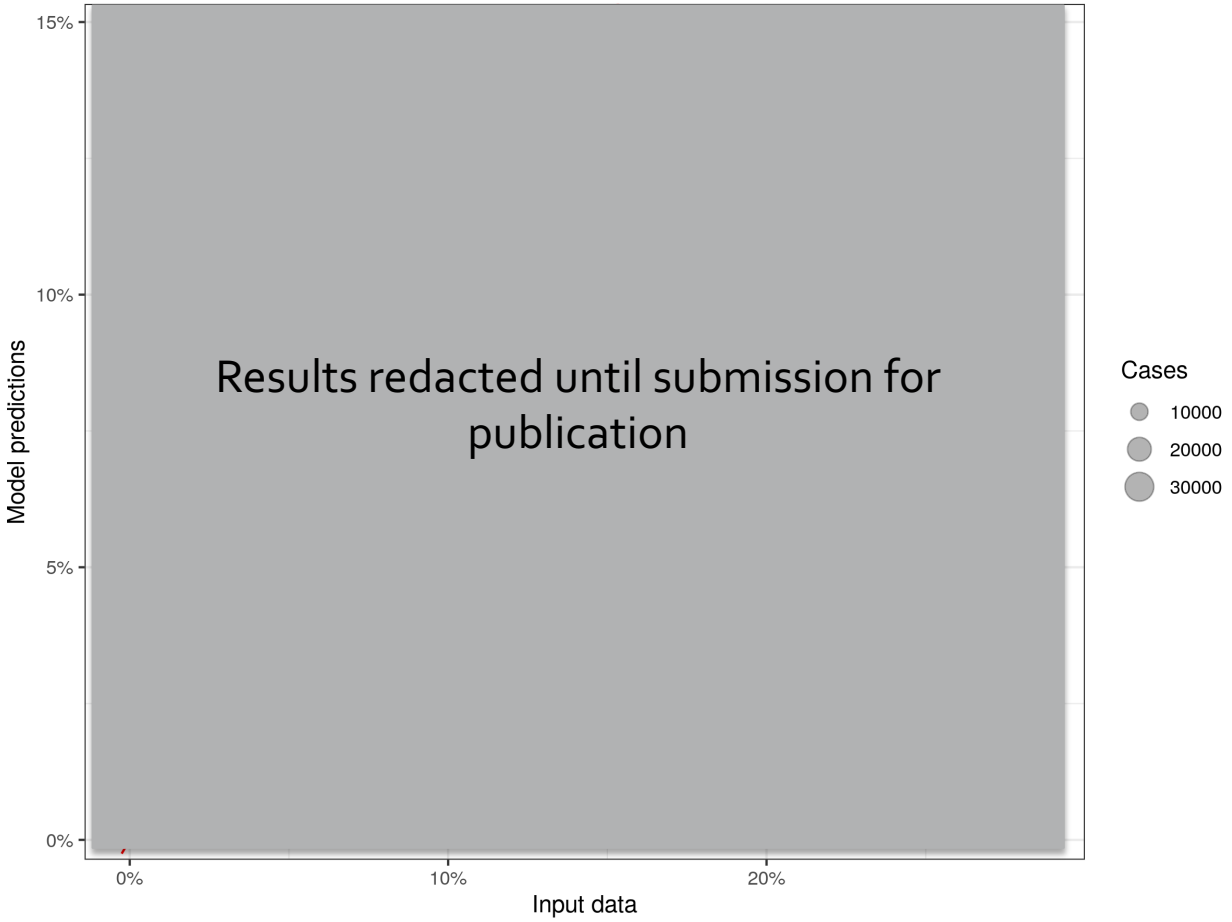
Compared to original data input

	IS	OOS
Correlation	0.5059	0.2454
RMSE	0.1169	0.0834
ME	0.0145	0.0003
MAE	0.0403	0.0345

Compared to age split data input

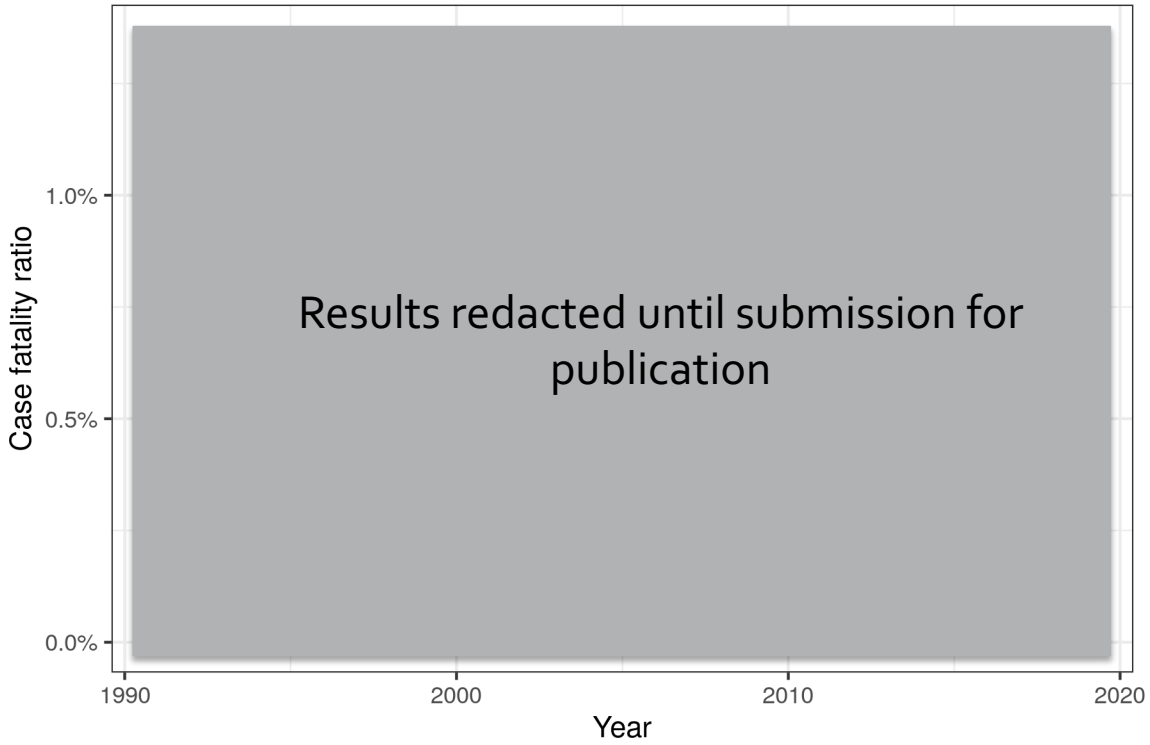
	IS	OOS
Correlation	0.5742	0.4575
RMSE	0.0435	0.0256
ME	0.0013	-0.0007
MAE	0.0166	0.0101

Validation comparing to new sources



Metric	Value
Correlation	0.2039
RMSE	0.0588
Mean error	-0.0017
Mean absolute error	0.0373

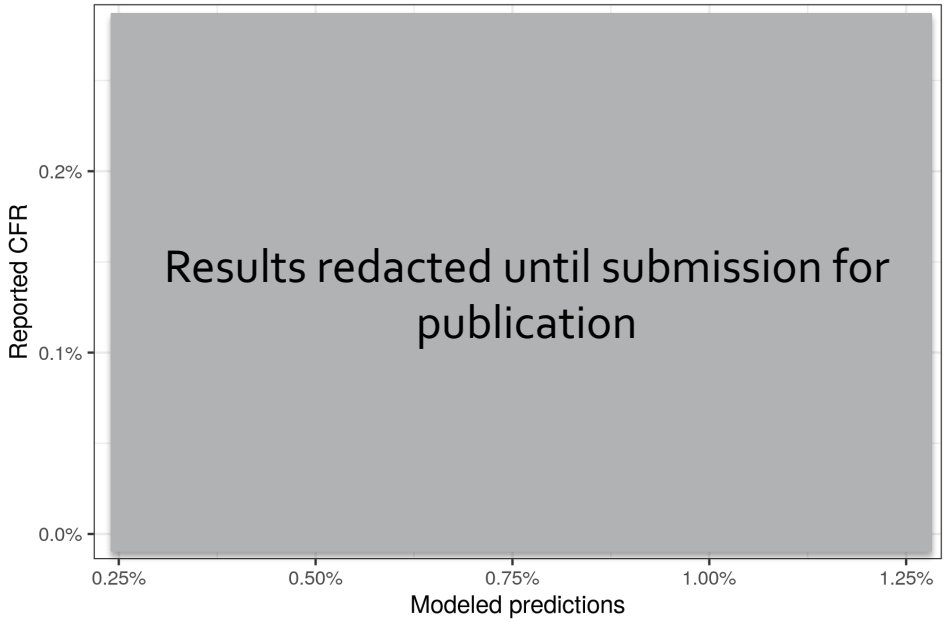
Validation comparing to China surveillance data



Key

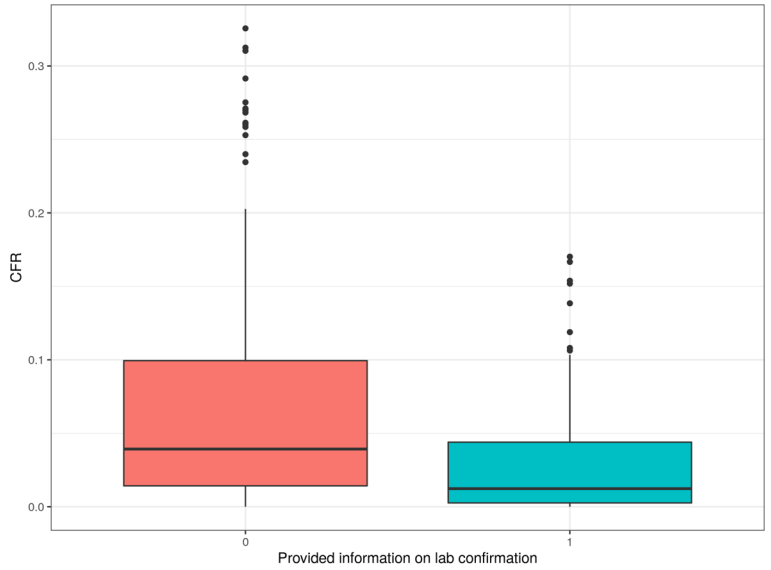
Modeled predictions

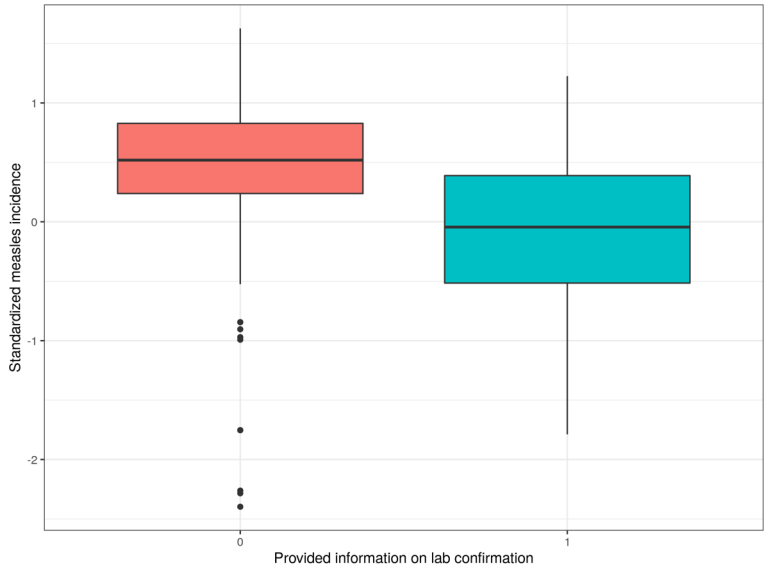
Reported CFR

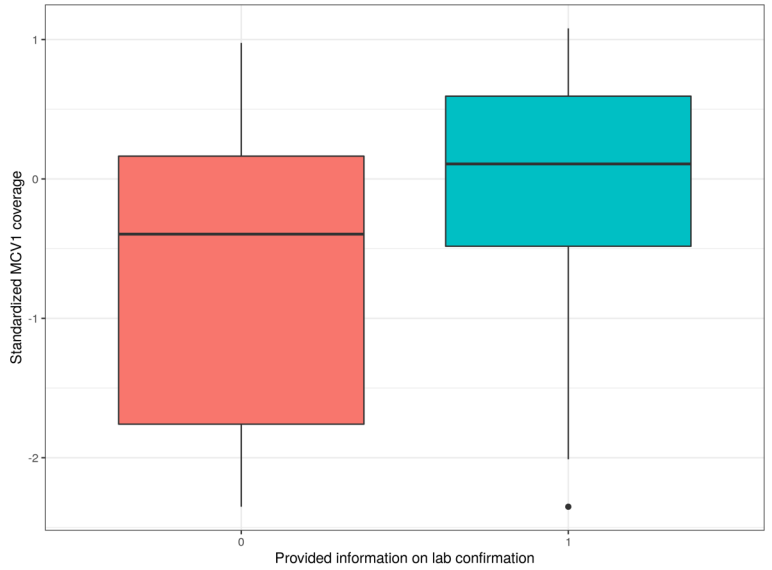


Sensitivity analyses – lab confirmation

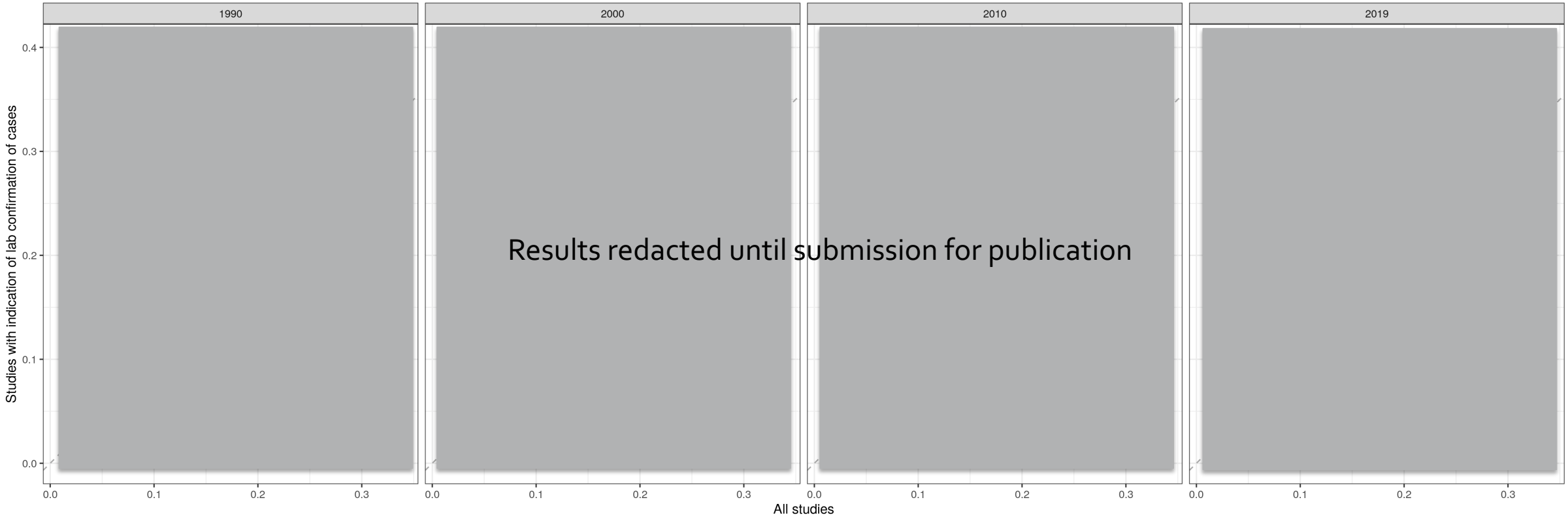
- 88 country-, year-level observations available (of 258)
- Possible differences in underlying study demographics and in CFR reported







Sensitivity analyses – lab confirmation (n = 88)



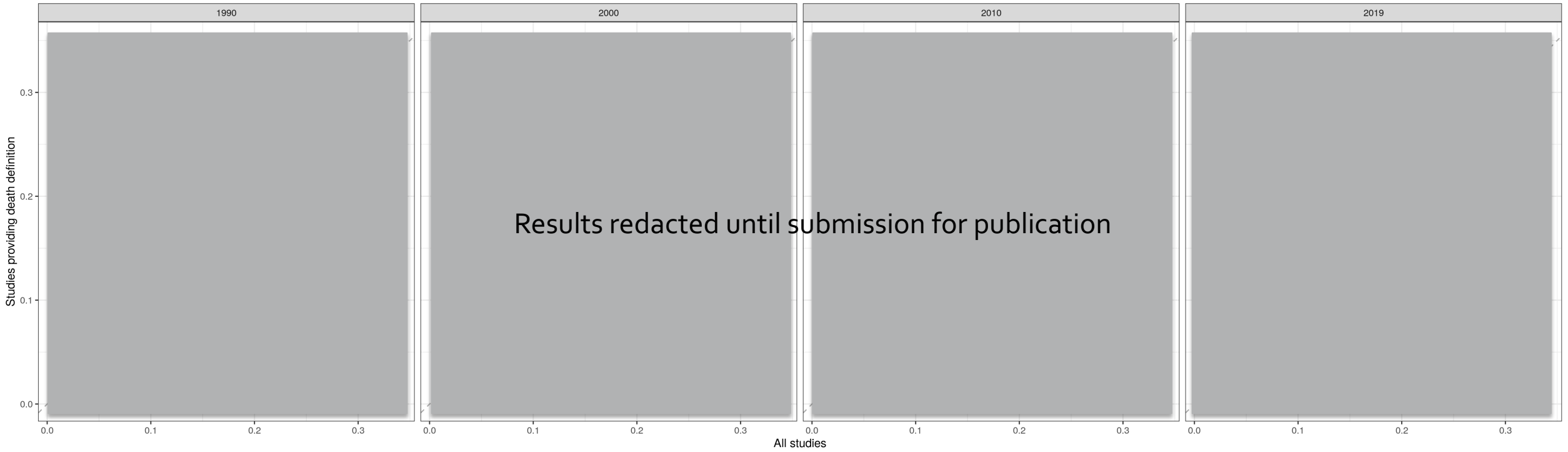
Sensitivity analyses – death definition

- 84 country-, year-level observations available (of 258)
- Possible differences in underlying study demographics

	Did not include death definition	Included death definition
Hospital-based	85	9
Community-based	112	75

$*\chi^2$ p-value < 0.0001

Sensitivity analyses – death definition (n = 84)



Outline

- Motivation
- Modelling and data updates
- Future work and discussion
    - 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

Exercise to examine impact of COVID-19 pandemic

- Informed by available data where possible, with multiple scenario analyses to account for uncertainty

- What covariates **definitely** / **most likely** / **unlikely** experienced a pandemic "shock" in value?
  - e.g., **MCV1 coverage**, **wasting prevalence**, **maternal education**

- Projecting into the future, what are the important considerations and scenarios for covariates to return to pre-pandemic levels and/or trends?
  - e.g., covariate returns to pre-pandemic levels in X number of years – how many scenarios of X?

Open access framework for continued updates

- Planned work: Development of user-friendly R package of the finalized measles CFR estimation framework with clear documentation for both WHO and community use
    - Use cases include annual WHO measles mortality estimation and health impact estimation conducted by the Vaccine Impact Modelling Consortium
- To ensure stability, most covariates will be pre-defined in the package, but some (e.g., measles incidence) will likely require user input
- Covariates for the finalized framework will be updated within the package on an annual basis with accompanying public notifications of the package update once released
- These annual updates do not include re-fitting the model to new primary data beyond what has been done for the current effort

Questions

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

What factors should be considered when applying the model framework to examine short- and long-term impact of COVID-19 pandemic on measles mortality burden?

Are there additional use cases that should be considered for the open access framework (i.e., user-friendly R package with clear documentation) for both WHO and community use?

World Health Organization

Session 6

TB Full Value of Vaccine Assessment (FVVA)

Full Vaccine Value Proposition for Tuberculosis vaccines

WHO IVIR-AC meeting

13 September 2022

- **Birgitte Giersing, WHO (IVB)**
- **Richard White, LSHTM**
- **Nicolas Menzies, Harvard TH Chan School of Public Health**

Overview of the session and objectives

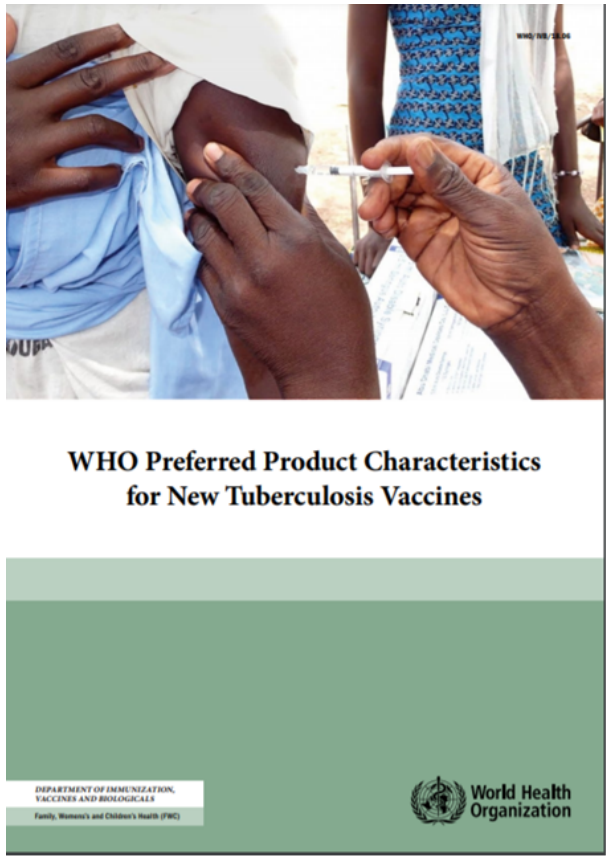
- Birgitte Giersing: Framing and context for the session
- Richard White: Potential **health impact** of new TB vaccines in LMICs that meet WHO Preferred Product Characteristics
- Nick Menzies: Potential **economic impact** of new TB vaccines that meet WHO Preferred Product Characteristics

- **Requests of IVIR-AC:**

➢ Review and comment upon the approach and outcome of the analysis to assess the health and economic impact of new TB vaccines

➢ Comment on/recommend any additional studies that may complement/broaden these initial analyses on the health and economic impact of new TB vaccines

WHO Preferred Product Characteristics guidance for TB vaccines



VI. PPC FOR NEW TUBERCULOSIS VACCINES: USE IN ADOLESCENTS AND ADULTS

Parameter	Preferred Characteristic	Comments
Indication	Immunization for prevention of active pulmonary TB disease.	
Target population	Adolescents and adults.	Adolescents and adults with TB disease represent the most common sources of *Mtb* spread and are therefore the WHO priority target for TB vaccine development. Demographic changes in some high endemicity countries justify inclusion of older adults in the target population. The optimal timing for paediatric evaluation should be discussed with regulators and policy makers but a paediatric clinical development program should certainly be considered when proof of concept is established in adolescents and adults.
Outcome measure and efficacy	50% or greater efficacy in preventing confirmed pulmonary TB.	A vaccine with lesser vaccine efficacy against confirmed TB in adolescents and adults, if widely used in areas of high TB endemicity, may still prove valuable and contribute to reducing the spread of *Mtb* in a cost-effective way *(4)*, but this would fall short of the requirements necessary to meet the End TB goals by the 2035 target date. A bacteriologically confirmed case of TB is the preferred endpoint for TB vaccine efficacy assessment. Preferred endpoint case definitions have been published *(35)*. A bacteriologically confirmed case is one from whom a biological specimen is confirmed positive by culture or WHO-approved rapid diagnostic method *(37)*. A clinically diagnosed TB case is one who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. The vaccine should be protective in both subjects with and without evidence of latent *Mtb* infection, in different geographical regions and latitudes, irrespective of environmental exposure to mycobacteria. In high endemicity countries, rapid population-level vaccine impact will be derived mostly from prevention of TB disease in subjects with latent *Mtb* infection. Vaccine efficacy against recurrent TB (PoR) should be characterized. Preferences regarding efficacy outcome measures are similar to those used in PoD studies when considering prevention of recurrent TB disease. It is anticipated that vaccines protecting against drug-sensitive TB would also protect against drug-resistant TB. Over the long term, the impact of vaccine use on the incidence of drug-resistant *Mtb* cases should be assessed to confirm this effect, given the enormous public health benefit that would accrue from a reduction in cases of drug-resistant *Mtb*.

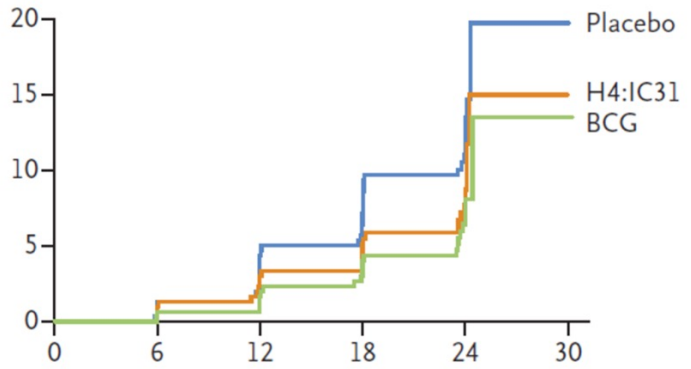
VII.PPC FOR NEW TUBERCULOSIS VACCINES: USE IN NEONATES AND INFANTS

Parameter	Preferred Characteristic	Notes
Indication	Prevention of TB disease, including severe, disseminated TB, TB meningitis and pulmonary TB, in infants and young children.	
Target population	Neonates and infants, in co-administration with other existing vaccines from the Expanded Program on Immunization.	
Outcome measure and efficacy	Equal to or greater than 80% vaccine efficacy as compared to baseline incidence, or superior efficacy as compared to BCG, in preventing TB disease, including severe, disseminated TB, TB meningitis and pulmonary TB, in infants and young children.	Considering existing recommendations and inclusion of neonatal BCG vaccination in standards of care based on the demonstrated efficacy profile of BCG, a new vaccine developed for BCG replacement should be compared to BCG in a randomized controlled study, powered to show superior vaccine efficacy as compared to BCG. Ethics committee(s) of record should confirm that the accrued evidence about the new candidate vaccines justify the absence or delay of BCG vaccination in at least one trial arm, if such a trial design is proposed. BCG provides partial protection against leprosy. Policy decisions related to BCG replacement will also give due consideration, where relevant, to available evidence about the effects against leprosy and Buruli ulcer, as well as evidence established in carefully designed prospective BCG trials with pre-defined endpoints about the possible role of 'non-specific effects' of BCG. Characterisation of vaccine efficacy against paediatric TB mortality and all-cause mortality is desirable, possibly in large-scale pilot introduction studies. BCG boosting strategies are also being considered.
Duration of protection	Ten or more years of protection should be conferred after primary immunization.	Demonstrated efficacy over 2 or more years after completion of the primary immunization regimen to support initial policy decision. Longer-term follow-up studies will be important to inform the duration of protection and possible booster requirements.

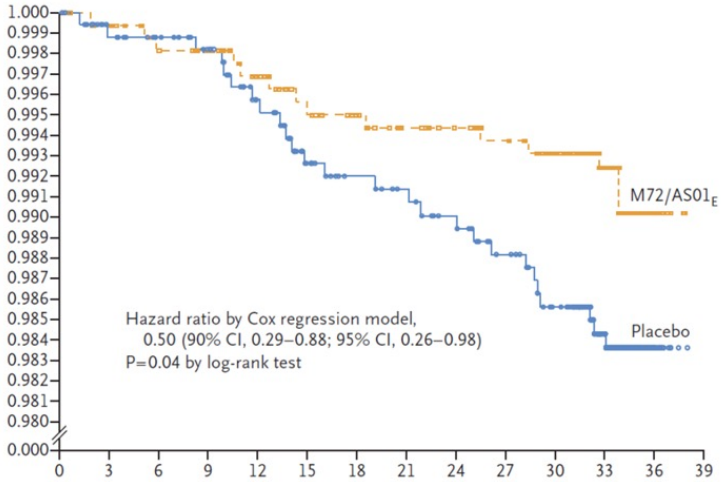
Please see WHO vaccine PPC guidance documents under:
[WHO Preferred Product Characteristics for New Tuberculosis Vaccine]

Current TB vaccine pipeline and proof-of-concept

Phase I	Phase IIa	Phase IIb	Phase III
AdHu5Ag85A[b] McMaster, CanSino	**ChAdOx185A-MVA85A**[b] (ID/IM/Aerosol) University of Oxford	**BCG ReVax**[c] Gates MRI	**GamTBvac**[d] Ministry of Health, Russian Federation
AEC/BC02[e] Anhui Zhifei Longcom	**ID93 + GLA-SE**[d] IDRI, Wellcome Trust, IAVI	**DAR-901 booster**[e] Dartmouth, GHIT	**MIP/Immuvac**[e] ICMR, Cadila Pharmaceuticals
	TB/FLU-04L[b] RIBSP	**H56: IC31**[d] SSI, Valneva, IAVI	**MTBVAC**[c] Biofabri, TBVI, University of Zaragoza
		M72/AS01E[d] GSK, Gates MRI	**VPM1002**[c] SIIPL, VPM
		RUTI®[e] Archivel Farma, S.L.	



DOI: 10.1056/NEJMoa1714021



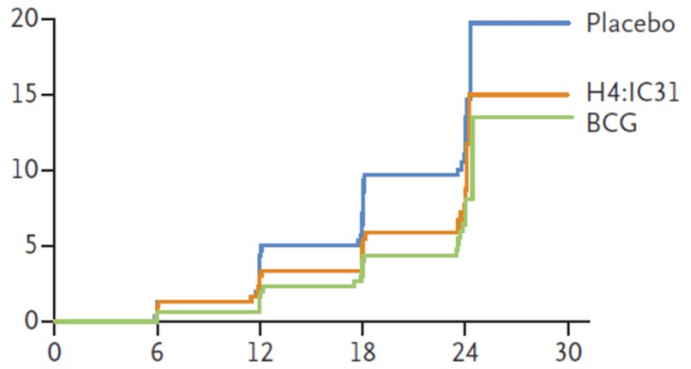
DOI: 10.1056/NEJMoa1803484 & DOI: 10.1056/NEJMoa1909953

- **9 candidates in Phase 2b/3 (POI/POD/POR studies), some targeting both infants and adolescents/adults**

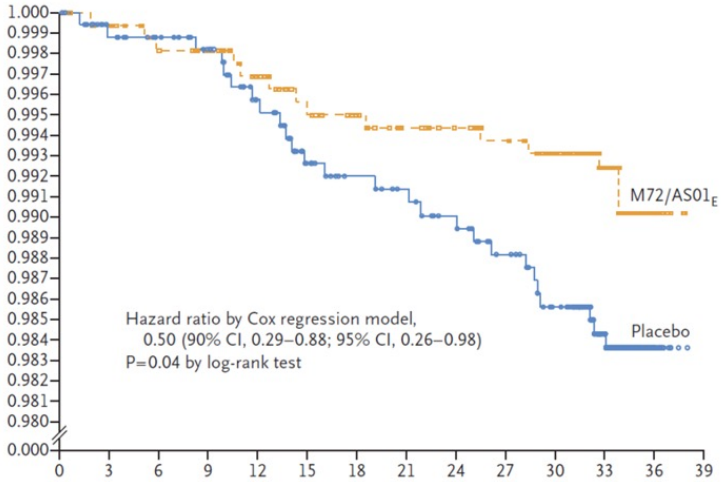
Source: https://www.who.int/publications/i/item/9789240037021

Current TB vaccine pipeline and proof-of-concept

Phase I	Phase IIa	Phase IIb	Phase III
AdHu5Ag85A[b] McMaster, CanSino	**ChAdOx185A-MVA85A**[b] (ID/IM/Aerosol) University of Oxford	**BCG ReVax**[c] Gates MRI	**GamTBvac**[d] Ministry of Health, Russian Federation
AEC/BC02[e] Anhui Zhifei Longcom	**ID93 + GLA-SE**[d] IDRI, Wellcome Trust, IAVI	**DAR-901 booster**[e] Dartmouth, GHIT	**MIP/Immuvac**[e] ICMR, Cadila Pharmaceuticals
	TB/FLU-04L[b] RIBSP	**H56: IC31**[d] SSI, Valneva, IAVI	**MTBVAC**[c] Biofabri, TBVI, University of Zaragoza
		M72/AS01E[d] GSK, Gates MRI	**VPM1002**[c] SIIPL, VPM
		RUTI®[e] Archivel Farma, S.L.	



DOI: 10.1056/NEJMoa1714021

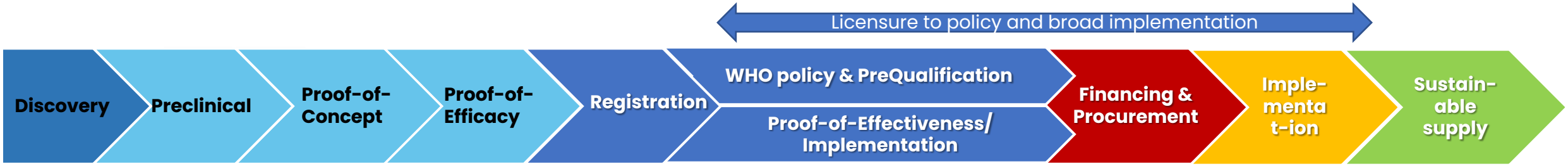


DOI: 10.1056/NEJMoa1803484 & DOI: 10.1056/NEJMoa1909953

- **9 candidates in Phase 2b/3 (POI/POD/POR studies), some targeting both infants and adolescents/adults**

Source: https://www.who.int/publications/i/item/9789240037021

Context for the need for evidence considerations for Vaccine Policy (ECVP)



Preferred Product Characteristics: (PPC): defines product attributes for LMIC use

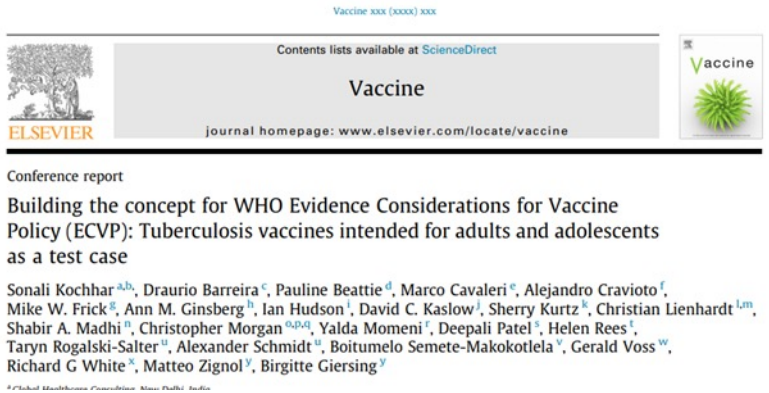
EVIDENCE CONSIDERATIONS FOR VACCINE POLICY: evidence anticipated to facilitate global policy recommendations developed ***before*** phase III clinical studies

SAGE Evidence to Recommendation framework

WHO Position paper

WHO PQ

Scientific advice meetings: Data on **safety, quality and efficacy** for licensure



Vaccine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Conference report

Building the concept for WHO Evidence Considerations for Vaccine Policy (ECVP): Tuberculosis vaccines intended for adults and adolescents as a test case

Sonali Kochhar [a,b], Draurio Barreira [c], Pauline Beattie [d], Marco Cavaleri [e], Alejandro Cravioto [f], Mike W. Frick [g], Ann M. Ginsberg [h], Ian Hudson [i], David C. Kaslow [j], Sherry Kurtz [k], Christian Lienhardt [l,m], Shabir A. Madhi [n], Christopher Morgan [o,p,q], Yalda Momeni [r], Deepali Patel [s], Helen Rees [t], Taryn Rogalski-Salter [u], Alexander Schmidt [u], Boitumelo Semete-Makokotlela [v], Gerald Voss [w], Richard G White [x], Matteo Zignol [y], Birgitte Giersing [y]

https://www.sciencedirect.com/science/article/pii/S0264410X21013955?via%3Dihub

Structure of the ECVP guidance

The ECVP is based on SAGE's **Evidence to Recommendation** framework and includes five tables:

- Table 1: **Vaccine Product** Related Parameters – incl. initial priority populations, target countries, efficacy, duration of protection
- Table 2: **Vaccine Delivery** related Parameters for the Priority Populations, including delivery strategy/setting
- Table 3: Vaccination of Specific Populations
- Table 4: Regulatory Strategy Considerations for Initial Licensure
- Table 5: **Implementation Considerations**

Tables 1, 2 and 3 identify evidence needs for initial and expanded policy recommendations.

Each section identifies:

- **High Priority** parameters in red: expected to be critical for SAGE and other policy bodies at the regional and country level;
- **Medium Priority** parameters in blue: for which data and evidence are likely to be beneficial for policy recommendation.

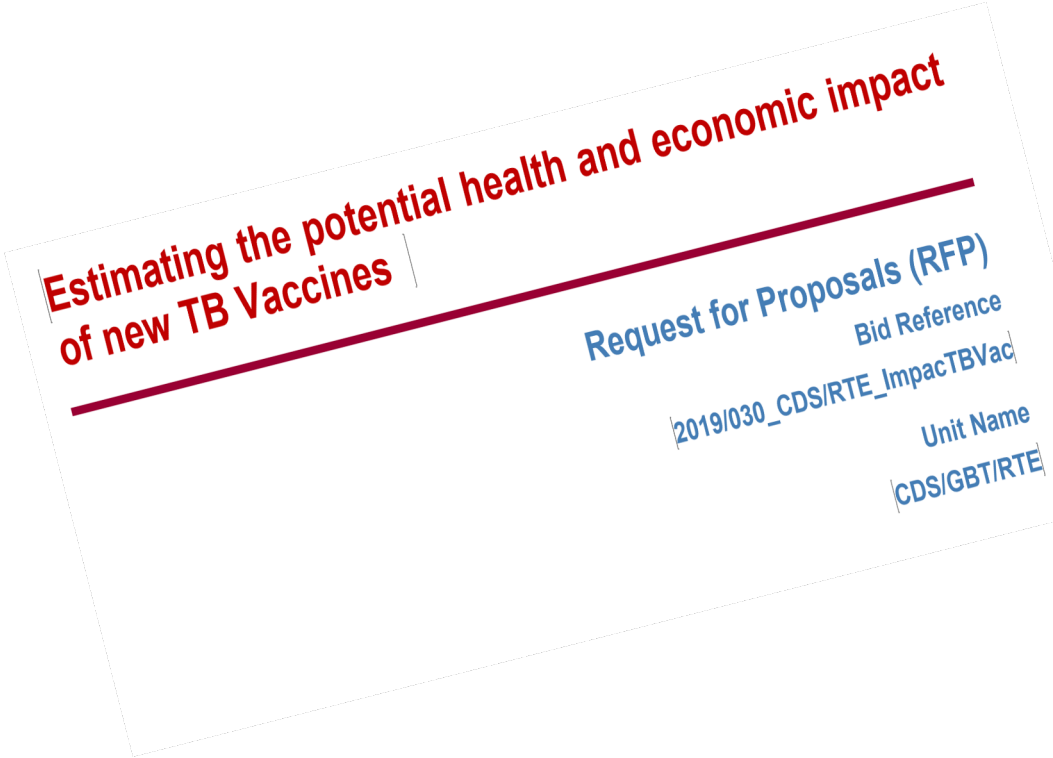
Requests of IVIR-AC:

As the TB vaccine ECVP is finalized, there are likely to be additional modelling questions with refined parameters/assumptions. As such we're seeking feedback on the approach and outcome of this initial FVVA, for future iterations.

- Review and comment upon the approach and outcome of the analysis to assess the health and economic impact of new TB vaccines
- Comment on/recommend any additional studies that may complement/broaden these initial analyses on the health and economic impact of new TB vaccines

Rationale

- TB leading cause of death from single infectious agent
- New TB vaccines needed
- Development expensive and long
- Lack of market incentives for diseases affecting poor people and LMICs
- Full Value Assessment of Vaccines Framework
- Apply to TB to quantify broader health & economic impacts of new TB vaccines
    - to govts and multinational partners
    - to support case for quicker development, adoption and implementation



Potential health impact of new TB vaccines in LMICs that meet WHO Preferred Product Characteristics

Rebecca A Clark, Christinah Mukandavire, Allison Portnoy, Chathika Weerasuriya, Arminder Deol, Danny Scarponi, Andrew Iskauskas, Roel Bakker, Matthew Quaife, Shelly Malhotra, Nebiat Gebreselassie, Matteo Zignol, Raymond Hutubessy, Birgitte Giersing, Mark Jit, Rebecca Harris, Nicolas A Menzies, Richard G White

richard.white@lshtm.ac.uk
rebecca.clark@lshtm.ac.uk

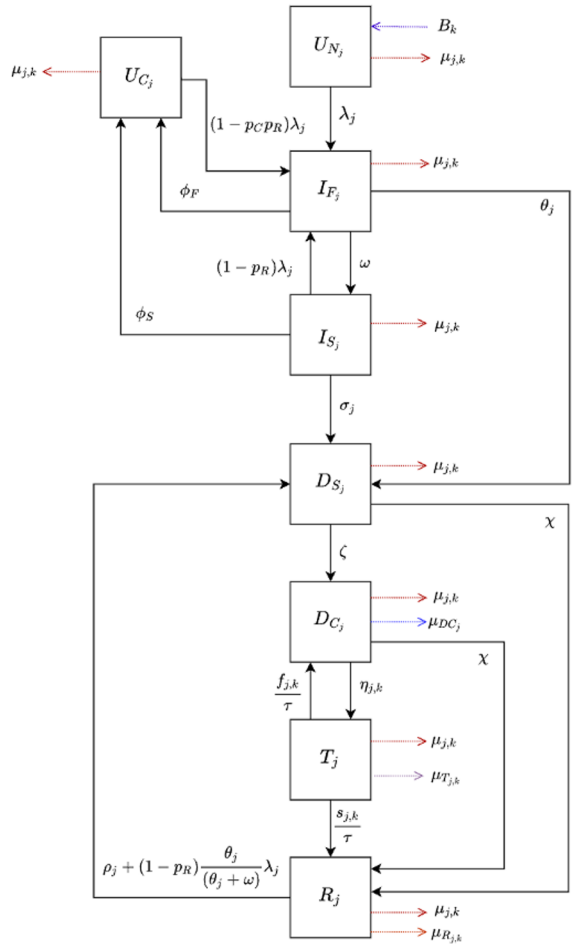
2022_09_13

Scope

- Estimated potential health and economic impact of vaccines meeting the technical specifications of the WHO Preferred Product Characteristics for New Tuberculosis Vaccines
- LMICs
- Impact over 2028–2050

Outcomes

- Health - Cumulative cases/treatments/deaths averted
- Economic - Whole slew (Nick, next)
- Grouped countries - WHO region, Income, WHO high TB burden



D_C = Clinical Disease, D_S = Subclinical Disease; I_F = Infection-Fast, I_S = Infection-Slow, R = Resolved, T = On-Treatment, U_C = Uninfected-Cleared, U_N = Uninfected-Naive

Vaccine Profile

Informed by WHO Preferred Product Characteristics for New Tuberculosis Vaccines

Vaccine Age Group	Infection status at time of vaccination required for vaccine efficacy	Prevents	Vaccine Efficacy	Duration of Protection
Adolescent / Adult	Pre and Post Infection with *Mtb*	Disease	**50%** 75%	**10 years** Lifelong
Infant	Pre Infection with *Mtb*	Disease	**80%**	**10 years** Lifelong

Clark RA, Mukandavire C, Portnoy A, et al. The impact of alternative delivery strategies for novel tuberculosis vaccines in low- and middle-income countries: a modelling study. *medRxiv* 2022.04.16.22273762; doi: https://doi.org/10.1101/2022.04.16.22273762.

Vaccine Delivery

Vaccine coverage at 5 years (low / medium / high)

Neonatal: 75% / **85%** / 95%

9-year-olds: 70% / **80%** / 90%

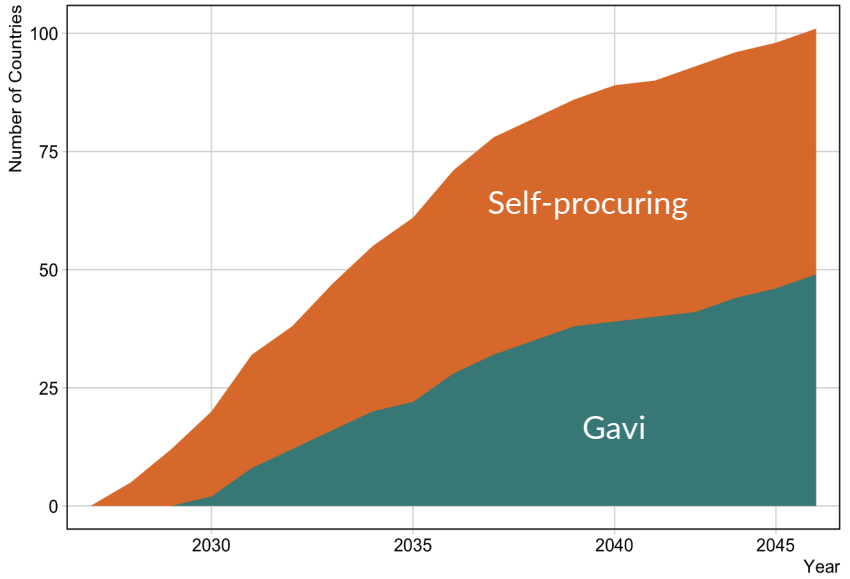
10+: 50% / **70%** / 90%

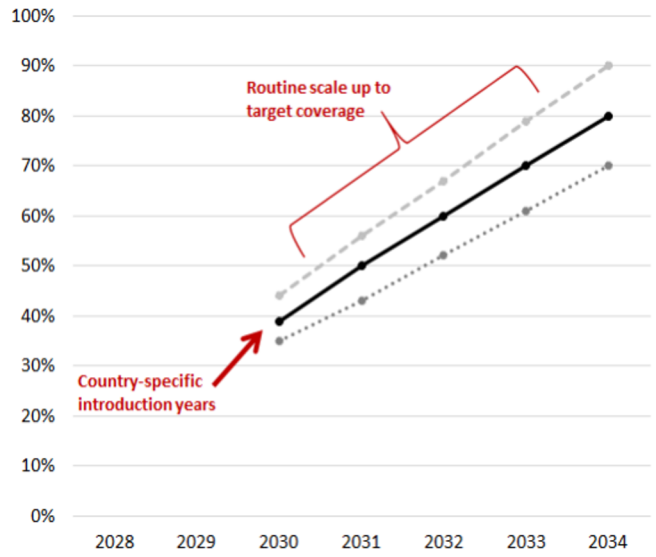
Vaccine Delivery Scenarios

Vaccine coverage at 5 years (low / medium / high)
Neonatal: 75% / **85%** / 95%
9-year-olds: 70% / **80%** / 90%
10+: 50% / **70%** / 90%

Basecase

- Country-specific intro years
- Scale-up to coverage over 5 years
- Infant vaccine: Routine neonatal
- Adolescent/adult vaccine: routine 9-year-olds; 1 campaign ages 10+



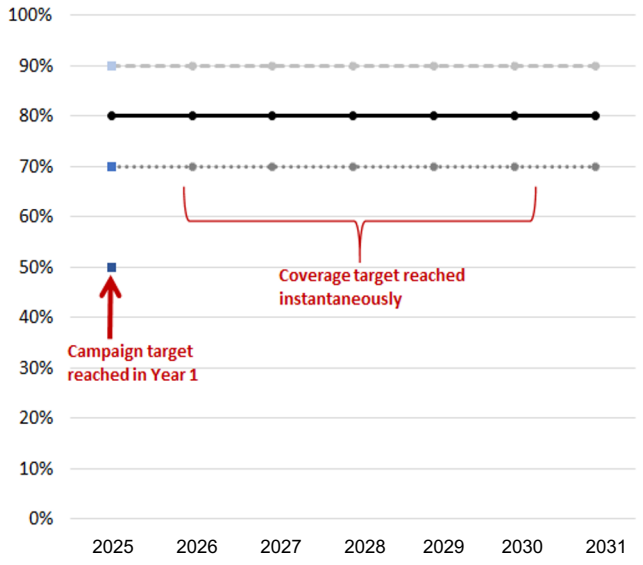


Vaccine Delivery Scenarios

Vaccine coverage at 5 years (low / medium / high)
Neonatal: 75% / **85%** / 95%
9-year-olds: 70% / **80%** / 90%
10+: 50% / **70%** / 90%

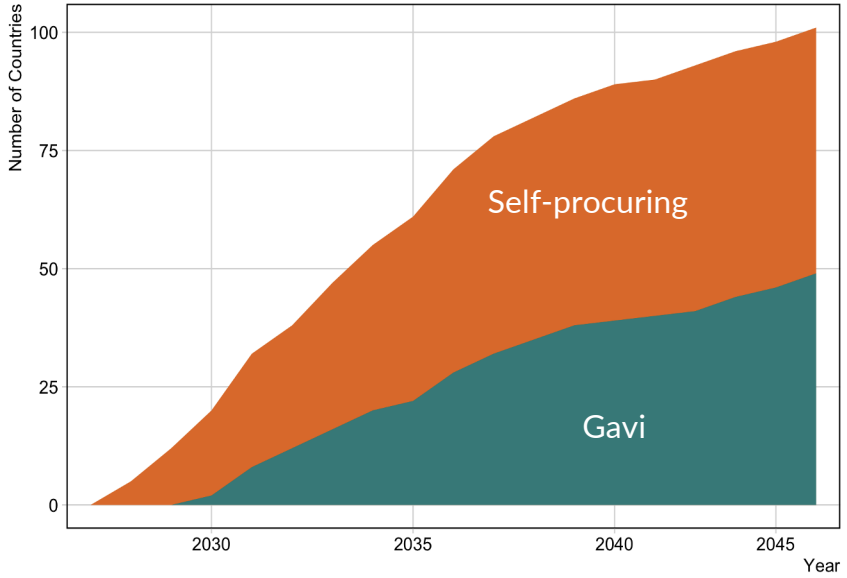
***Accelerated* Scale-up**

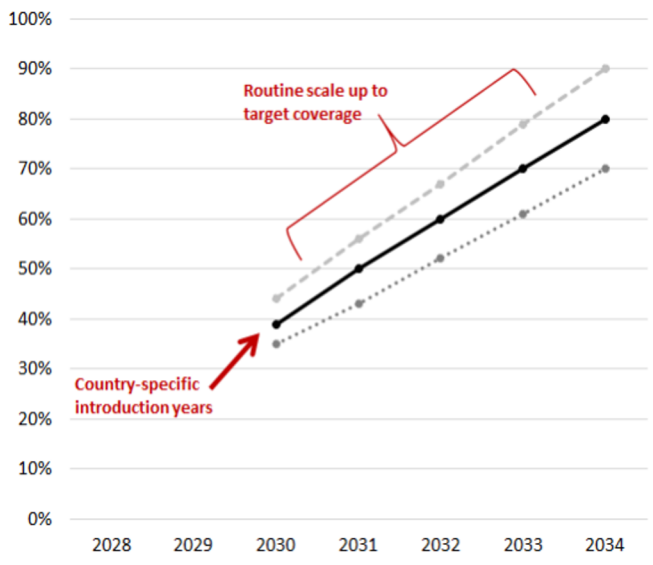
- All countries introduce in 2025
- Instant scale-up to coverage
- Infant vaccine: Routine neonatal
- Adolescent/adult vaccine: routine 9-year-olds; 1 campaign ages 10+



Basecase

- Country-specific intro years
- Scale-up to coverage over 5 years
- Infant vaccine: Routine neonatal
- Adolescent/adult vaccine: routine 9-year-olds; 1 campaign ages 10+



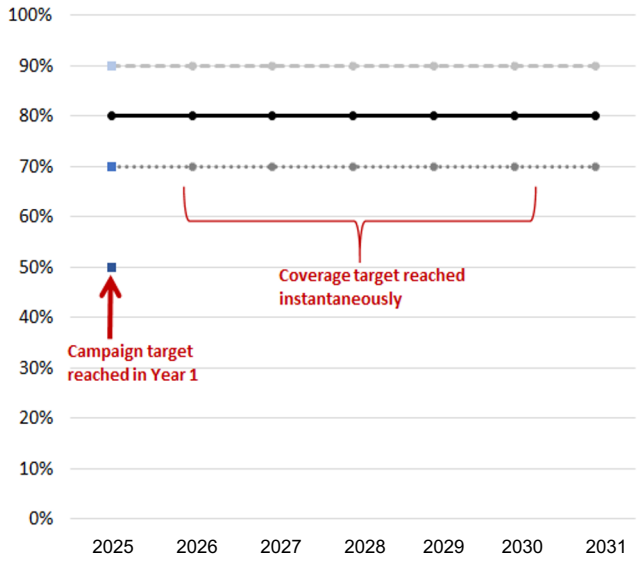


Vaccine Delivery Scenarios

Vaccine coverage at 5 years (low / medium / high)
Neonatal: 75% / **85%** / 95%
9-year-olds: 70% / **80%** / 90%
10+: 50% / **70%** / 90%

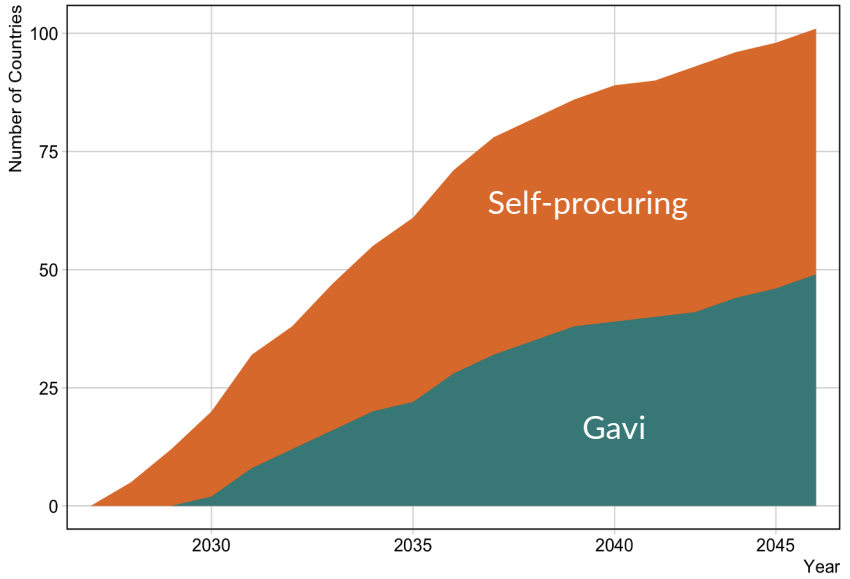
***Accelerated* Scale-up**

- All countries introduce in 2025
- Instant scale-up to coverage
- Infant vaccine: Routine neonatal
- Adolescent/adult vaccine: routine 9-year-olds; 1 campaign ages 10+



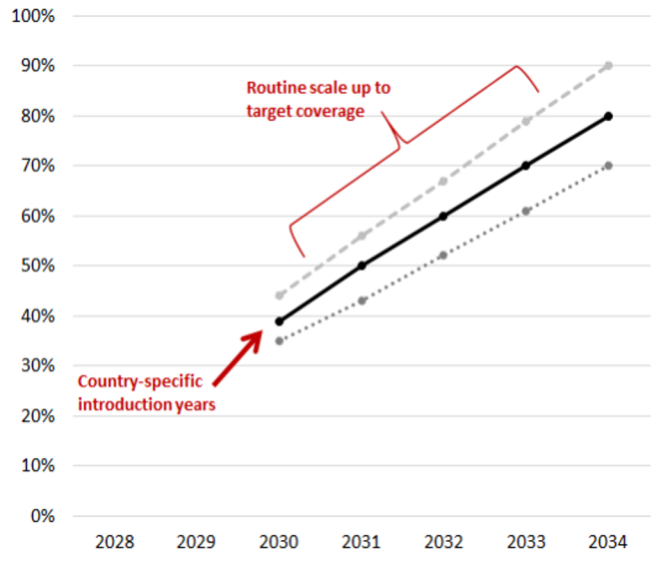
Basecase

- Country-specific intro years
- Scale-up to coverage over 5 years
- Infant vaccine: Routine neonatal
- Adolescent/adult vaccine: routine 9-year-olds; 1 campaign ages 10+



Routine Only

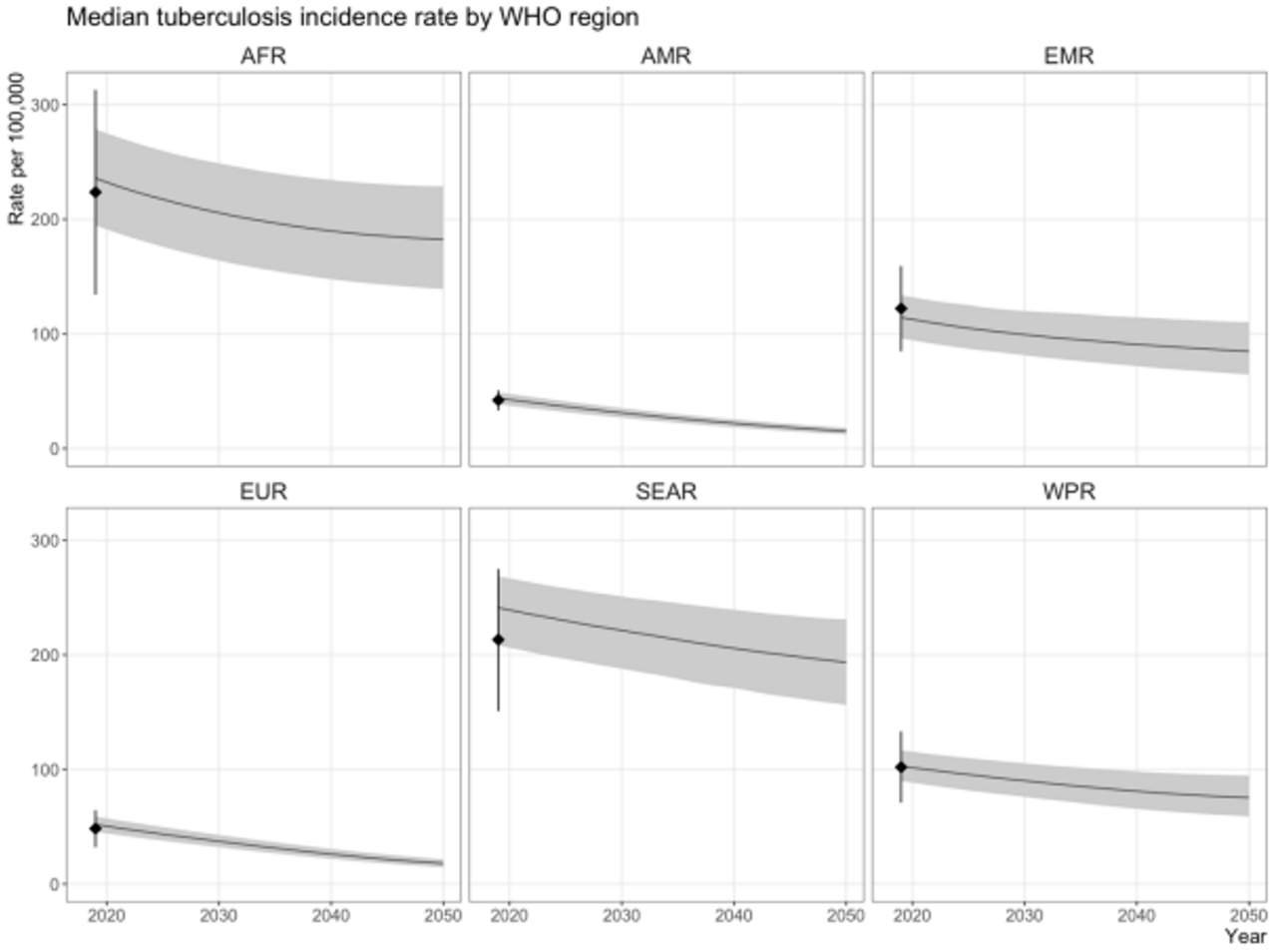
- Country-specific intro years
- Scale-up to coverage over 5 years
- Adolescent/adult vaccine: routine 9-year-olds



Results

105 countries successfully calibrated

Account for 93% of global TB cases and 94% of deaths in 2019



TB Incidence Rate Reduction

Adol/Adult, 50% efficacy, Basecase delivery, 10y protect, med coverage

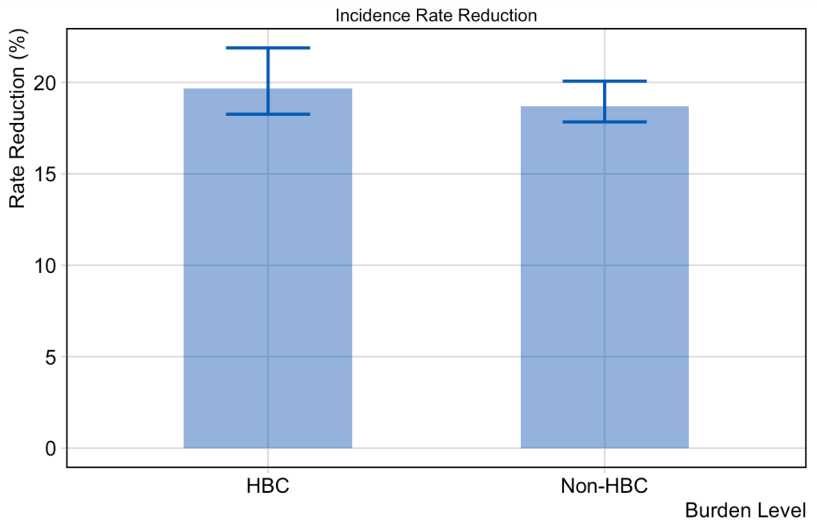
TB incidence rate reduction in 2050

In line with previous LMIC modelling (Knight 2014)

- Important health impact

  → **~ 19-20%** reduction in cases in 2050

- Slightly higher impact in high TB burden countries (HBC) compared to Non-HBC



TB Incidence Rate Reduction

Adol/Adult, 50% efficacy, Basecase delivery, 10y protect, med coverage

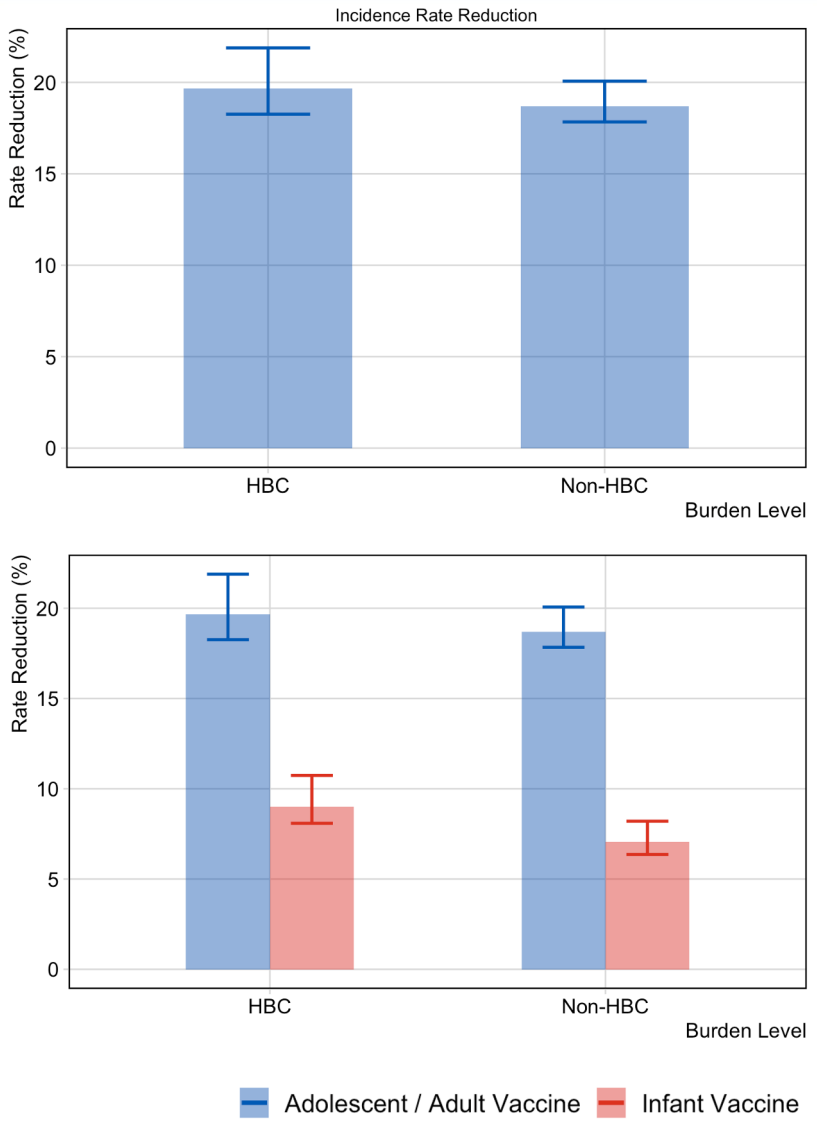
TB incidence rate reduction in 2050

In line with previous LMIC modelling (Knight 2014)

- Important health impact
  → **~ 19-20%** reduction in cases in 2050
- Slightly higher impact in high TB burden countries (HBC) compared to Non-HBC

vs Infant, 80% efficacy, Basecase delivery, 10y protect, med coverage

- Greater impact from an adolescent / adult vaccine vs. infant vaccine before 2050
  → Targeting the age group with the largest burden

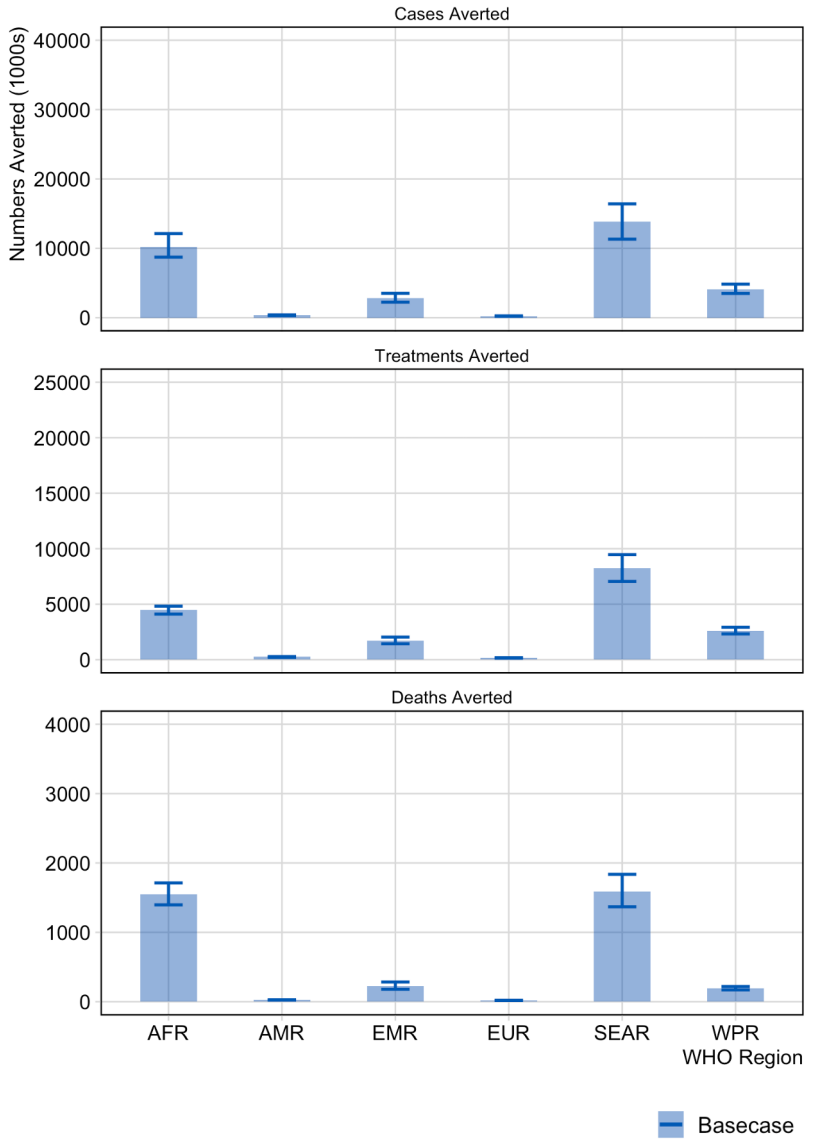


Cumulative cases, treatments, deaths averted

Adol/Adult, 50% efficacy, Basecase delivery, 10y protect, med coverage

Cumulative cases averted between vaccine introduction and 2050

- Potential to avert **~32 million** cases
- Particularly in AFR and SEAR



Cumulative cases, treatments, deaths averted

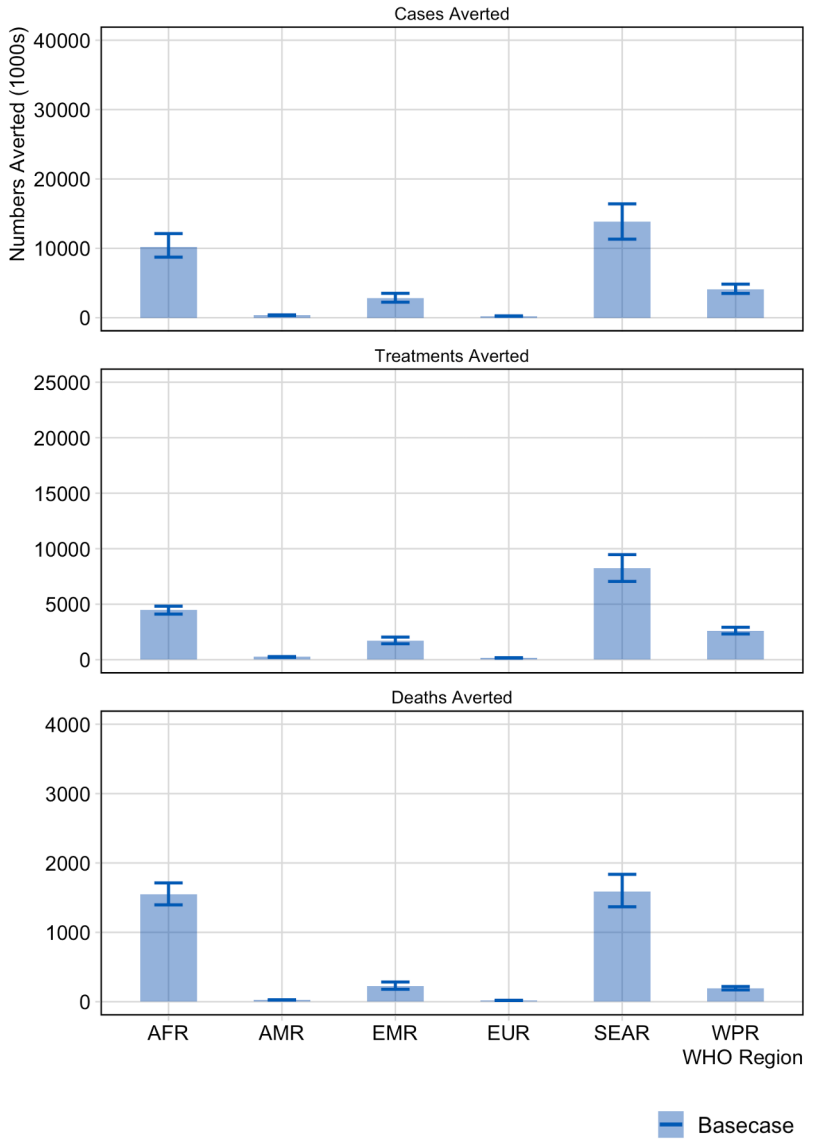
Adol/Adult, 50% efficacy, Basecase delivery, 10y protect, med coverage

Cumulative cases averted between vaccine introduction and 2050

- Potential to avert **~32 million** cases
- Particularly in AFR and SEAR

Cumulative treatments averted between vaccine introduction and 2050

- Potential to avert **~18 million** treatments by 2050
- Valuable contribution to averting antimicrobial resistance



Cumulative cases, treatments, deaths averted

Adol/Adult, 50% efficacy, Basecase delivery, 10y protect, med coverage

Cumulative cases averted between vaccine introduction and 2050

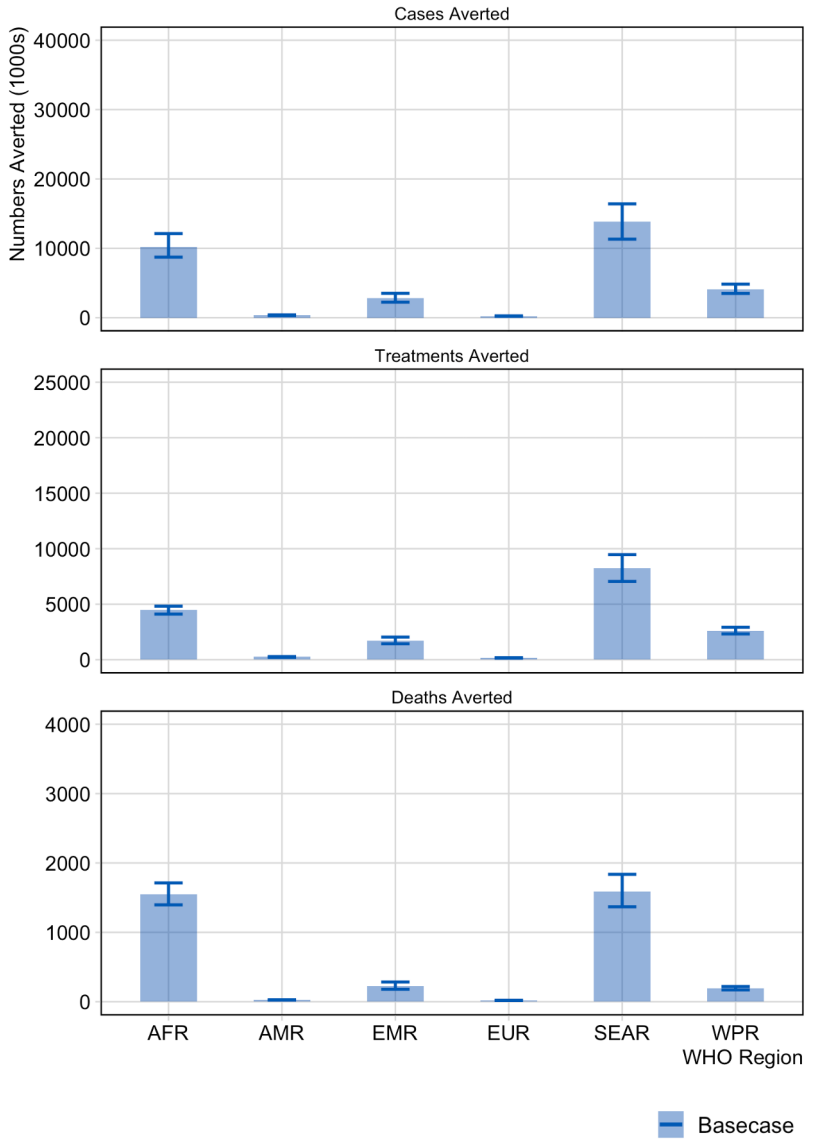
- Potential to avert **~32 million** cases
- Particularly in AFR and SEAR

Cumulative treatments averted between vaccine introduction and 2050

- Potential to avert **~18 million** treatments by 2050
- Valuable contribution to averting antimicrobial resistance

Cumulative deaths averted between vaccine introduction and 2050

- Potential to avert **~4 million** deaths by 2050



Cumulative numbers averted by scale up speed

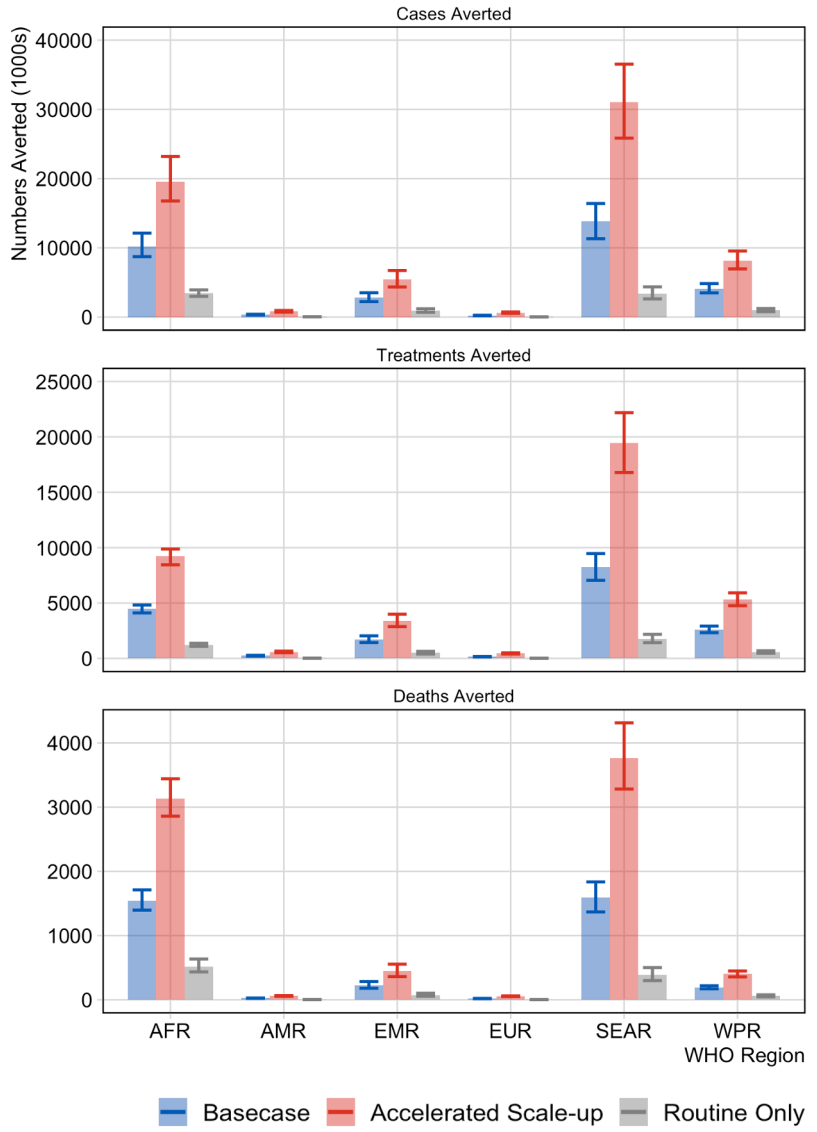
Adol/Adult, 50% efficacy, varying delivery, 10y protect, med coverage

Cases, treatments, and deaths averted by delivery:

We assumed more 'realistic' introduction & scale up scenarios than previous modelling

In the *Basecase* scenario, **31.5 million** cases, **17.5 million** treatments, and **3.6 million** deaths were averted.

- An increased scale-up speed (*Accelerated Scale-up*) could prevent **34.2 million additional** cases, **21.1 million** additional treatments, and **4.3 million** additional deaths **(~ Double)**



Cumulative numbers averted by scale up speed

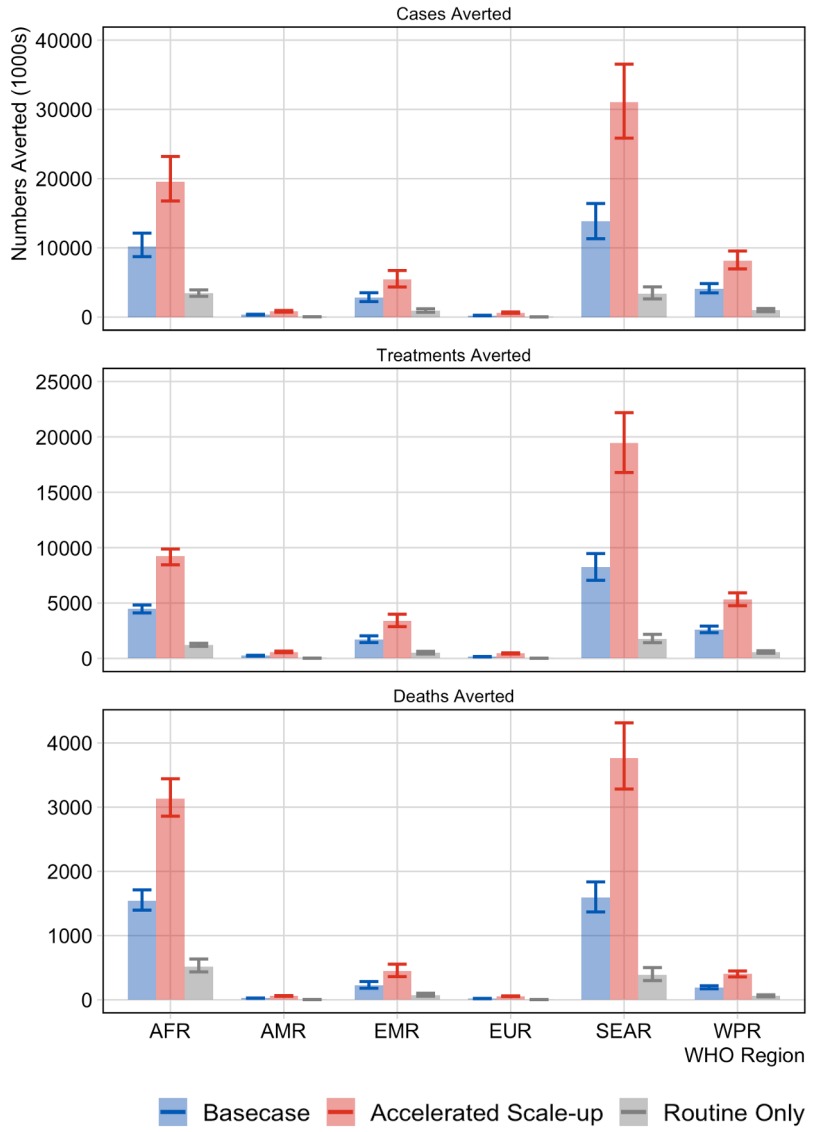
Adol/Adult, 50% efficacy, varying delivery, 10y protect, med coverage

Cases, treatments, and deaths averted by delivery:

We assumed more 'realistic' introduction & scale up scenarios than previous modelling

In the *Basecase* scenario, **31.5 million** cases, **17.5 million** treatments, and **3.6 million** deaths were averted.

- An increased scale-up speed (*Accelerated Scale-up*) could prevent **34.2 million additional** cases, **21.1 million** additional treatments, and **4.3 million** additional deaths **(~ Double)**
- By only offering this new TB vaccine routinely to adolescents (*Routine Only*), **22.7 million fewer** cases, **13.4 million** fewer treatments, and **2.5 million** fewer deaths would be averted **(~70% fewer)**



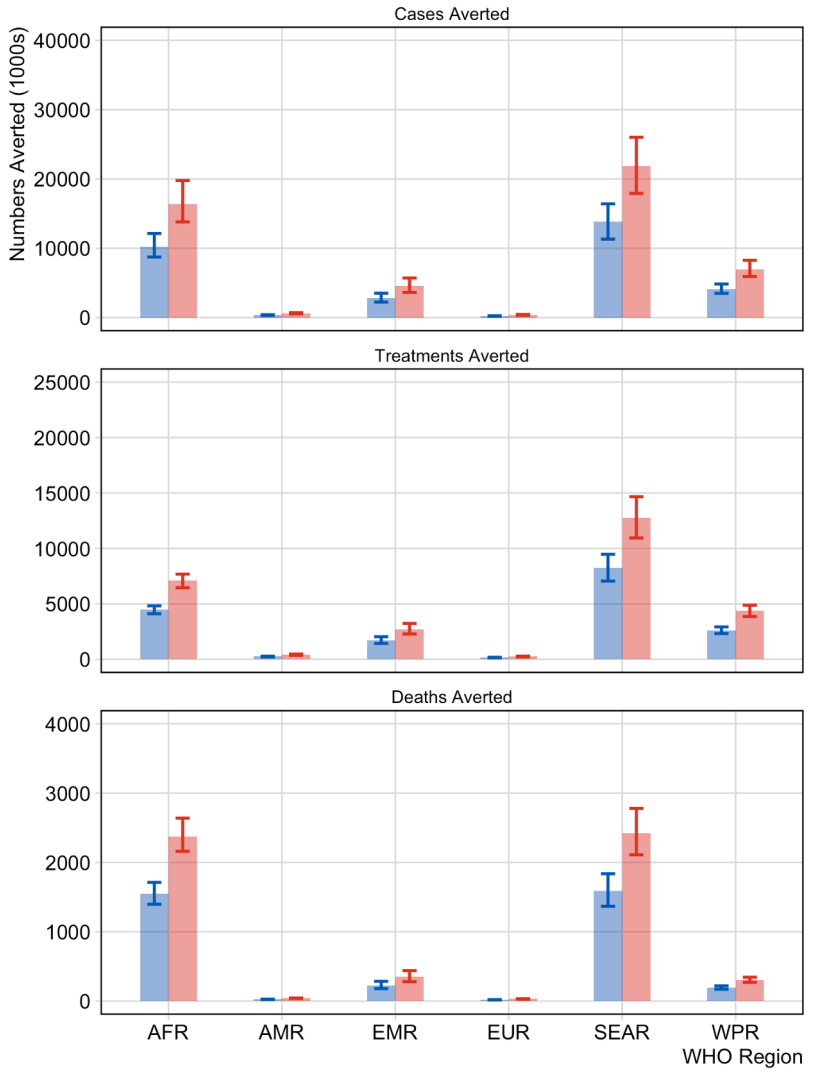
Cumulative numbers averted with lifelong duration of protection

Adol/Adult, 50% efficacy, Basecase delivery, 10y protect vs LL, med coverage

Cases, treatments, and deaths averted by Basecase delivery with 10 years vs lifelong duration of protection

In the *Basecase - 10 years protection* scenario, **31.5 million** cases, **17.5 million** treatments, and **3.6 million** deaths were averted

- A lifelong duration of protection vaccine could prevent **19.3 million additional** cases, **10.2 million additional** treatments, and **1.9 million additional** deaths **(~50% more)**



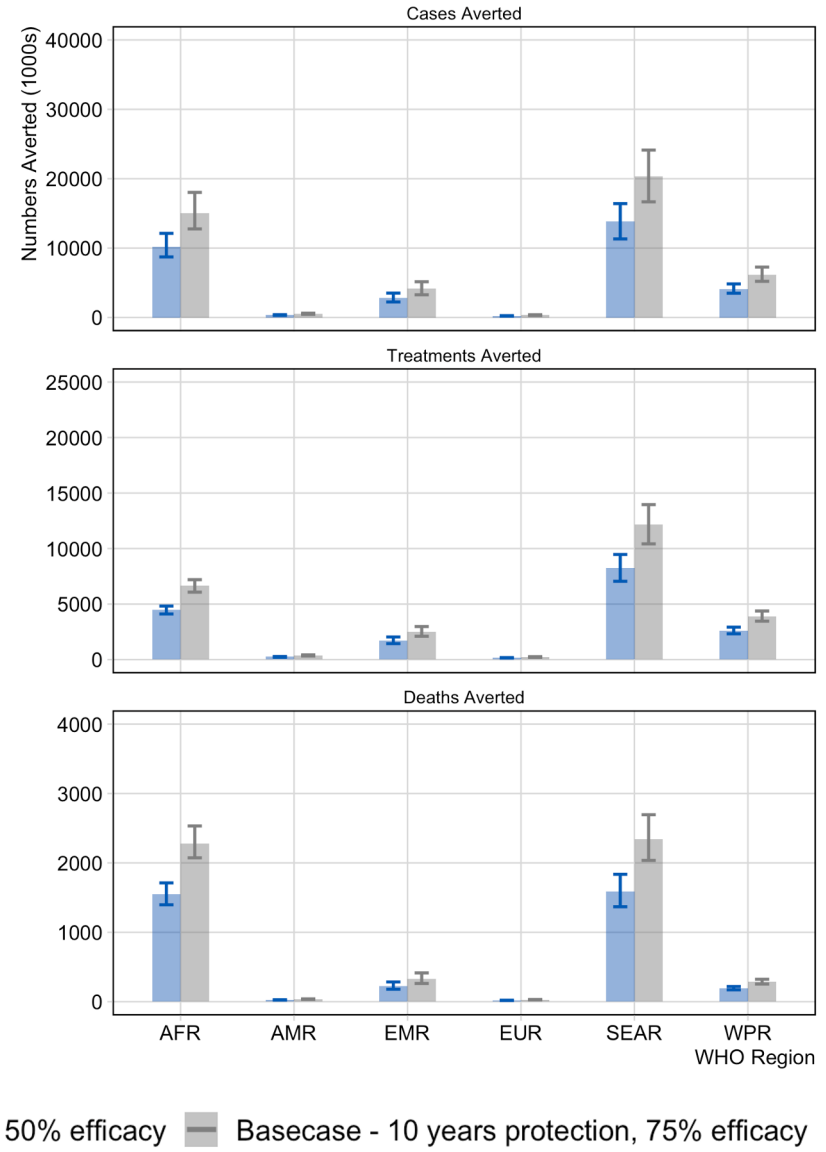
Cumulative numbers averted with 75% efficacy

Adol/Adult, 50% / 75% efficacy, Basecase delivery, 10y protect, med coverage

Cases, treatments, and deaths averted by Basecase delivery with vaccine efficacy increased to 75%

In the *Basecase - 50% efficacy* scenario, **31.5 million** cases, **17.5 million** treatments, and **3.6 million** deaths were averted

- A vaccine with 75% efficacy could prevent **15 million additional** cases, **8.5 million additional** treatments, and **1.7 million additional** deaths **(~50% more)**



Selected limitations

Models are always simplifications of reality, and have limitations, eg

Assumed “un-targeted” vaccination

- Countries may vaccinate vulnerable / high-risk groups first, or sub-nationally, which will affect impact

Assumed equivalent vaccine efficacy in people living with HIV

- Lower efficacy will reduce impact in countries with a high HIV/TB co-epidemic

…

Summary

- Important potential health impact
- Greater impact of adolescent / adult vaccine vs infant

Summary

- Important potential health impact
- Greater impact of adolescent / adult vaccine vs infant

- Pre and post infection TB vaccine, 50% efficacy, to adults and adolescents, scaled up 2028-47, could
  - Reduce TB incidence by **~19-20%** in 2050
  - Avert **~32 million** TB cases and **~4 million** deaths
  - Avert **~18 million** TB treatments, reducing pressure on AMR
  - Particularly AFR and SEAR

Summary

- Important potential health impact
- Greater impact of adolescent / adult vaccine vs infant

- Pre and post infection TB vaccine, 50% efficacy, to adults and adolescents, scaled up 2028-47, could
  - Reduce TB incidence by **~19-20%** in 2050
  - Avert **~32 million** TB cases and **~4 million** deaths
  - Avert **~18 million** TB treatments, reducing pressure on AMR
  - Particularly AFR and SEAR

- But we should prepare to do better. **If we scaled-up more quickly**, similar to delivery of COVID-19 vaccine, **could avert around double** the cases, treatments and deaths

  → We need to prepare for more rapid production and implementation now

  → Need incentives / guarantees for vaccine manufacturers to ensure supply

Summary

- Important potential health impact
- Greater impact of adolescent / adult vaccine vs infant

- Pre and post infection TB vaccine, 50% efficacy, to adults and adolescents, scaled up 2028-47, could
  - Reduce TB incidence by **~19-20%** in 2050
  - Avert **~32 million** TB cases and **~4 million** deaths
  - Avert **~18 million** TB treatments, reducing pressure on AMR
  - Particularly AFR and SEAR

- But we should prepare to do better. **If we scaled-up more quickly**, similar to delivery of COVID-19 vaccine, **could avert around double** the cases, treatments and deaths

  → We need to prepare for more rapid production and implementation now

  → Need incentives / guarantees for vaccine manufacturers to ensure supply

- Vaccines with **higher efficacy** (75% efficacy vs 50% efficacy) or **longer duration** (lifelong vs 10y) **averted ~50% more** cases, treatments and deaths

  → We should continue to develop better vaccines

Potential **economic impact** of new TB vaccines that meet WHO Preferred Product Characteristics

Allison Portnoy, Rebecca Clark, Matthew Quaife, Chathika Weerasuriya, Christinah Mukandavire, Roel Bakker, Arminder Deol, Shelly Malhotra, Nebiat Gebreselassie, Matteo Zignol, So Yoon Sim, Raymond Hutubessy, Inés Garcia Baena, Jean-Louis Arcand, Edith Patouillard, Nobuyuki Nishikiori, Mark Jit, Richard White, Nicolas Menzies

Nicolas Menzies
Harvard TH Chan School of Public Health

IVIR-AC
September 13, 2022

Approach for economic evaluation

- Applied the WHO Full Value of Vaccines Assessment (FVVA) Framework

→ Express the global public health rationale for developing a vaccine

→ Inform decision-making across the duration of vaccine development and uptake

1. Health impact
2. Value for money
3. Equity and social protection impact
4. Economic impact
5. Global health security impact
6. Market and implementation scenarios
7. Vaccine cost
8. Alternative strategies
9. Implementation feasibility

Approach for economic evaluation

- Estimated a range of economic outcomes relevant to different decision-makers or for different goals

Cost-effectiveness (health system perspective)	Budget impact	Health equity
Cost-effectiveness (societal perspective)	Return on investment (Net Monetary Benefit)	Macroeconomic impact

- Same countries, time period, introduction scenarios, and vaccine profiles (infant 80% efficacy, adult 50% efficacy) as health impact analyses
- Results organized by major country groupings (WHO region, World Bank income group, high TB burden)

Study-specific methods and results

Cost-effectiveness (health system perspective)	Budget impact	Health equity & financial risk protection
Cost-effectiveness (societal perspective)	Return on investment (Net Monetary Benefit)	Macroeconomic impact

CEA methods

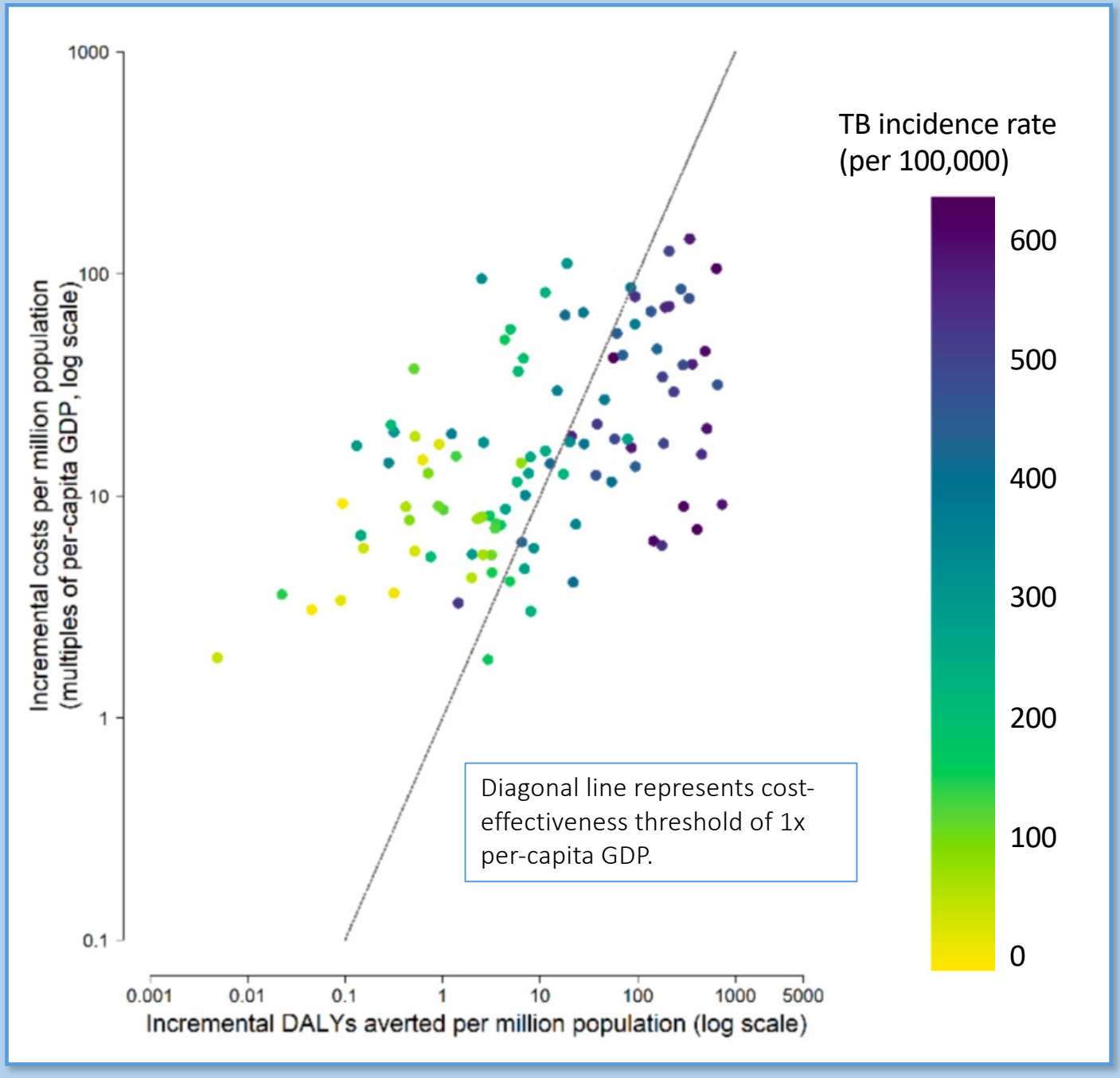
- Health outcome: Disability-adjusted life years (DALYs)
- Costs (health system perspective): Costs of vaccine introduction (vax price = $4.60), costs of TB and HIV services indirectly affected by vaccine introduction
- Costs (societal perspective): As above, plus patient out-of-pocket costs, productivity losses
- Unit cost inputs based on published analyses, new meta-regression syntheses of available data
- Costs and health outcomes assessed over 2028-2050, discounted at 3%
- Incremental cost-effectiveness ratios (ICERs) compared to cost-effectiveness thresholds defined as multiples of per capita GDP for each country

Cost-effectiveness results for country groupings (2020 USD)

	Adolescent/adult vaccine		Infant vaccine	
	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	352 (253, 535)	cost-saving	368 (283, 522)	cost-saving
High-TB burden	275 (194, 421)	cost-saving	267 (206, 381)	cost-saving
AFR	170 (130, 237)	cost-saving	226 (170, 307)	cost-saving
AMR	5190 (3440, 8900)	cost-saving (cost-saving, 3650)	9520 (6680, 14900)	3350 (537, 8730)
EMR	578 (403, 850)	cost-saving	567 (366, 873)	cost-saving
EUR	3990 (2630, 7000)	cost-saving (cost-saving, 1710)	9930 (6660, 17100)	4130 (953, 10900)
SEAR	208 (143, 313)	cost-saving	254 (173, 388)	cost-saving
WPR	1430 (913, 2540)	cost-saving	920 (587, 1510)	cost-saving

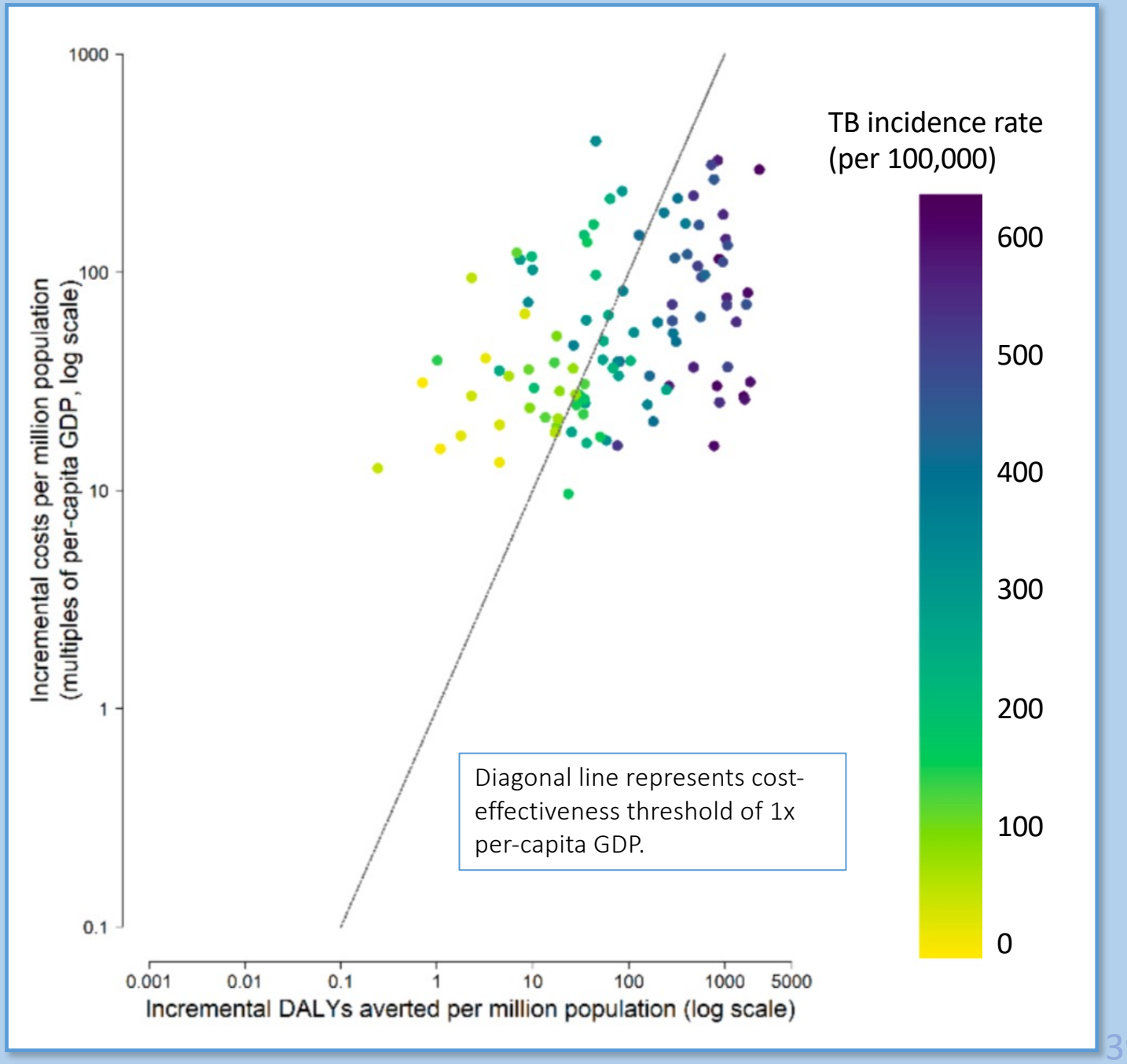
Cost-effectiveness results for individual countries (infant vaccine, health system perspective)

- Higher country incidence rate associated with higher impact per capita, more favorable CE

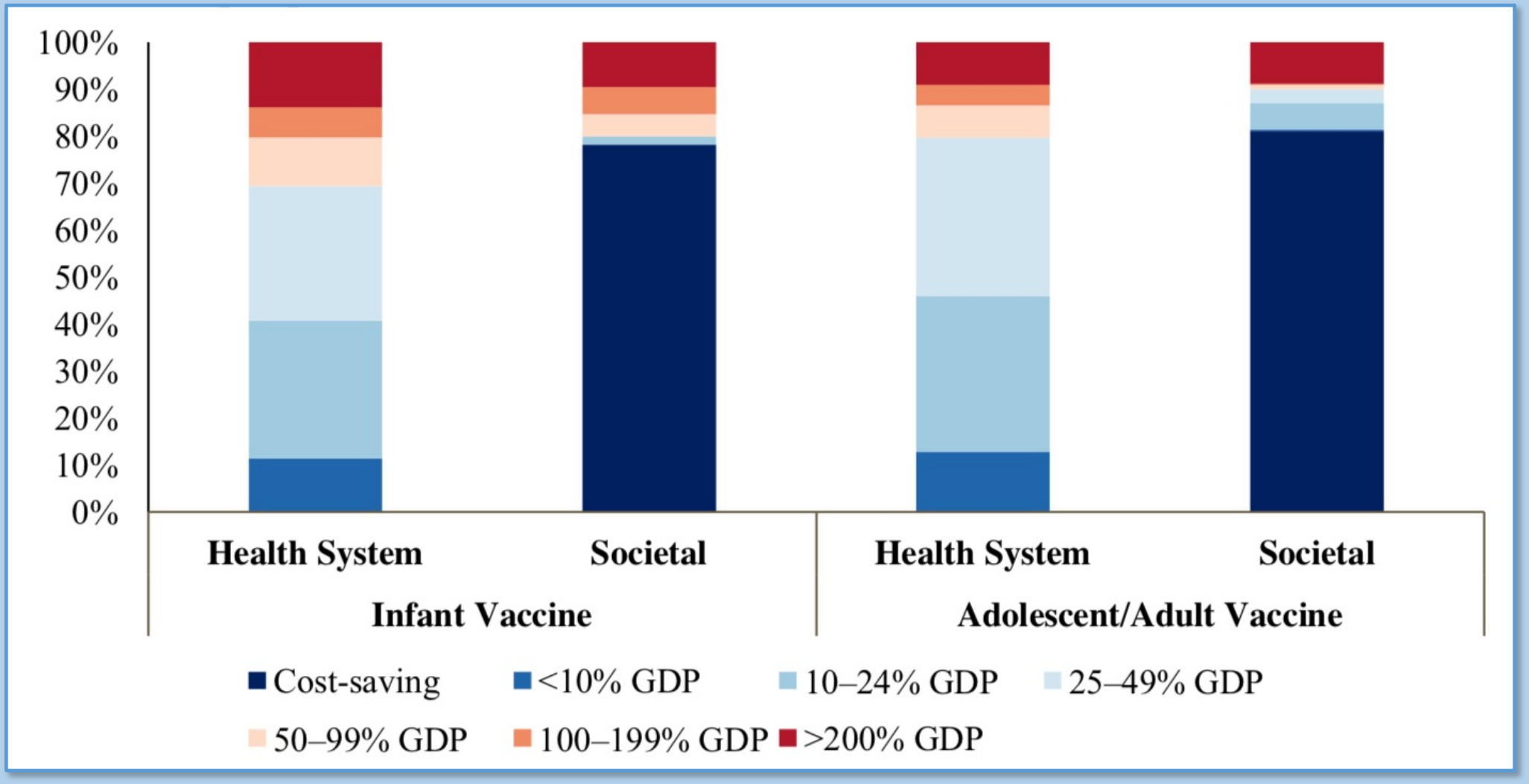


Cost-effectiveness results for individual countries (adult vaccine, health system perspective)

- Higher country incidence rate associated with higher impact per capita, more favorable CE
- Same story for adult vaccine, with higher average costs and impact



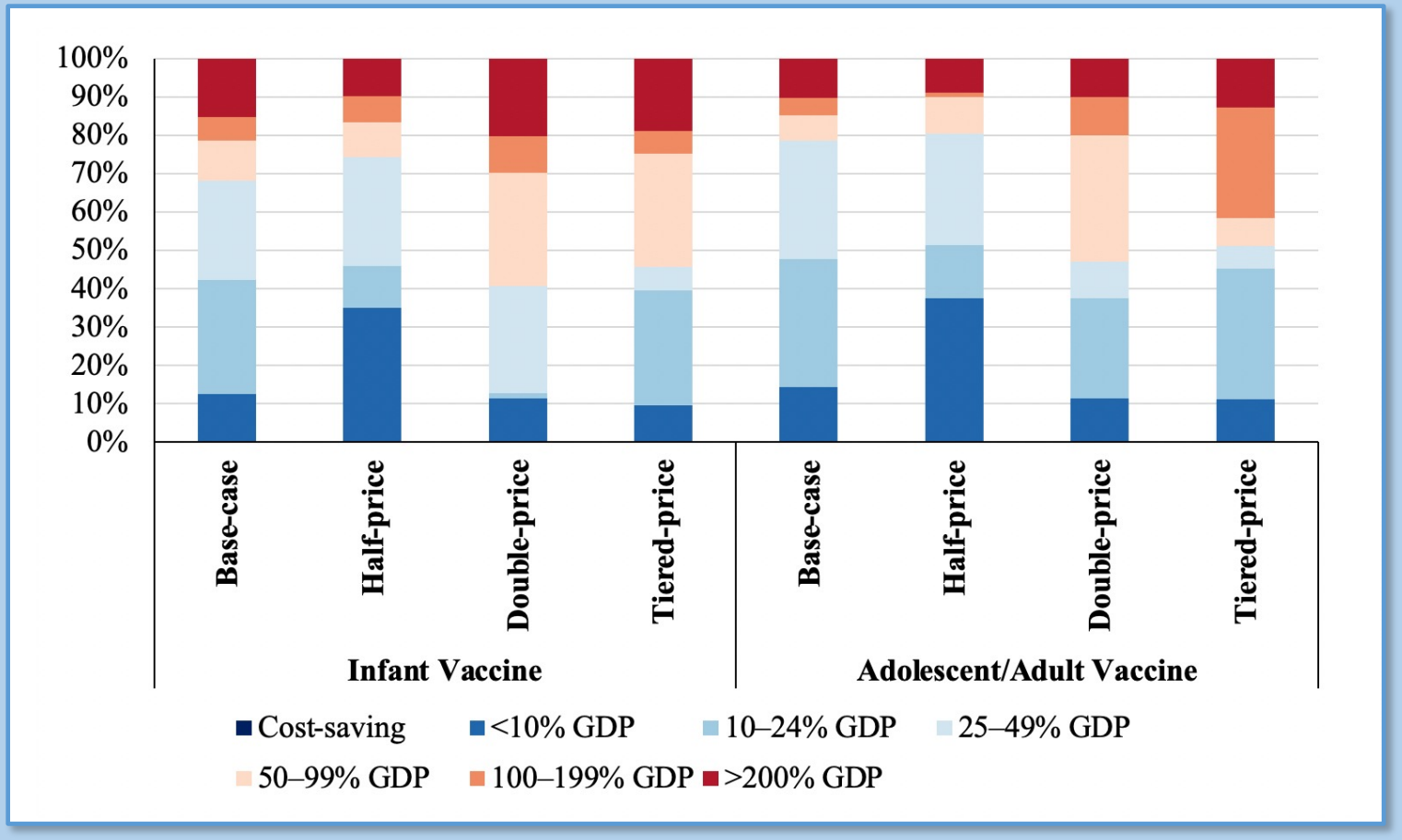
Percentage of LMIC population living in country where vaccination is projected to be cost-effective, for a given cost-effectiveness threshold



Percentage of population living in countries where vaccination is projected to be cost-effective: alternative vaccine price assumptions

- Vaccine price currently unknown, but results reasonably robust to moderate deviations from base case ($4.60 per dose)

Health system perspective

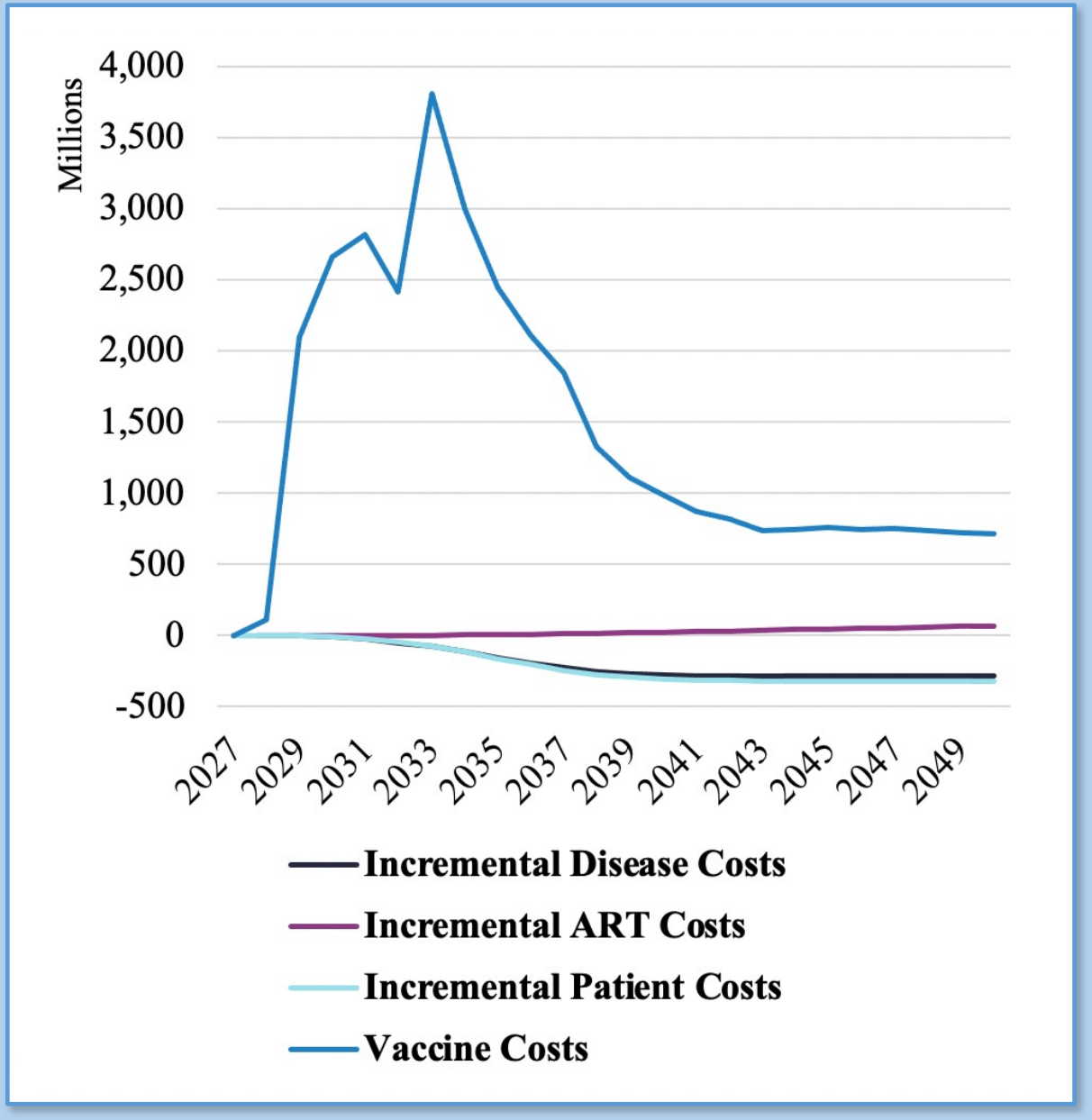


Study-specific methods and results

Cost-effectiveness (health system perspective)	**Budget impact**	Health equity & financial risk protection
Cost-effectiveness (societal perspective)	Return on investment (Net Monetary Benefit)	Macroeconomic impact

Annual incremental costs over study period, by broad cost category (adolescent vaccine, all modelled countries)

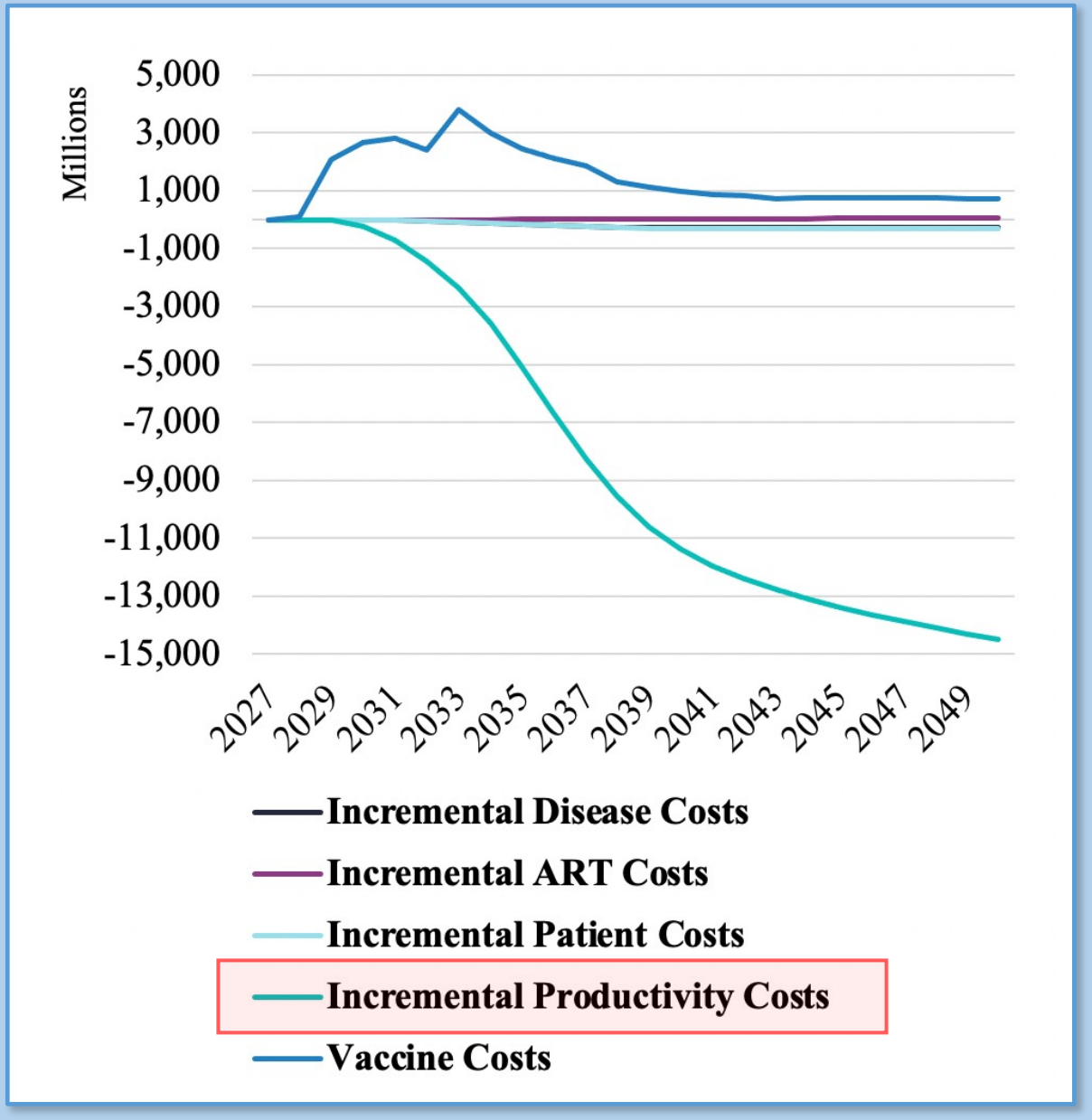
- High upfront vaccine introduction cost, drops after campaign period
- Costs due to secondary affects on HIV and TB care grow slowly
- Smaller upfront costs in infant vaccine scenario (no campaign)



Annual incremental costs over study period, by broad cost category (adolescent vaccine, all modelled countries)

+ patient productivity costs

- High upfront vaccine introduction cost, drops after campaign period
- Costs due to secondary affects on HIV and TB care grow slowly
- Smaller upfront costs in infant vaccine scenario (no campaign)
- Lagged impact on patient productivity costs, but substantial



Incremental costs by programmatic area, 2028-2050 (all modelled countries, excluding productivity costs, 2020 USD)

	TB Costs (provider)	**TB Costs (patient OOP)**	**ART Costs**	**Vaccine Costs**
Infant Vaccine	-710 (3% reduction)	-290 (3% reduction)	59 (0.01% increase)	9,100
Ado/Adult Vaccine	-4,000 (19% reduction)	-1,900 (19% reduction)	1,100 (0.2% increase)	33,000

Study-specific methods and results

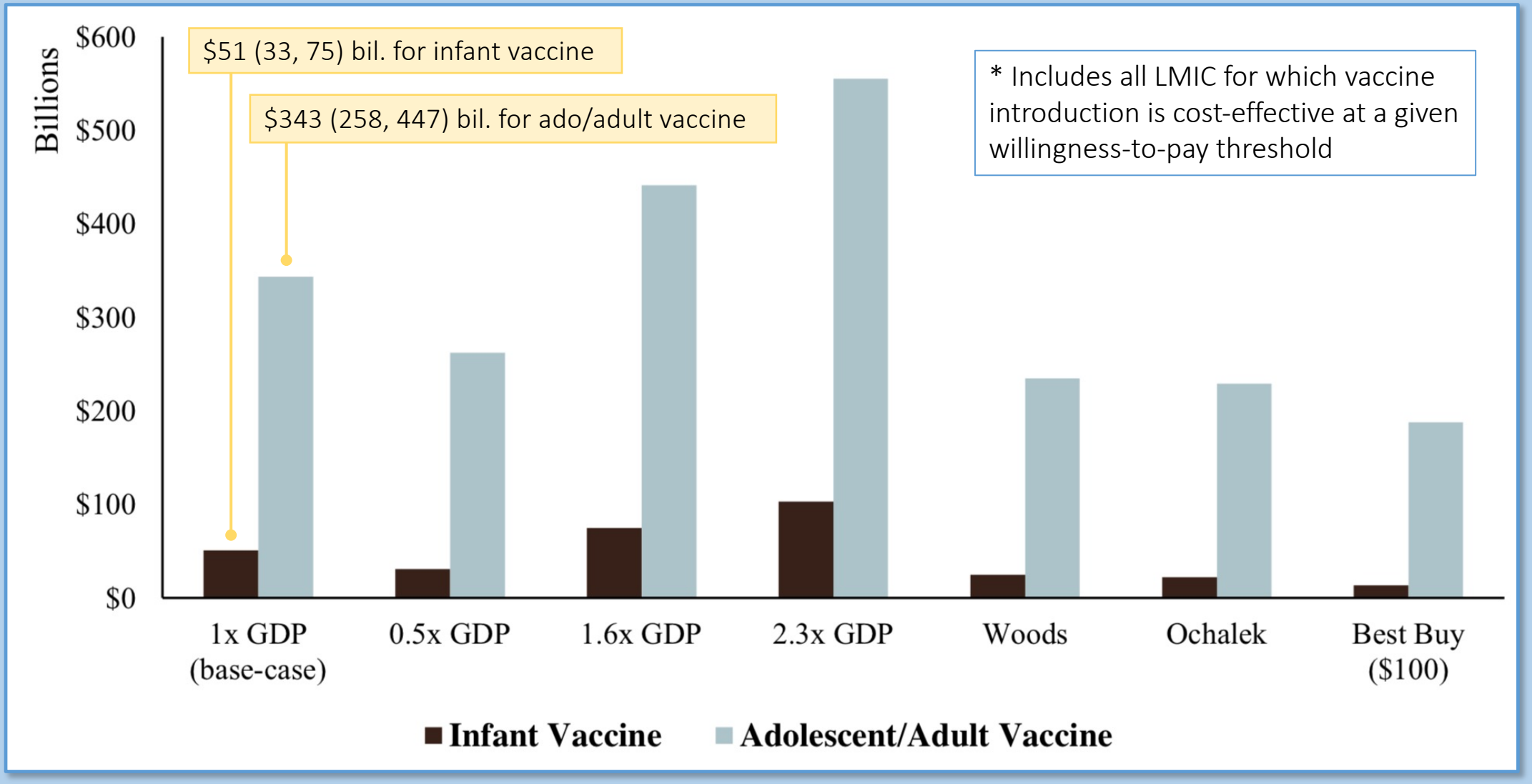
Cost-effectiveness (health system perspective)	Budget impact	Health equity & financial risk protection
Cost-effectiveness (societal perspective)	**Return on investment (Net Monetary Benefit)**	Macroeconomic impact

Return on investment

Net Monetary Benefit (NMB) = health benefits * CE threshold – costs

- Health benefits = DALYs averted
- CE threshold = multiples of per capita GDP, assessed range of values
- Costs assessed from societal perspective

Net Monetary Benefit of novel tuberculosis vaccines, assessed from the societal perspective, for several willingness-to-pay thresholds*



Study-specific methods and results

Cost-effectiveness (health system perspective)	Budget impact	**Health equity & financial risk protection**
Cost-effectiveness (societal perspective)	Return on investment (Net Monetary Benefit)	Macroeconomic impact

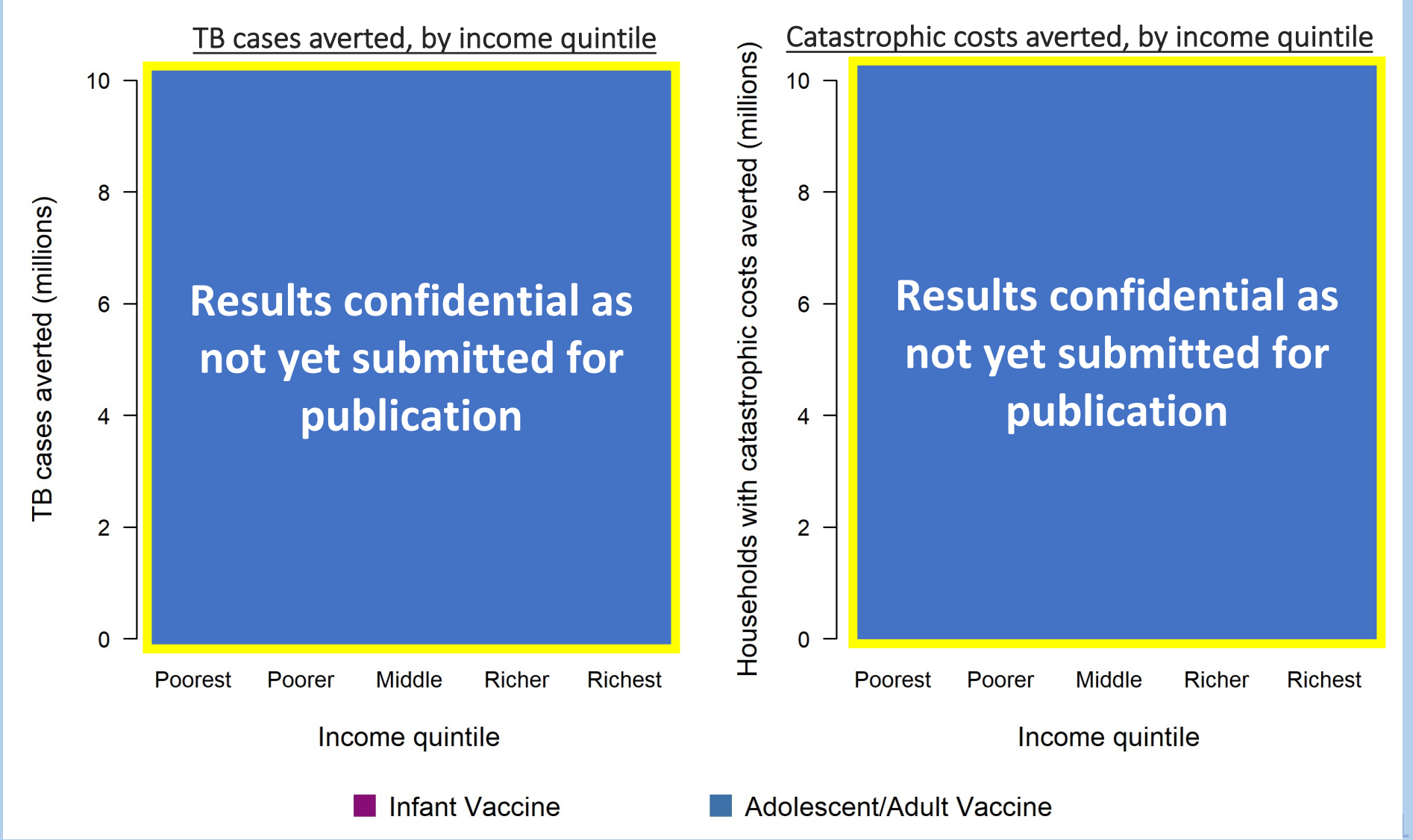
Health equity and financial risk protection

- Stratified outcomes across 5 income quintiles within each modeled country, based on current distribution of TB burden
- For each country and quintile, costs incurred by patients (direct medical, direct non-medical, indirect costs) estimated by extrapolating from national TB patient cost survey data (N=20 surveys)
- Catastrophic costs of TB defined as patient costs per TB episode > 20% of household annual income

Equity impact: TB cases and catastrophic costs averted for all modelled countries, by income quintile

Lower income quintiles:

- Higher TB incidence
- Greater fraction with catastrophic costs, per case



Study-specific methods and results

Cost-effectiveness (health system perspective)	Budget impact	Health equity & financial risk protection
Cost-effectiveness (societal perspective)	Return on investment (Net Monetary Benefit)	**Macroeconomic impact**

Macroeconomic impact

- Outputs of earlier analysis used to parameterize published macroeconomic model (EPIC model) to estimate impact on TB vaccination on country GDP
- Timeline extended to 2080 to capture long-term effects

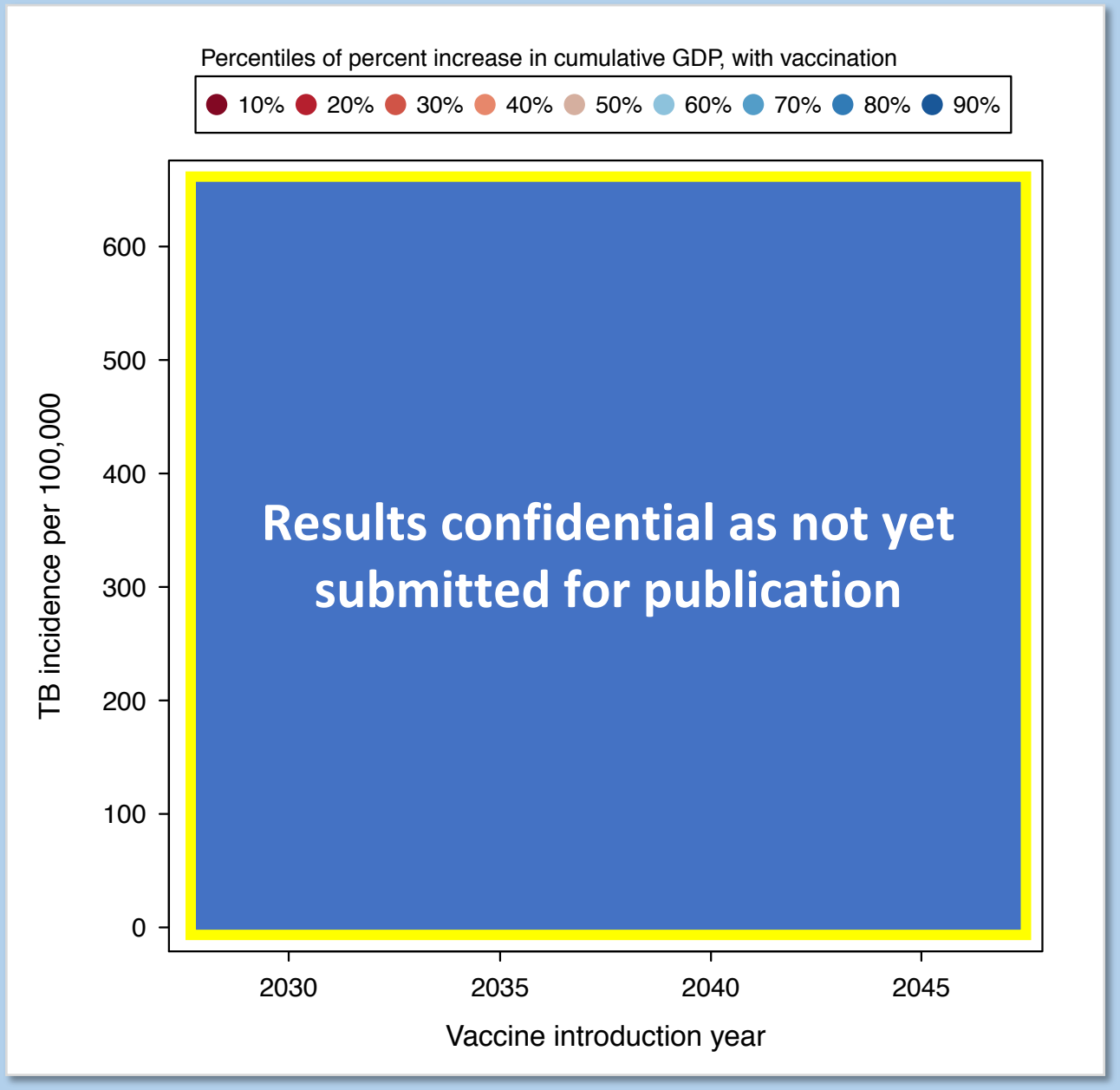
Macroeconomic impact: absolute and percentage gains in GDP over 2028-2080 period, for modelled countries

	Adolescent/adult vaccine		Infant vaccine	
	Absolute gains in GDP (billions US$2020)	**Percentage gain in GDP (%)**	**Absolute gains in GDP (billions US$2020)**	**Percentage gain in GDP (%)**
All countries				
High-TB burden				
AFR				
AMR				
EMR				
EUR				
SEAR				
WPR				

Results confidential as not yet submitted for publication

Gains in GDP (%) over 2028-2080, by TB incidence and vaccine intro year

- Macroeconomic impact strongly related to current TB incidence level
- Earlier vaccine introduction, lower current GDP per capita also related to greater % impact



Summary

- Largest health benefits from adolescent/adult vaccine introduced with 1-time campaign, but this has high upfront costs
- Major cost savings + productivity gains, these accrue slowly, then accelerate
- From health system perspective, vaccination projected to be cost-effective in most LMIC, for a range of vaccine prices and CE criteria
- From societal perspective, vaccination projected to be cost-saving
- Health and economic benefits concentrated in high burden countries, lower wealth quintiles
- Major uncertainties: [i] vaccine characteristics, [ii] pace and reach of vaccine introduction

Acknowledgements and Thanks

Contributors/Advisors:

- **India** (Kieran Rade, Raguram Rao, Sandip Mandal, Hisham Moosan & confidential interviewees)
- **China** (Li Tao, Chen Chen, Sharon Chan, Lixia Wang(ex) & confidential interviewees)
- **South Africa** (Mark Hatherill, Michele Tamaris, Gavin Churchyard, Willem Hanekom & confidential interviewees)
- **WHO** (Nebiat Gebreselassie, Matteo Zignol, Gitte Giersing, Raymond Hutubessy)
- **IAVI** (Shelly Malhotra, Johan Vekemans, Derek Tait(ex))
- **BMGF** (Geoff Garnett, Ann Ginsburg, Anne Kasmar(ex))
- **TBVI** (Bernard Fritzell, Nick Drager)
- **Vaccitech** (Tom Evans)
- **Harvard** (Allison Portnoy, Nicolas Menzies)
- **LSHTM** (Rebecca Clark, Christinah Mukandavire, Chathika Weerasuriya, Matt Quaife, Puck Pelzer, Rebecca Harris, Mark Jit, Danny Scarponi…)
- And many, many others…

Funders:

The cost and cost-effectiveness of novel tuberculosis vaccines in low- and middle-income countries: a modelling study

Authors

Allison Portnoy, ScD[1], Rebecca A. Clark, MSc[2-4], Matthew Quaife, PhD[2-4], Chathika K. Weerasuriya, PhD[2-4], Christinah Mukandavire, PhD[2-4], Roel Bakker, PhD[2-5], Arminder K. Deol, PhD[2-4,6], Shelly Malhotra, PhD[7,8], Nebiat Gebreselassie, PhD[9], Matteo Zignol, MD[9], So Yoon Sim, MA, MSPH[10], Raymond C.W. Hutubessy, PhD[10], Inés Garcia Baena, MSc[9], Nobuyuki Nishikiori, PhD[9], Mark Jit, PhD[3,4,11], Richard G. White, PhD[2-4,*], Nicolas A. Menzies, PhD[1,12*]

* Co-senior authors

Affiliations

1. Center for Health Decision Science, Harvard T.H. Chan School of Public Health, Boston, MA, USA
2. TB Modelling Group, London School of Hygiene and Tropical Medicine, London, UK
3. Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, London, UK
4. Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK
5. KNCV Tuberculosis Foundation, The Hague, Netherlands
6. Coalition for Epidemic Preparedness Innovations, London, UK
7. Market Access, Global Alliance for TB Drug Development, New York, New York, USA

8. Global Access, International AIDS Vaccine Initiative, New York, New York, USA
9. Global TB Programme, World Health Organization, Geneva, Switzerland
10. Department of Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland
11. School of Public Health, University of Hong Kong, Hong Kong SAR, China
12. Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, MA, USA

Corresponding Author: Allison Portnoy, Center for Health Decision Science, Harvard T.H. Chan School of Public Health, 718 Huntington Avenue 2nd Floor, Boston MA 02115, USA. Phone: +1(617) 432-2019. Email: aportnoy@mail.harvard.edu.

Acknowledgements: The views expressed are those of the authors and do not necessarily represent the views of their respective organizations.

Abstract

Background: Tuberculosis (TB) is preventable and curable but eliminating it has proven challenging. Safe and effective TB vaccines that can rapidly reduce disease burden are essential for achieving TB elimination. We assessed future costs, cost-savings, and cost-effectiveness of introducing novel TB vaccines in low- and middle-income countries (LMICs) for a range of product characteristics and delivery strategies.

Methods and Findings: We developed a system of epidemiological and economic models, calibrated to demographic, epidemiological, and health service data in 105 LMICs. For each country, we assessed the likely future course of TB-related outcomes under several vaccine introduction scenarios, compared to a 'no-new-vaccine' counterfactual. We estimated the incremental impact of vaccine introduction for a range of health and economic outcomes. In the base-case, we assumed a vaccine price of $4.60, and used a 1x per-capita GDP cost-effectiveness threshold (both varied in sensitivity analyses). Vaccine introduction was estimated to require substantial near-term resources, offset by future cost-savings from averted TB burden. From a health system perspective, vaccination was cost-effective in 65 of 105 LMICs. From a societal perspective (including productivity gains and averted patient costs), vaccination was projected to be cost-effective in 75 of 105 LMICs and cost-saving in 57 of 105 LMICs, including 96% of countries with higher TB burden. When considering the monetized value of health gains, we estimated that introduction of an adolescent/adult vaccine could produce $258–447 billion in economic benefits by 2050.

Conclusions: TB vaccination would be highly impactful and cost-effective in most LMICs. Further efforts are needed for future development, adoption, and implementation of novel TB vaccines.

Funding: World Health Organization (2020/985800-0)

Background

Tuberculosis (TB) is the world's second greatest cause of infectious disease death after COVID-19.[1] It remains the leading cause of death for people living with HIV and a major contributor to antimicrobial-resistance-related deaths. The COVID-19 pandemic has reversed years of progress in providing TB services and, consequently, the number of people who died from TB increased to 1.5 million in 2020.[1]

The World Health Organization (WHO)'s End TB Strategy targets a 90% reduction in TB mortality and 80% decline in TB incidence by 2030, compared to 2015.[2] Achieving these targets will require a comprehensive multisectoral response, along with transformational new tools. The cost of not meeting the End TB Targets by 2030 and facing the excess deaths resulting from COVID-19-related disruptions to TB services may translate into 31.8 million TB deaths globally corresponding to an economic loss of $17.5 trillion between 2020 and 2050.[3] Developing new safe, affordable, and effective TB vaccines is critical for achieving these targets. While promising candidates exist (for example, the M72/AS01$_E$ candidate vaccine[4]), limited market incentives to invest in TB prevention has delayed the development of novel TB vaccines.

The WHO promotes the Full Value of Vaccines Assessment framework to improve decision-making around vaccine development and use.[5,6] Using this framework, we estimated the costs, cost-effectiveness, and net monetary benefit of TB vaccine introduction, from health system and societal perspectives, to inform global-level decision-making for novel TB vaccine investment and introduction.[5,6]

Methods

Analytic overview

We estimated a range of outcomes quantifying the health and economic impact of new vaccine introduction for affected countries. To do so, we used linked epidemiological and economic models to project changes in healthcare utilization, health outcomes, and healthcare costs for various vaccine introduction scenarios compared to a 'no-new-vaccine' counterfactual (full epidemiological model details have been previously described by Clark and colleagues[7]). We estimated outcomes for each of 105 low- and middle-income countries (LMICs) over a 2028–2050 evaluation period (Appendix S1). We summarized results as the incremental costs, cost-effectiveness, and incremental net monetary benefits of vaccine introduction. Results are presented for a range of analytic assumptions and introduction scenarios, organized by major country groupings (WHO region, World Bank income level,[8] and WHO high-TB burden grouping[9]).

Vaccination scenarios

We constructed a 'no-new-vaccine' baseline with current TB interventions continuing into the future at current levels. Compared to this baseline, we evaluated two different vaccine product profiles: an infant 'pre-infection' vaccine (i.e., efficacious for individuals uninfected at time of vaccination) with 80% efficacy targeting neonates, and an adolescent/adult 'pre- and post-infection' vaccine (i.e., efficacious in all individuals aside from those with active TB disease at time of vaccination) with 50% efficacy, based on WHO preferred product characteristics.[10] For both vaccine product profiles, we assumed an average ten-year duration of protection, with exponential waning. We assumed the infant vaccine would be delivered through the routine vaccination program, and the adolescent/adult vaccine delivered through routine vaccination of

nine-year-olds plus a one-time vaccination campaign for ages 10+. In the base-case scenario, we assumed countries would achieve linear scale-up to a specified coverage over five years. Based on consultation with global stakeholders, we assumed a coverage target of 85% for the infant vaccine (average coverage of diphtheria-tetanus-pertussis third dose for LMICs[11]), 80% for routine delivery of adolescent/adult vaccine, and 70% of the adolescent/adult vaccination campaign.[12] We assumed country-specific introduction years from 2028–2047, determined based on indicators for disease burden, immunization capacity, classification of the country as an "early adopter/leader," lack of regulatory barriers, and commercial prioritization.[7]

Epidemiological outcomes and health service utilization

We projected future TB epidemiology and health service utilization using an age-structured TB transmission model calibrated to reported demography, TB burden estimates, and TB service utilization in each modelled country.[7] Out of 135 LMICs,[8] we excluded 20 due to lack of critical calibration data and 10 due to unsuccessful calibration results. We analyzed the remaining 105 countries (Appendix S1), representing 93.3% of global TB burden.[13] In countries with a significant burden of HIV-associated TB, the model included the effects of HIV and antiretroviral therapy (ART) on TB infection and progression risks. Using this model, we estimated changes in TB epidemiology and related service utilization for each modelled scenario.

Summary health outcomes

We estimated disability-adjusted life-years (DALYs) averted to quantify the health gains achieved by vaccination. To calculate years lost due to disability (YLDs), we assigned each modelled health state a disability weight from the Global Burden of Disease classification system (Appendix S2).[14] For each scenario and year, total YLDs were calculated by summing life-years

lived across all health states, weighted by the disability weight for each state. For each scenario and year, years of life lost were calculated by multiplying deaths at each year of age by reference life expectancy at that age[15], and summing across all ages.

Cost outcomes

We estimated the costs of vaccine introduction, as well as changes in the costs of other health services (TB care, HIV care) by multiplying health service volume indicators (vaccines delivered, TB cases diagnosed and treated, ART patient-years) by country-specific unit costs. Diagnostics costs for drug-susceptible (DS) and rifampicin-resistant (RR) TB were obtained from published literature,[16] and extrapolated to all LMICs by country income level.[8] Unit costs for TB treatment were calculated as an average of DS-TB[17] and RR-TB[16,18] treatment costs, weighted by country-level RR-TB prevalence.[1]

For ART costs, direct non-medical costs (travel, accommodation, food, nutritional supplements) to the patient, and productivity costs (income loss experienced by patients during TB care), we derived unit costs by extrapolating estimates reported by the Global Health Cost Consortium[19] (sample size = 39) and WHO patient cost surveys (sample size = 20).[20,21] Productivity costs due to premature death were estimated as the incremental number of life-years gained under a given vaccination scenario, multiplied by 2020 per-capita GDP as an approximation of income.

As the per-dose cost for novel TB vaccines is unclear while products are still under development, the base-case used an LMIC price of human papillomavirus (HPV) vaccine ($4.60) for a novel vaccine proxy with an injection supply cost per dose of $0.11 and 5% wastage.[22,23] Country-specific vaccine delivery costs were based on a meta-analysis of childhood[24] and HPV vaccine delivery unit costs for the infant and adolescent/adult vaccines, respectively, plus additional one-

time vaccine introduction costs ($0.65 and $2.40 per targeted individual in the first year of introduction for infant and adolescent/adult vaccines, respectively).[25] Costs are reported in 2020 US dollars.

Cost-effectiveness analysis

Incremental cost-effectiveness ratios (ICERs) were calculated from health system and societal perspectives, with a 3% discount rate, across the 2028–2050 evaluation period. We also reported a specification in which costs are discounted but not health outcomes. The health system perspective considered costs of vaccine introduction, plus the costs of TB and HIV services indirectly affected by vaccine introduction. The societal perspective additionally included patient non-medical and productivity costs. ICERs were compared to a range of country-specific cost-effectiveness thresholds, including multiples of per-capita GDP[26] and recent estimates of the opportunity cost of healthcare spending.[27,28]

Return on investment

We quantified the return on investment as the incremental net monetary benefit (iNMB) from the societal perspective of each vaccine scenario compared to baseline for a range of willingness-to-pay thresholds.[26-28] iNMB was calculated as the sum of monetized health gains (DALYs averted multiplied by the estimated willingness-to-pay per DALY averted) minus incremental costs. We estimated the market size for each vaccine product profile, summing all individuals across 2028–2050 who were vaccinated in the model in the base-case scenario in countries in which the vaccine was cost-effective (ICER less than per-capita GDP). We also estimated market size based on countries in which vaccination was cost-saving under the societal perspective.

Statistical analysis

We explored estimation uncertainty using a 2nd-order Monte Carlo simulation.[29] We constructed probability distributions representing uncertainty in economic inputs and disability weights and drew 1000 random values for each uncertain parameter. We represented uncertainty in healthcare utilization and epidemiological outcomes (counts of each outcome by scenario, year, and population stratum) using 1000 results sets from the transmission-dynamic model. This analysis generated 1000 estimates for each outcome of interest, which we summarized as equal-tailed 95% uncertainty intervals.

Sensitivity analysis

Compared to the base-case coverage targets (85%, 80%, 70% for routine infant vaccine delivery, routine adolescent vaccine delivery, and campaign adolescent/adult vaccine delivery, respectively), we examined a low-coverage scenario (75%, 70%, and 50%, respectively) and a high-coverage scenario (95%, 90%, and 90%, respectively).

We examined two alternative vaccine delivery scenarios. First, we modelled an accelerated scale-up scenario in which all countries introduced vaccination in 2025 and achieved instantaneous scale-up to the specified coverage target. Second, we modelled a routine-only scenario which removed the one-time campaign-delivery component of the adolescent/adult base-case scenario.

We examined three alternative vaccine price scenarios, including scenarios in which the base-case vaccine price of $4.60 was both halved ($2.30) and doubled ($9.20), respectively. A third scenario examined high-middle-tier vaccine pricing, with higher prices for middle-income countries based on UNICEF vaccine pricing data ($10.25 for non-Gavi countries with gross

national income (GNI) per capita less than $3,995 and $14.14 for non-Gavi countries with GNI per capita greater than $3,995; Appendix S1).[22]

We also estimated results with an alternative set of assumptions about TB incidence trends in the no-new-vaccine baseline, with incidence assumed to decline more rapidly through the scale-up of existing preventive treatment and case detection, meeting the 2025 'End TB' incidence reduction target without introduction of a new vaccine.[2]

Compared to the base-case assumption of ten-year duration of protection, we also examined lifelong duration of protection conferred by vaccination.

Results

Costs and cost-effectiveness analysis

In the no-new-vaccine baseline, over 2028–2050, total undiscounted costs of TB diagnosis and treatment were estimated to be $17.6 (95% uncertainty interval: 10.8–26.7) billion for DS-TB and $14.8 (12.0–17.9) billion for RR-TB (Appendix S3). For the infant vaccine scenario, vaccine introduction costs were $9.7 (7.9–13.9) billion, and averted TB diagnosis and treatment costs were $295 (192–419) million for DS-TB and $244 (205–290) million for RR-TB over 2028–2050 (Appendix S4). For the adolescent/adult vaccine scenario, vaccine introduction costs were $32.7 (24.7–49.1) billion, and averted TB diagnosis and treatment costs were $2.1 (1.3–3.1) billion for DS-TB and $1.8 (1.5–2.1) billion for RR-TB over 2028–2050 (Appendix S5)—greater than the averted disease costs in the infant vaccine scenario. There would also be $18.1 (13.7–24.7) million and $276 (215–356) million in additional ART costs under the infant and

adolescent/adult vaccine scenarios, respectively, due to extended survival among people living with HIV (Appendices S6–S7).

There was greater, and more rapid, impact from an adolescent/adult vaccine compared to an infant vaccine over the study period (Appendices S8–S9). Across 2028–2050, infant vaccine costs were projected to increase smoothly from the year of vaccine introduction, whereas the adolescent/adult vaccine scenario required major upfront investments during vaccine introduction and 5-year campaign roll-out, then decreased substantially after campaigns were completed.

In the base-case analysis, from the health system perspective, we found that infant vaccination would be cost-effective (ICER below 1-times per-capita GDP) compared to no vaccination in 48 of 105 modelled LMICs (46%) and 26 of 27 with high-TB burden (96%). Using the same assumptions, we found that adolescent/adult vaccination would be cost-effective in 65 out of 105 countries (62%) and all 27 with high-TB burden. Neither vaccine strategy would be cost-saving in any country. Figure 1 displays the distribution of country-level cost-effectiveness results from the health system perspective for infant and adolescent/adult vaccines, stratified by TB incidence level. Vaccine introduction was more likely to be cost-effective in countries with higher TB incidence.

From the societal perspective, the infant vaccine was cost-effective in 55 out of 105 countries (52%), including all with high-TB burden, and cost-saving in 47 countries (45%). Similarly, the adolescent/adult vaccine was cost-effective in 75 out of 105 countries (71%), remaining cost-effective in all with high-TB burden, and cost-saving in 57 countries (54%). Figure 2 displays the percentage of the modelled population that live in countries where vaccination was cost-

effective based on different cost-effectiveness thresholds (Appendix S10 shows the percentage of countries where vaccination was cost-effective; Appendices S11–S12 present tabular results).

Tables 1 and 2 report summary health outcomes, costs, and cost-effectiveness of the base-case vaccination scenarios. Across all 105 analyzed countries, the majority of TB cost-savings accrued in high-TB-burden settings, particularly in lower middle-income settings and WHO African region (AFR) and South-East Asian region (SEAR). Assuming 0% discounting on health outcomes decreased ICERs (indicating greater cost-effectiveness) for the infant vaccine by approximately 76% and for the adolescent/adult vaccine by approximately 69% from the health system perspective (Appendices S13–S14).

Return on investment

With each averted DALY valued at per-capita GDP and costs assessed from the societal perspective, we estimated a cumulative $50.8 (range: $32.6–74.7 across examined thresholds) billion incremental net monetary benefit (iNMB) globally for infant vaccine introduction in countries where introduction was cost-effective at 1-times per-capita GDP (Figure 3; tabular results in Appendix S15). For the adolescent/adult vaccine, we estimated iNMB of $343 billion for countries in which vaccination was cost-effective (range: $258–447 billion). These benefits were concentrated in regions (AFR, SEAR) with higher disease burden. For the infant vaccine, the market size (i.e., the vaccinated population in countries in which the vaccine would be cost-effective at per-capita GDP from the societal perspective) would be 1.26 (1.25–1.27) billion individuals, while for the adolescent/adult vaccine this population size would be 3.602 (3.599–3.604) billion individuals. Under a more restrictive assumption where the vaccine is only introduced in countries where the societal ICER is cost-saving, the market size would be 1.19 (1.18–1.20) billion individuals for the infant vaccine, and 3.224 (3.222–3.226) billion individuals

for the adolescent/adult vaccine. The largest markets were in the WHO SEAR and WPR regions (Appendices S16–S17).

Sensitivity analysis

From both health system and societal perspectives, DALYs averted and costs decreased in the low-coverage scenario, and increased in the high-coverage scenario, for both the infant and the adolescent/adult vaccine, with evidence of diminishing returns as coverage increases (Appendices S18–S21).

Compared to the base-case vaccination introduction and delivery scenario, the accelerated scale-up scenario had greater health impact (DALYs averted) and better cost-effectiveness (assuming per-unit vaccination costs were unchanged), with vaccination being cost-effective in a greater number of countries compared to a per-capita GDP threshold (i.e., 70 compared to 48 for the infant vaccine and 98 compared to 65 for the adolescent/adult vaccine from the health system perspective; Appendices S22–S25). Conversely, the routine-only scenario had a much smaller health impact and modestly worse cost-effectiveness profile, as compared to the base-case analysis (Appendix S26).

Reducing the vaccine price by half decreased infant vaccination costs from $9.7 to $6.5 billion (33% decrease) and adolescent/adult vaccination costs from $32.7 to $24.7 billion (25% decrease; Appendices S27–S36). Doubling the vaccine price increased infant vaccination costs to $17.5 billion (80% increase) and adolescent/adult vaccination costs to $53.7 billion (64% increase). Switching to high-middle-tier vaccine pricing (higher vaccine prices for middle-income countries) increased infant vaccine costs to $14.6 billion (50% increase) and adolescent/adult vaccination costs to $48.7 billion (a 49% increase). From the health system

perspective, reducing the vaccine price by half increased the number of countries in which infant vaccination was cost-effective at a per-capita GDP threshold from 48 to 51, whereas doubling the vaccine price decreased the number of cost-effective countries to 33. Assuming higher vaccine prices for middle-income countries reduced the number of countries in which the infant vaccine was cost-effective at a per-capita GDP threshold from 48 to 42. Similarly, the half-price scenario, double-price scenario, and high-middle-tier-price scenario changed the number of countries in which the adolescent/adult vaccine was considered cost-effective from the health system perspective at a per-capita GDP threshold from 65 in the base-case, to 70, 52, and 56, respectively.

Assuming the no-new-vaccine baseline with faster incidence reductions through strengthening of current TB interventions to meet the 2025 End TB targets, a number of countries remained cost-saving from the societal perspective (9 countries for infant vaccine and 25 countries for adolescent/adult vaccine; Appendices S37–S38).

An infant vaccine with lifelong duration of protection averted 27.5 (23.9–31.6) million DALYs, a 52% increase compared to the base-case assumption of 10-year protection (Appendix S39). An adolescent/adult vaccine with lifelong duration of protection averted 94.8 (86.7–103) million DALYs (36% greater than the base-case; Appendix S40). Both vaccine products remained cost-saving from the societal perspective; assuming lifelong duration of protection decreased the ICER by approximately 40% and 35% for the infant and adolescent/adult vaccine, respectively (health system perspective).

Discussion

An effective novel TB vaccine would offer large potential health and economic benefits over 2028–2050. These results demonstrate that, when available, TB vaccines could be cost-effective in a majority of LMICs, particularly from the societal perspective, and essentially in all high-burden countries. Introducing novel TB vaccines could also offer high value in terms of incremental net monetary benefit to patients, the health system, and society, particularly in countries with high burden of TB, HIV-associated TB, and/or multidrug-resistant/RR-TB.

For both vaccine product profiles, vaccination was more likely to be cost-effective in lower middle-income countries (relative to low-income and upper middle-income countries), as countries in this income group are more likely to have both significant TB burden and sufficient economic resources to justify additional TB investments without displacing other important health interventions. Vaccination was more frequently cost-effective in AFR and SEAR regions and both vaccines were estimated to be cost-effective in all countries in the 27 modelled high-TB burden countries that accounted for 81.8% of global incident TB cases and 80.9% of global TB deaths in 2020.[9,13] Although vaccines can be economically less viable for manufacturers, we estimated large potential markets for vaccinees in high-burden, middle-income settings.

There was greater, and more rapid, impact from an adolescent/adult vaccine over the 2028–2050 time horizon compared to an infant vaccine, as this vaccine is targeted to a population with the highest burden of TB, and the delay between vaccination and TB prevention impact is shorter with the adolescent/adult vaccine. For the adolescent/adult vaccine, we estimated major short-term costs from introduction and one-time vaccination campaigns, with the highest costs incurred during the ten years following vaccine introduction. In contrast, the cost-savings from averted TB disease were realized gradually over 2028–2050, growing in magnitude towards the end of the time horizon. By assuming the no-new-vaccine baseline meeting the End TB targets,

the remaining TB burden that could be averted by vaccination was estimated to be smaller, yielding results that were less cost-effective.

This analysis had several limitations. We were constrained by data availability, with only 105 countries successfully parameterized and calibrated. However, these 105 countries represent 93.3% of LMIC TB incidence and 93.6% of LMIC TB mortality globally in 2020.[13] As a "pre- and post-infection" vaccine, the adolescent/adult vaccine was assumed to be equally effective regardless of previous infection status, which may have led to an overestimation of averted TB cases and deaths if the vaccine is less effective in infected vaccinees. We also extrapolated from published literature[16-18] for several major unit cost inputs, potentially omitting important country-level heterogeneity in these costs. The sample size of patient cost surveys used for non-medical and productivity costs was small (20); therefore, the extrapolation to other country settings may not capture the level of potential variation in these costs. We did not investigate targeting high-risk subgroups for vaccination; vaccination could still be cost-effective when targeted to subgroups in settings where vaccination was not estimated to be cost-effective in a national roll-out. Finally, we did not consider all possible product and introduction scenarios, but demonstrated the potential value of novel TB vaccines according to specified characteristics.

Across this analysis, introduction of a novel TB vaccine was found to be impactful and cost-effective for a range of assumptions on vaccine price and delivery strategies, with aggregate health and economic benefits of similar scale to the most influential health interventions in LMIC settings in recent years.[30] TB vaccines are still under development, so their potential effectiveness and impact are uncertain. Accelerating the timeline for vaccine introduction, decreasing the vaccine price, or increasing vaccine efficacy could all impact the cost-effectiveness profile of vaccination and increase the magnitude of the benefits, directly

improving the welfare of individuals and households which would otherwise experience the health and economic consequences of TB in coming years. Future work should investigate country-level vaccine policy questions to support introduction preparedness. The results of these analyses can be used by global and country stakeholders to inform these questions, as well as decision-making around future development, adoption, and implementation of novel TB vaccines.

Acknowledgements

We are grateful for the support of the World Health Organization for funding this research (2020/985800-0). We thank all the attendees at the WHO meetings on the Full Value Assessment of TB Vaccines for insightful advice and direction.

Ethics approval and consent to participate

Not applicable.

Author contributions

AP, NAM, RGW, MQ, and MJ conceptualized and designed the study. AP conducted the analysis with support from NAM, RAC, MQ, MJ, CKW, CM, AKD, and RGW. AP, NAM, RAC, and RGW drafted the initial manuscript and approved the final manuscript as submitted. MQ, CKW, CM, RB, AKD, SM, NG, MZ, SYS, RH, IGB, NN, and MJ critically reviewed the analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted. All authors read and approved the final manuscript.

Financial disclosure

This study was funded by the World Health Organization (2020/985800-0). The funder was involved in developing the research question, study design, and provided comments on the manuscript draft, but had no role in the collection, analysis, and interpretation of the data, or writing of the report. All authors had the opportunity to access and verify the data, and all authors were responsible for the decision to submit the manuscript for publication.

Competing interests

RAC is funded by BMGF (INV-001754) and received a grant from the Canadian Centennial Scholarship Fund. CKW is funded by UKRI/MRC (MR/N013638/1). RGW is funded by the Wellcome Trust (218261/Z/19/Z), NIH (1R01AI147321-01), EDTCP (RIA208D-2505B), UK MRC (CCF17-7779 via SET Bloomsbury), ESRC (ES/P008011/1), BMGF (OPP1084276, OPP1135288 & INV-001754) and the WHO (2020/985800-0). All other authors declare no conflicts of interest.

Table 1. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of infant tuberculosis vaccines

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	6.61 (5.38, 9.23)	*-28.5* (*-33.6*, *-23.5*)	18.1 (15.7, 20.9)	368 (283, 522)	cost-saving[c]
High-TB burden[d]	4.43 (3.66, 6.18)	*-28.9* (*-33.9*, *-24.1*)	16.7 (14.3, 19.5)	267 (206, 381)	cost-saving[c]
High-TB/HIV burden[d]	3.13 (2.6, 4.23)	*-25.5* (*-30.5*, *-21.0*)	14.6 (12.2, 17.3)	216 (166, 303)	cost-saving[c]
High-MDR/RR-TB burden[d]	3.90 (3.18, 5.49)	*-27.2* (*-32.1*, *-22.4*)	14.8 (12.4, 17.6)	266 (201, 386)	cost-saving[c]
Income level[e]					
LIC	0.97 (0.83, 1.25)	*-0.25* (*-0.51*, 0.05)	2.02 (1.69, 2.45)	485 (373, 645)	cost-saving (cost-saving, 28.3)
LMIC	3.41 (2.84, 4.61)	*-23.8* (*-28.4*, *-19.5*)	14.9 (12.7, 17.7)	230 (178, 323)	cost-saving[c]
UMIC	2.22 (1.67, 3.52)	*-4.43* (*-6.48*, *-2.63*)	1.11 (0.84, 1.5)	2044 (1273, 3346)	cost-saving[c]
World region					
AFR	2.09 (1.78, 2.73)	*-13.6* (*-17.3*, *-10.6*)	9.36 (7.73, 11.3)	226 (170, 307)	cost-saving[c]
AMR	0.59 (0.44, 0.92)	0.20 (0.04, 0.54)	0.06 (0.05, 0.07)	9520 (6680, 14900)	3350 (537, 8730)
EMR	0.90 (0.74, 1.23)	*-0.70* (*-1.39*, *-0.11*)	1.65 (1.15, 2.26)	567 (366, 873)	cost-saving[c]
EUR	0.37 (0.26, 0.62)	0.15 (0.04, 0.39)	0.04 (0.03, 0.04)	9930 (6660, 17100)	4130 (953, 10900)
SEAR	1.38 (1.13, 1.89)	*-10.2* (*-13.3*, *-7.73*)	5.54 (4.18, 7.36)	254 (173, 388)	cost-saving[c]
WPR	1.28 (0.99, 2.00)	*-4.27* (*-5.97*, *-2.88*)	1.43 (1.04, 1.95)	920 (587, 1510)	cost-saving[c]

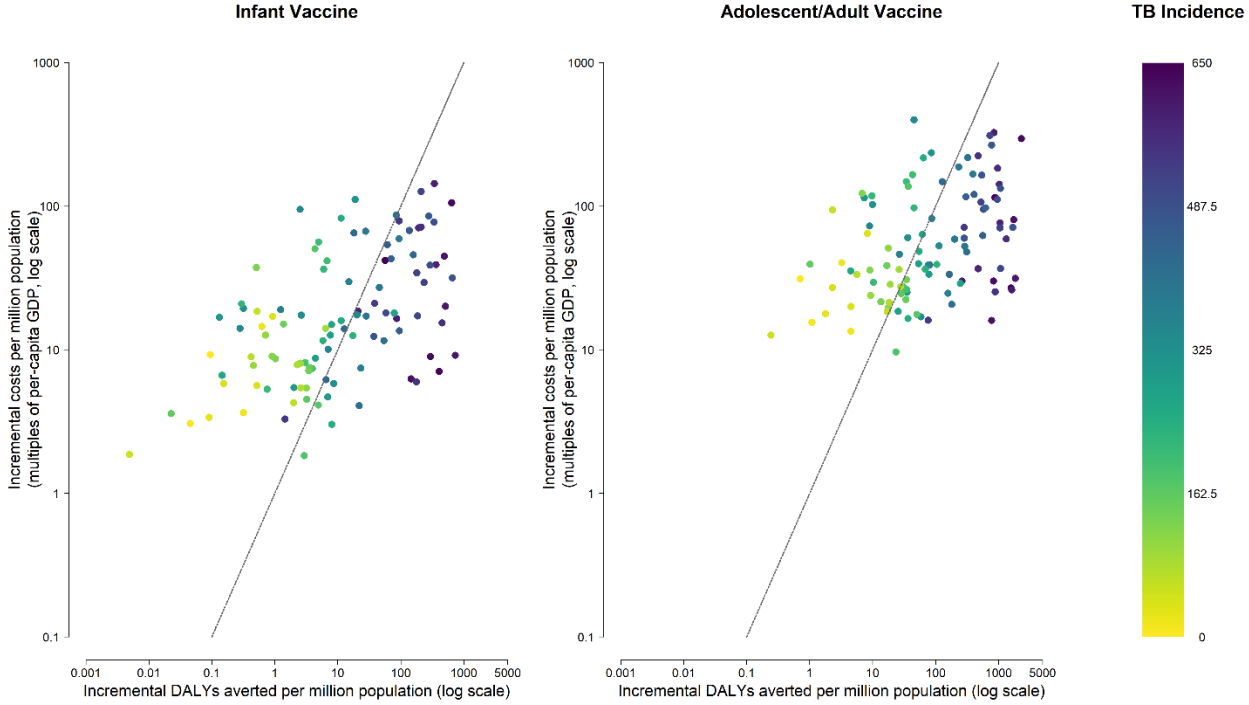
[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates are cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[9]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; GDP = gross domestic product; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

Table 2. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of adolescent/adult tuberculosis vaccines

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	Incremental DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	24.5 (18.1, 37.1)	*-108* (*-122*, *-92.1*)	69.7 (63.3, 76.5)	352 (253, 535)	cost-saving[c]
High-TB burden[d]	17.5 (12.8, 26.8)	*-106* (*-119*, *-91.0*)	63.6 (57.3, 70.4)	275 (194, 421)	cost-saving[c]
High-TB/HIV burden[d]	10.7 (8.03, 15.6)	*-97.5* (*-110*, *-84.8*)	56.8 (51.0, 63.2)	190 (135, 277)	cost-saving[c]
High-MDR/RR-TB burden[d]	16.0 (11.5, 25.0)	*-99.4* (*-113*, *-85.4*)	56.6 (50.5, 62.9)	284 (196, 441)	cost-saving[c]
Income level[e]					
LIC	2.64 (2.10, 3.53)	*-1.63* (*-2.43*, *-0.62*)	7.05 (6.20, 7.92)	376 (285, 514)	cost-saving[c]
LMIC	11.6 (8.80, 16.6)	*-89.3* (*-100*, *-78.3*)	57.6 (51.8, 64)	202 (147, 292)	cost-saving[c]
UMIC	10.2 (6.70, 18.1)	*-17.2* (*-24.0*, *-7.69*)	5.03 (4.11, 6.29)	2060 (1230, 3900)	cost-saving[c]
World region					
AFR	4.93 (3.93, 6.64)	*-41.7* (*-49.6*, *-35.2*)	29.1 (26.0, 32.4)	170 (130, 237)	cost-saving[c]
AMR	2.55 (1.73, 4.37)	*-0.09* (*-1.00*, 1.81)	0.49 (0.44, 0.55)	5190 (3440, 8900)	cost-saving (cost-saving, 3650)
EMR	2.80 (2.19, 3.87)	*-1.91* (*-3.25*, *-0.49*)	4.92 (3.86, 6.16)	578 (403, 850)	cost-saving[c]
EUR	1.37 (0.92, 2.35)	*-0.40* (*-0.90*, 0.56)	0.35 (0.31, 0.38)	3990 (2630, 7000)	cost-saving (cost-saving, 1710)
SEAR	6.22 (4.63, 9.07)	*-53.2* (*-62.0*, *-44.5*)	30.2 (25.7, 35.3)	208 (143, 313)	cost-saving[c]
WPR	6.58 (4.31, 11.55)	*-10.8* (*-13.9*, *-5.45*)	4.62 (3.99, 5.30)	1430 (913, 2540)	cost-saving[c]

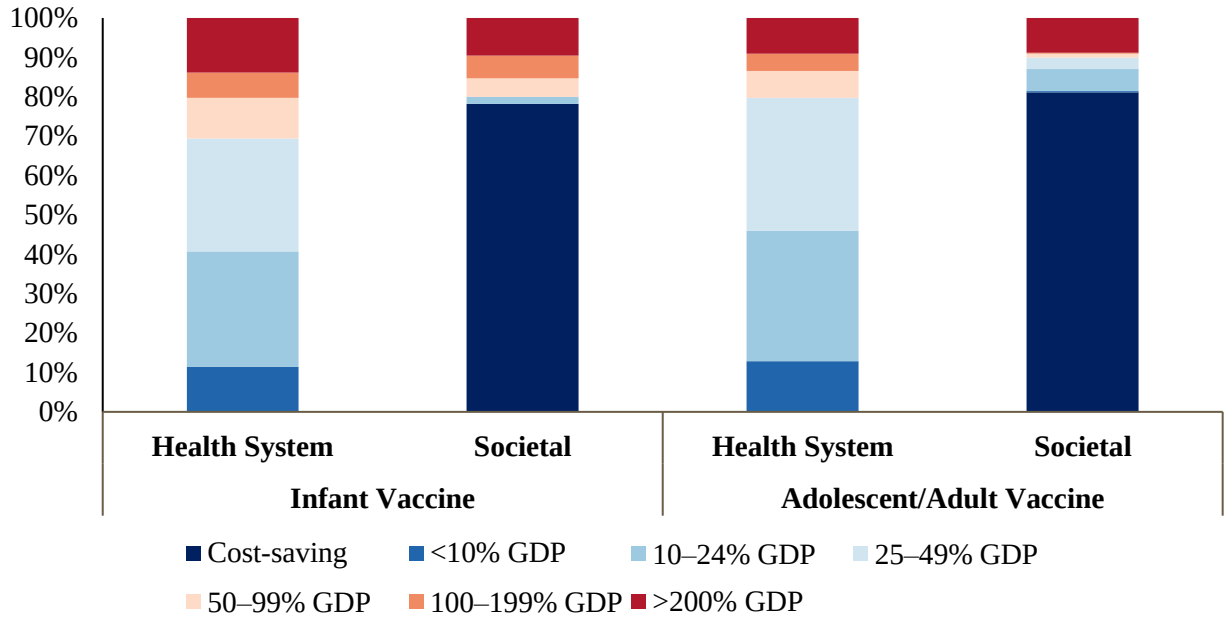
[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates are cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[9]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; GDP = gross domestic product; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

Figure 1. Cost-effectiveness results from the health system perspective for novel tuberculosis vaccines by country and vaccine.



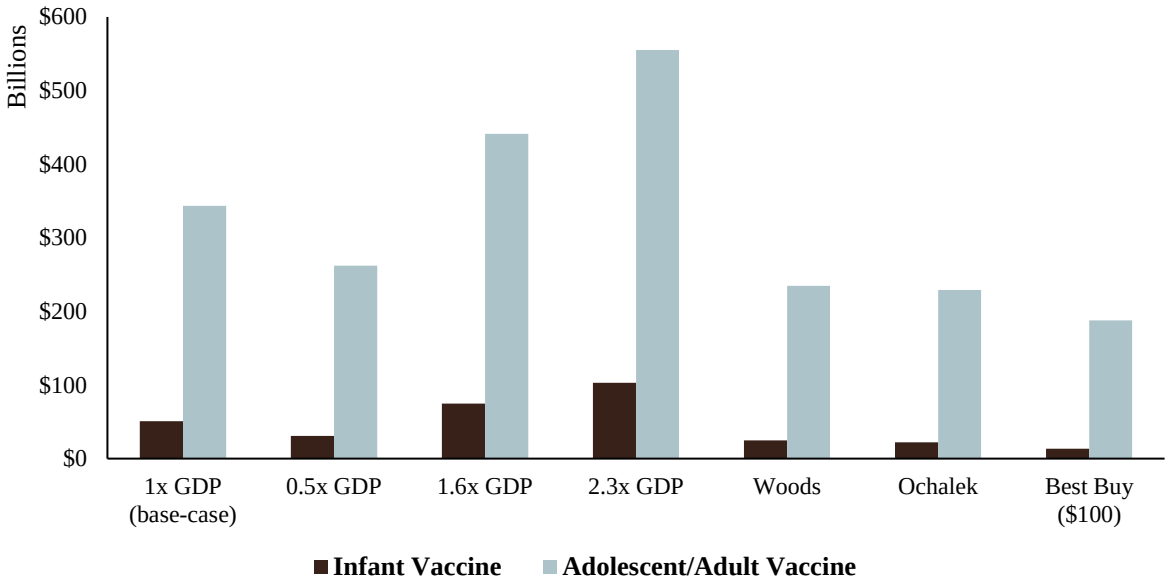
Note: Points represent each of 105 low- and middle-income countries analyzed in the base-case scenario, stratified by tuberculosis incidence per 100,000. Line represents a cost-effectiveness threshold of 1x per-capita GDP in 2020. Vaccine introduction would be considered cost-effective for countries falling underneath this line. DALY = disability-adjusted life year; GDP = gross domestic product.

Figure 2. Percentage of population that live in countries where vaccination was cost-effective compared to percentage of GDP per capita thresholds, comparing health system and societal perspectives.



Note: Countries include 105 low- and middle-income countries analyzed. Population includes vaccinated individuals 2028–2050. GDP estimates from 2020. GDP = gross domestic product per capita.

Figure 3. Incremental net monetary benefit of novel tuberculosis vaccines assessed from the societal perspective, for several willingness-to-pay thresholds.



Note: Estimates include the incremental net monetary benefit from the countries that are cost-effective at the respective threshold.[26-28] GDP estimates from 2020. GDP = gross domestic product per capita.

References

1. World Health Organization. Global Tuberculosis Report 2021. Geneva: World Health Organization. 14 October 2021. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2021 (accessed 1 December 2021).
2. World Health Organization. The End TB Strategy. Geneva: World Health Organization. 16 August 2015. https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy (accessed 1 July 2021).
3. Silva S, Arinaminpathy N, Atun R, Goosby E, Reid M. Economic impact of tuberculosis mortality in 120 countries and the cost of not achieving the Sustainable Development Goals tuberculosis targets: a full-income analysis. *Lancet Glob Health* 2021; **9**(10): e1372-e9.
4. Tait DR, Hatherill M, Van Der Meeren O, et al. Final Analysis of a Trial of M72/AS01(E) Vaccine to Prevent Tuberculosis. *N Engl J Med* 2019; **381**(25): 2429-39.
5. Hutubessy R, Lauer JA, Giersing B, et al. The Full Value of Vaccine Assessments (FVVA): A Framework to Assess and Communicate the Value of Vaccines for Investment and Introduction Decision Making. 7 May 2021. http://dx.doi.org/10.2139/ssrn.3841999 (accessed 27 May 2021).
6. Gebreselassie N, Hutubessy R, Vekemans J, den Boon S, Kasaeva T, Zignol M. The case for assessing the full value of new tuberculosis vaccines. *Eur Respir J* 2020; **55**(3).
7. Clark RA, Mukandavire C, Portnoy A, et al. The impact of alternative delivery strategies for novel tuberculosis vaccines in low- and middle-income countries: a modelling study. medRxiv 2022.04.16.22273762; doi: https://doi.org/10.1101/2022.04.16.22273762.
8. World Bank. World Bank Country and Lending Groups. Washington, DC: The World Bank; 2019. https://blogs.worldbank.org/opendata/new-country-classifications-income-level-2019-2020 (accessed 4 December 2020).
9. World Health Organization. WHO releases new global lists of high-burden countries for TB, HIV-associated TB and drug-resistant TB. 17 June 2021. https://www.who.int/news/item/17-06-2021-who-releases-new-global-lists-of-high-burden-countries-for-tb-hiv-associated-tb-and-drug-resistant-tb (accessed 1 July 2021).
10. World Health Organization. WHO Preferred Product Characteristics for New Tuberculosis Vaccines. Geneva: World Health Organization. Licence: CC BY-NC-SA 3.0 IGO. 13 July 2018. https://www.who.int/publications/i/item/WHO-IVB-18.06 (accessed 18 October 2021).
11. World Health Organization. WHO-UNICEF estimates of DTP3 coverage: monitoring system 2019 global summary. Geneva: WHO/UNICEF. 15 July 2020. http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragedtp3.html (accessed 20 April 2021).
12. Harris RC, Sumner T, Knight GM, Zhang H, White RG. Potential impact of tuberculosis vaccines in China, South Africa, and India. *Sci Transl Med* 2020; **12**(564).
13. World Health Organization. WHO TB Burden Estimates. Geneva: World Health Organization. 14 October 2021. https://www.who.int/tb/country/data/download/en/ (accessed 17 December 2021).
14. Salomon JA, Haagsma JA, Davis A, et al. Disability weights for the Global Burden of Disease 2013 study. *Lancet Glob Health* 2015; **3**(11): e712-23.
15. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Reference Life Table. Seattle, United States of America: Institute for Health

Metrics and Evaluation (IHME). 5 January 2021. https://doi.org/10.6069/1D4Y-YQ37 (accessed 17 February 2021).
16. Laurence YV, Griffiths UK, Vassall A. Costs to Health Services and the Patient of Treating Tuberculosis: A Systematic Literature Review. *Pharmacoeconomics* 2015; **33**(9): 939-55.
17. Siapka M, Vassall A, Cunnama L, et al. Cost of tuberculosis treatment in low- and middle-income countries: systematic review and meta-regression. *Int J Tuberc Lung Dis* 2020; **24**(8): 802-10.
18. van den Hof S, Collins D, Hafidz F, Beyene D, Tursynbayeva A, Tiemersma E. The socioeconomic impact of multidrug resistant tuberculosis on patients: results from Ethiopia, Indonesia and Kazakhstan. *BMC Infect Dis* 2016; **16**(1): 470.
19. Global Health Cost Consortium. Unit Cost Study Repository, Version 5.0. 8 May 2020. https://ghcosting.org/pages/data/ucsr/app/ (accessed 3 February 2021).
20. World Health Organization. Tuberculosis patient cost surveys: a hand book. Geneva: World Health Organization. 2 November 2017. https://www.who.int/publications/i/item/9789241513524 (accessed 23 March 2021).
21. World Health Organization. National surveys of costs faced by TB patients and their households, 2015-2021. Geneva: 2022. In press (2022).
22. UNICEF. Vaccines pricing data. 8 March 2022. https://www.unicef.org/supply/vaccines-pricing-data (accessed 17 March 2022).
23. UNICEF. Costs of Vaccinating a Child. 14 August 2020. https://immunizationeconomics.org/recent-activity/2021/6/15/standard-costs-of-vaccinating-a-child (accessed 20 January 2021).
24. Portnoy A, Vaughan K, Clarke-Deelder E, et al. Producing Standardized Country-Level Immunization Delivery Unit Cost Estimates. *Pharmacoeconomics* 2020; **38**(9): 995-1005.
25. Gavi The Vaccine Alliance. GAVI Alliance Vaccine Introduction Grant and Operational Support for Campaigns Policy. Version No. 1.0. Geneva: Gavi, The Vaccine Alliance. 2 April 2013. www.gavi.org (accessed 12 July 2018).
26. World Bank. World development indicators. Washington, DC: The World Bank; 2021. http://data.worldbank.org/ (accessed 19 January 2022).
27. Ochalek J, Lomas J, Claxton K. Estimating health opportunity costs in low-income and middle-income countries: a novel approach and evidence from cross-country data. *BMJ Glob Health* 2018; **3**(6): e000964.
28. Woods B, Revill P, Sculpher M, Claxton K. Country-Level Cost-Effectiveness Thresholds: Initial Estimates and the Need for Further Research. *Value Health* 2016; **19**(8): 929-35.
29. Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--6. *Value Health* 2012; **15**(6): 835-42.
30. The Global Fund. Fight for What Counts: The Global Fund Investment Case. Seventh Replenishment 2022. 23 February 2022. https://www.theglobalfund.org/en/fight-for-what-counts/ (accessed 16 March 2022).

Appendix

S1. Analyzed low- and middle-income country list.

Country	WHO Region	Income level[a]	Gavi status	High-TB burden[b]	High-TB/HIV burden[b]	High-MDR/RR-TB burden[b]	Base-case vaccine introduction year
Afghanistan	EMR	LIC	Gavi	No	No	No	2031
Angola	AFR	LMIC	Gavi	Yes	No	Yes	2032
Albania	EUR	UMIC	Non-Gavi	No	No	No	2035
Argentina	AMR	UMIC	Non-Gavi	No	No	No	2031
Armenia	EUR	UMIC	Gavi	No	No	No	2033
Azerbaijan	EUR	UMIC	Gavi	No	No	Yes	2028
Burundi	AFR	LIC	Gavi	No	No	No	2044
Benin	AFR	LMIC	Gavi	No	No	No	2037
Burkina Faso	AFR	LIC	Gavi	No	No	No	2039
Bangladesh	SEAR	LMIC	Gavi	Yes	No	Yes	2035
Bulgaria	EUR	UMIC	Non-Gavi	No	No	No	2029
Belarus	EUR	UMIC	Non-Gavi	No	No	Yes	2028
Bolivia	AMR	LMIC	Gavi	No	No	No	2037
Brazil	AMR	UMIC	Non-Gavi	Yes	Yes	No	2030
Bhutan	SEAR	LMIC	Gavi	No	No	No	2034
Botswana	AFR	UMIC	Non-Gavi	No	Yes	No	2028
Central African Republic	AFR	LIC	Gavi	Yes	Yes	No	2033
China	WPR	UMIC	Non-Gavi	Yes	No	Yes	2029
Côte d'Ivoire	AFR	LMIC	Gavi	No	No	No	2034
Cameroon	AFR	LMIC	Gavi	No	Yes	No	2031
Colombia	AMR	UMIC	Non-Gavi	No	No	No	2030
Costa Rica	AMR	UMIC	Non-Gavi	No	No	No	2033
Cuba	AMR	UMIC	Gavi	No	No	No	2035
Dominican Republic	AMR	UMIC	Non-Gavi	No	No	No	2031
Ecuador	AMR	UMIC	Non-Gavi	No	No	No	2033
Egypt	EMR	LMIC	Non-Gavi	No	No	No	2033
Eritrea	AFR	LIC	Gavi	No	No	No	2047

Ethiopia	AFR	LIC	Gavi	Yes	Yes	No	2030
Fiji	WPR	UMIC	Non-Gavi	No	No	No	2031
Gabon	AFR	UMIC	Non-Gavi	Yes	Yes	No	2038
Georgia	EUR	UMIC	Gavi	No	No	No	2029
Ghana	AFR	LMIC	Gavi	No	No	No	2040
Guinea	AFR	LIC	Gavi	No	Yes	No	2033
Gambia	AFR	LIC	Gavi	No	No	No	2039
Equatorial Guinea	AFR	UMIC	Non-Gavi	No	No	No	2042
Guatemala	AMR	UMIC	Non-Gavi	No	No	No	2036
Honduras	AMR	LMIC	Gavi	No	No	No	2037
Indonesia	SEAR	UMIC	Gavi	Yes	Yes	Yes	2034
India	SEAR	LMIC	Gavi	Yes	Yes	Yes	2033
Iran	EMR	UMIC	Non-Gavi	No	No	No	2031
Iraq	EMR	UMIC	Non-Gavi	No	No	No	2033
Jordan	EMR	UMIC	Non-Gavi	No	No	No	2037
Kazakhstan	EUR	UMIC	Non-Gavi	No	No	Yes	2028
Kenya	AFR	LMIC	Gavi	Yes	Yes	No	2032
Kyrgyz Republic	EUR	LMIC	Gavi	No	No	Yes	2044
Cambodia	WPR	LMIC	Gavi	No	No	No	2036
Lao People’s Democratic Republic	WPR	LMIC	Gavi	No	No	No	2035
Liberia	AFR	LIC	Gavi	Yes	Yes	No	2037
Libya	EMR	UMIC	Non-Gavi	No	No	No	2035
Sri Lanka	SEAR	LMIC	Gavi	No	No	No	2028
Lesotho	AFR	LMIC	Gavi	Yes	Yes	No	2039
Morocco	EMR	LMIC	Non-Gavi	No	No	No	2029
Moldova, Republic of	EUR	LMIC	Gavi	No	No	Yes	2034
Madagascar	AFR	LIC	Gavi	No	No	No	2031
Maldives	SEAR	UMIC	Non-Gavi	No	No	No	2034
Mexico	AMR	UMIC	Non-Gavi	No	No	No	2029
Mali	AFR	LIC	Gavi	No	No	No	2037
Myanmar	SEAR	LMIC	Gavi	Yes	Yes	Yes	2031
Montenegro	EUR	UMIC	Non-Gavi	No	No	No	2044

Mongolia	WPR	LMIC	Gavi	Yes	No	Yes	2032
Mozambique	AFR	LIC	Gavi	Yes	Yes	Yes	2032
Mauritania	AFR	LMIC	Gavi	No	No	No	2042
Malawi	AFR	LIC	Gavi	No	Yes	No	2038
Malaysia	WPR	UMIC	Non-Gavi	No	No	No	2028
Namibia	AFR	UMIC	Non-Gavi	Yes	Yes	No	2030
Niger	AFR	LIC	Gavi	No	No	No	2036
Nigeria	AFR	LMIC	Gavi	Yes	Yes	Yes	2030
Nicaragua	AMR	LMIC	Gavi	No	No	No	2047
Nepal	SEAR	LMIC	Gavi	No	No	Yes	2036
Pakistan	EMR	LMIC	Gavi	Yes	No	Yes	2031
Peru	AMR	UMIC	Non-Gavi	No	No	Yes	2029
Philippines	WPR	LMIC	Non-Gavi	Yes	Yes	Yes	2030
Papua New Guinea	WPR	LMIC	Gavi	Yes	No	Yes	2032
Paraguay	AMR	UMIC	Non-Gavi	No	No	No	2035
Russian Federation	EUR	UMIC	Non-Gavi	No	Yes	Yes	2030
Rwanda	AFR	LIC	Gavi	No	No	No	2045
Sudan	EMR	LIC	Gavi	No	No	No	2036
Senegal	AFR	LMIC	Gavi	No	No	No	2038
Solomon Islands	WPR	LMIC	Gavi	No	No	No	2047
Sierra Leone	AFR	LIC	Gavi	Yes	No	No	2037
El Salvador	AMR	LMIC	Non-Gavi	No	No	No	2039
Serbia	EUR	UMIC	Non-Gavi	No	No	No	2036
South Sudan	AFR	LIC	Gavi	No	No	No	2034
São Tomé and Principe	AFR	LMIC	Gavi	No	No	No	2044
Suriname	AMR	UMIC	Non-Gavi	No	No	No	2040
Swaziland	AFR	LMIC	Non-Gavi	No	Yes	No	2036
Syrian Arab Republic	EMR	LIC	Gavi	No	No	No	2036
Chad	AFR	LIC	Gavi	No	No	No	2033
Togo	AFR	LIC	Gavi	No	No	No	2041
Thailand	SEAR	UMIC	Non-Gavi	Yes	Yes	No	2031
Tajikistan	EUR	LIC	Gavi	No	No	Yes	2045

Timor-Leste	SEAR	LMIC	Gavi	No	No	No	2031
Tunisia	EMR	LMIC	Non-Gavi	No	No	No	2036
Turkey	EUR	UMIC	Non-Gavi	No	No	No	2030
Tanzania, United Republic of	AFR	LMIC	Gavi	Yes	Yes	No	2031
Uganda	AFR	LIC	Gavi	Yes	Yes	No	2034
Ukraine	EUR	LMIC	Non-Gavi	No	No	Yes	2033
Uzbekistan	EUR	LMIC	Gavi	No	No	Yes	2038
Venezuela	AMR	UMIC	Non-Gavi	No	No	No	2035
Vietnam	WPR	LMIC	Gavi	Yes	No	Yes	2038
Vanuatu	WPR	LMIC	Non-Gavi	No	No	No	2042
Yemen	EMR	LIC	Gavi	No	No	No	2036
South Africa	AFR	UMIC	Non-Gavi	Yes	Yes	Yes	2029
Zambia	AFR	LMIC	Gavi	Yes	Yes	Yes	2034
Zimbabwe	AFR	LMIC	Gavi	No	Yes	Yes	2032

[a] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).

[b] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]

Note: Vaccine introduction was assumed to commence in 2028 and end in 2047. See Clark et al. (https://doi.org/10.1101/2022.04.16.22273762) for introduction year methodology. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; TB = tuberculosis; UMIC = upper middle-income; WPR = Western Pacific region.

S2. Disability weight assumptions: mean, lower bound, upper bound.

Disability weight	Mean	Lower bound	Upper bound
TB	0.333	0.224	0.454
TB/HIV+	0.408	0.274	0.549
HIV+	0.2893	0.1987	0.3837
ART	0.078	0.052	0.111

Note: ART = antiretroviral therapy; HIV = human immunodeficiency virus; TB = tuberculosis.

S3. Undiscounted total health system costs (billions) of no-vaccine scenario by programmatic area across 2028–2050.

Country grouping	Drug-susceptible TB direct medical costs	Rifampicin-resistant TB direct medical costs	ART costs	Vaccination costs

All countries	17.6 (10.8, 26.7)	14.8 (12.0, 17.9)	442 (378, 495)	0
High-TB burden[a]	16.1 (9.88, 24.4)	13.3 (10.8, 16.0)	182 (158, 203)	0
High-TB/HIV burden[a]	12.6 (7.70, 19.1)	9.45 (7.69, 11.5)	195 (169, 219)	0
High-MDR/RR-TB burden[a]	15.1 (9.25, 22.8)	13.7 (11.1, 16.5)	180 (158, 200)	0
Income level[b]				
LIC	0.68 (0.43, 1.00)	0.33 (0.23, 0.39)	81.0 (68.7, 91.3)	0
LMIC	11.0 (8.12, 20.2)	9.61 (8.79, 13.4)	208 (175, 234)	0
UMIC	5.96 (2.28, 5.49)	4.16 (3.00, 4.91)	153 (134, 171)	0
World region				
AFR	3.36 (2.04, 5.07)	2.19 (1.75, 2.67)	223 (191, 252)	0
AMR	0.47 (0.28, 0.71)	0.25 (0.20, 0.30)	42.2 (36.9, 46.9)	0
EMR	1.06 (0.65, 1.58)	1.26 (0.99, 1.55)	39.2 (33.3, 43.9)	0
EUR	0.13 (0.08, 0.19)	0.68 (0.54, 0.85)	47.1 (40.5, 52.1)	0
SEAR	9.06 (5.53, 13.8)	7.10 (5.72, 8.59)	21.7 (17.7, 24.7)	0
WPR	3.58 (2.25, 5.31)	3.37 (2.82, 3.99)	68.6 (58.5, 76.1)	0

[a] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]

[b] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).

Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; TB = tuberculosis; UMIC = upper middle-income; WPR = Western Pacific region.

S4. Undiscounted total health system costs (billions) of infant tuberculosis vaccines by programmatic area across 2028–2050 and percent change compared to no vaccination.

Country grouping	Drug-susceptible TB direct medical costs	Rifampicin-resistant TB direct medical costs	ART costs	Vaccination costs
All countries	17.4 (10.6, 26.3) *1.7% reduction*	14.6 (11.8, 17.7) *1.6% reduction*	442 (378, 495) *0.01% increase*	9.71 (7.88, 13.91)
High-TB burden[a]	15.8 (9.70, 24) *1.7% reduction*	13.1 (10.6, 15.7) *1.7% reduction*	182 (158, 203) *0.01% increase*	6.59 (5.48, 9.26)
High-TB/HIV burden[a]	12.4 (7.55, 18.8) *1.8% reduction*	9.27 (7.45, 11.2) *1.8% reduction*	195 (169, 219) *0.01% increase*	4.74 (3.97, 6.48)
High-MDR/RR-TB burden[a]	14.8 (9.08, 22.4) *1.7% reduction*	13.5 (10.9, 16.3) *1.7% reduction*	180 (158, 200) *0.01% increase*	5.83 (4.81, 8.29)

Income level[b]				
LIC	0.67 (0.42, 0.97) *2.4% reduction*	0.33 (0.23, 0.38) *2.3% reduction*	81.0 (68.2, 90.5) *0.01% increase*	1.44 (1.23, 1.88)
LMIC	10.8 (7.96, 19.9) *1.8% reduction*	9.42 (8.61, 13.1) *1.9% reduction*	208 (175, 234) *0.01% increase*	4.79 (4.39, 7.11)
UMIC	5.88 (2.26, 5.44) *1.3% reduction*	4.85 (2.98, 4.13) *1.1% reduction*	153 (135, 171) *0.01% increase*	3.47 (2.26, 4.92)
World region				
AFR	3.28 (1.98, 4.96) *2.4% reduction*	2.13 (1.70, 2.61) *2.6% reduction*	223 (191, 252) *0.01% increase*	3.1 (2.62, 4.16)
AMR	0.47 (0.28, 0.71) *0.6% reduction*	0.25 (0.20, 0.30) *0.7% reduction*	42.2 (36.9, 46.9) *0.01% increase*	0.81 (0.61, 1.27)
EMR	1.02 (0.63, 1.53) *3.2% reduction*	1.22 (0.96, 1.50) *3.4% reduction*	39.2 (33.3, 43.9) *0.01% increase*	1.35 (1.11, 1.85)
EUR	0.13 (0.08, 0.19) *0.5% reduction*	0.68 (0.54, 0.85) *0.4% reduction*	47.1 (40.5, 52.1) *0.01% increase*	0.51 (0.36, 0.88)
SEAR	8.93 (5.45, 13.65) *1.4% reduction*	7.00 (5.64, 8.46) *1.5% reduction*	21.7 (17.7, 24.7) *0.01% increase*	2.16 (1.81, 2.95)
WPR	3.53 (2.21, 5.24) *1.5% reduction*	3.33 (2.79, 3.94) *1.1% reduction*	68.6 (58.5, 76.1) *0.01% increase*	1.79 (1.38, 2.80)

[a] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]

[b] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).

Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; TB = tuberculosis; UMIC = upper middle-income; WPR = Western Pacific region.

S5. Undiscounted total health system costs (billions) of adolescent/adult tuberculosis vaccines by programmatic area across 2028–2050 and percent change compared to no vaccination.

Country grouping	Drug-susceptible TB direct medical costs	Rifampicin-resistant TB direct medical costs	ART costs	Vaccination costs
All countries	15.5 (9.52, 23.5) *11.9% reduction*	13.1 (10.6, 15.8) *11.8% reduction*	443 (379, 496) *0.15% increase*	32.7 (24.7, 49.1)
High-TB burden[a]	14.2 (8.67, 21.5) *12.1% reduction*	11.7 (9.44, 14.1) *12.1% reduction*	182 (159, 203) *0.19% increase*	23.7 (17.9, 35.3)

High-TB/HIV burden[a]	11.0 (6.72, 16.8) *12.5% reduction*	8.27 (6.62, 10.0) *12.5% reduction*	196 (169, 219) *0.18% increase*	15.4 (12.1, 21.8)
High-MDR/RR-TB burden[a]	13.2 (8.11, 20.1) *12.0% reduction*	12.1 (9.74, 14.6) *11.9% reduction*	180 (158, 200) *0.18% increase*	21.9 (16.6, 33.0)
Income level[b]				
LIC	0.60 (0.38, 0.87) *12.3% reduction*	0.30 (0.20, 0.34) *11.3% reduction*	81.1 (68.7, 91.4) *0.1% increase*	3.66 (2.89, 4.83)
LMIC	9.68 (7.11, 17.8) *12.1% reduction*	8.45 (7.69, 11.8) *12.1% reduction*	208 (176, 234) *0.14% increase*	15.3 (13.6, 23.2)
UMIC	5.26 (2.03, 4.92) *11.6% reduction*	4.35 (2.67, 3.73) *11.3% reduction*	154 (135, 171) *0.18% increase*	13.8 (8.18, 21.1)
World region				
AFR	2.92 (1.76, 4.43) *13.1% reduction*	1.90 (1.50, 2.33) *13.3% reduction*	224 (192, 252) *0.16% increase*	6.88 (5.49, 9.32)
AMR	0.42 (0.26, 0.64) *9.4% reduction*	0.22 (0.18, 0.27) *10.3% reduction*	42.3 (36.9, 47) *0.13% increase*	3.05 (2.09, 5.23)
EMR	0.91 (0.56, 1.36) *13.8% reduction*	1.08 (0.84, 1.33) *14.1% reduction*	39.3 (33.4, 43.9) *0.12% increase*	3.76 (2.97, 5.22)
EUR	0.12 (0.07, 0.18) *8.4% reduction*	0.63 (0.50, 0.79) *7.4% reduction*	47.1 (40.6, 52.1) *0.11% increase*	1.76 (1.24, 2.96)
SEAR	8.00 (4.88, 12.21) *11.7% reduction*	6.25 (5.04, 7.55) *11.9% reduction*	21.7 (17.7, 24.8) *0.16% increase*	9.32 (7.43, 12.78)
WPR	3.18 (1.99, 4.72) *11.3% reduction*	3.01 (2.50, 3.57) *10.6% reduction*	68.7 (58.6, 76.2) *0.13% increase*	7.96 (5.47, 13.64)

[a] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]

[b] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).

Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; TB = tuberculosis; UMIC = upper middle-income; WPR = Western Pacific region.

S6. Undiscounted incremental societal costs (millions) of infant tuberculosis vaccines across 2028–2050 and percent change compared to no vaccination.

Country grouping	Drug-susceptible TB non-medical costs	Rifampicin-resistant TB non-medical costs	Drug-susceptible TB productivity loss	Rifampicin-resistant TB productivity loss	Productivity loss due to premature death

			due to testing and treatment[a]	due to testing and treatment[a]	
All countries	646 (569, 755) *1.8% reduction*	75.5 (67.2, 85.2) *1.5% reduction*	744 (657, 864) *1.6% reduction*	24.0 (21.3, 27.7) *1.3% reduction*	57600 (57000, 65100) *0.1% reduction*
High-TB burden[b]	597 (526, 698) *1.8% reduction*	68.7 (61.2, 77.6) *1.7% reduction*	697 (616, 810) *1.7% reduction*	21.6 (19.2, 24.9) *1.5% reduction*	54200 (61500, 55300) *0.1% reduction*
High-TB/HIV burden[b]	484 (427, 570) *1.9% reduction*	52.3 (46.5, 57.7) *1.7% reduction*	571 (513, 666) *1.8% reduction*	16.5 (15.2, 19.2) *1.6% reduction*	46700 (51800, 49600) *0.2% reduction*
High-MDR/RR-TB burden[b]	530 (467, 619) *1.8% reduction*	69.1 (61.7, 77.9) *1.5% reduction*	638 (567, 741) *1.6% reduction*	22.3 (19.9, 25.7) *1.3% reduction*	50700 (58200, 51600) *0.1% reduction*
Income level[c]					
LIC	77.5 (64.2, 94.7) *2.6% reduction*	5.16 (4.15, 6.24) *2.5% reduction*	54.4 (45.3, 67.8) *2.5% reduction*	1.1 (0.89, 1.41) *2.5% reduction*	1910 (1760, 2390) *0.1% reduction*
LMIC	444 (389, 522) *1.9% reduction*	50.1 (44.2, 55.8) *2.0% reduction*	479 (422, 557) *1.9% reduction*	14.3 (12.9, 16.6) *2.0% reduction*	37300 (35000, 45100) *0.2% reduction*
UMIC	125 (116, 139) *1.3% reduction*	20.2 (18.9, 23.2) *0.9% reduction*	210 (190, 240) *1.1% reduction*	8.56 (7.58, 9.69) *0.8% reduction*	17900 (17500, 20800) *0.04% reduction*
World region					
AFR	199 (187, 225) *2.5% reduction*	19.8 (17.9, 22.3) *2.6% reduction*	208 (186, 238) *2.5% reduction*	6.03 (5.56, 6.74) *2.5% reduction*	25700 (23600, 31400) *0.4% reduction*
AMR	4.70 (4.22, 5.07) *0.6% reduction*	0.75 (0.58, 0.86) *0.7% reduction*	9.37 (8.28, 9.94) *0.6% reduction*	0.327 (0.292, 0.334) *0.7% reduction*	606 (463, 771) *0.01% reduction*
EMR	88.2 (77.0, 102) *3.4% reduction*	12.0 (10.5, 14.5) *3.4% reduction*	74.5 (62.8, 88) *3.2% reduction*	2.99 (2.50, 3.53) *3.3% reduction*	2480 (1540, 3630) *0.1% reduction*
EUR	2.02 (1.89, 2.19) *0.5% reduction*	2.86 (2.69, 3.08) *0.4% reduction*	3.80 (3.43, 4.36) *0.5% reduction*	1.33 (1.21, 1.52) *0.4% reduction*	339 (284, 387) *0.01% reduction*
SEAR	246 (193, 311) *1.4% reduction*	27.7 (23.7, 30.6) *1.5% reduction*	290 (264, 348) *1.4% reduction*	8.37 (7.70, 10.1) *1.5% reduction*	20100 (19100, 20900) *0.2% reduction*
WPR	106 (105, 110) *1.6% reduction*	12.4 (11.9, 13.9) *0.9% reduction*	158 (132, 176) *1.3% reduction*	4.96 (4.08, 5.52) *0.8% reduction*	8730 (8720, 10800) *0.03% reduction*

[a] Costs include patient costs due to time lost for tuberculosis testing and treatment.

[b] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]

[c] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).

Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; TB = tuberculosis; UMIC = upper middle-income; WPR = Western Pacific region.

S7. Undiscounted incremental societal costs (billions) of adolescent/adult tuberculosis vaccines across 2028–2050 and percent change compared to no vaccination.

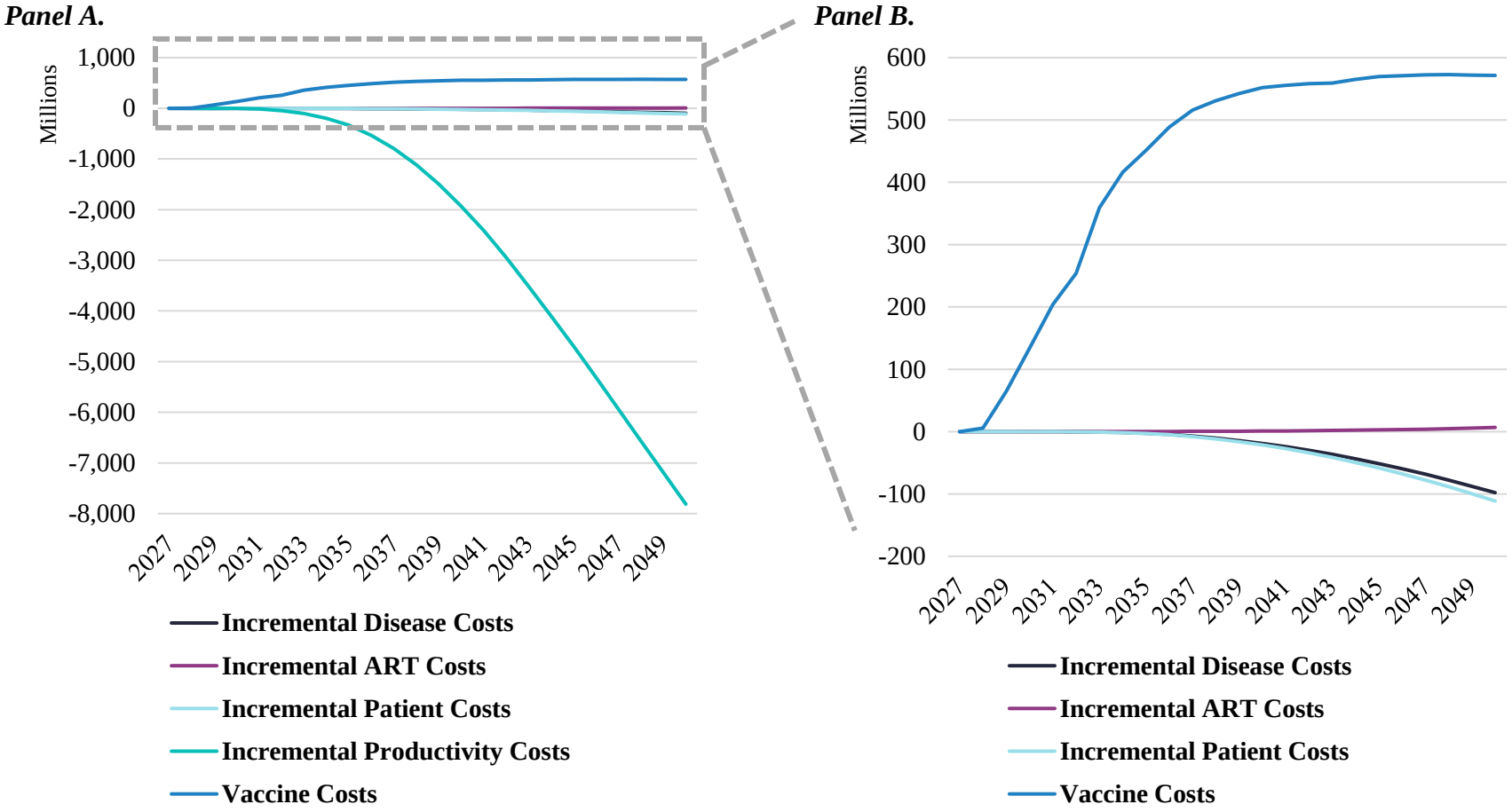
Country grouping	Drug-susceptible TB non-medical costs	Rifampicin-resistant TB non-medical costs	Drug-susceptible TB productivity loss due to testing and treatment[a]	Rifampicin-resistant TB productivity loss due to testing and treatment[a]	Productivity loss due to premature death
All countries	4.38 (3.76, 5.04) *12.1% reduction*	0.58 (0.50, 0.66) *11.5% reduction*	5.46 (4.65, 6.30) *11.8% reduction*	0.21 (0.18, 0.24) *11.1% reduction*	194 (184, 221) *0.3% reduction*
High-TB burden[b]	4.00 (3.44, 4.60) *12.3% reduction*	0.49 (0.43, 0.56) *12.0% reduction*	5.02 (4.28, 5.78) *12.0% reduction*	0.17 (0.15, 0.20) *11.7% reduction*	181 (173, 205) *0.4% reduction*
High-TB/HIV burden[b]	3.24 (2.78, 3.72) *12.6% reduction*	0.37 (0.32, 0.42) *12.1% reduction*	3.88 (3.30, 4.46) *12.5% reduction*	0.12 (0.10, 0.14) *11.8% reduction*	160 (157, 178) *0.7% reduction*
High-MDR/RR-TB burden[b]	3.64 (3.12, 4.18) *12.1% reduction*	0.53 (0.47, 0.61) *11.5% reduction*	4.68 (3.99, 5.39) *12.0% reduction*	0.19 (0.17, 0.22) *11.2% reduction*	169 (161, 194) *0.3% reduction*
Income level[c]					
LIC	0.39 (0.33, 0.47) *13.1% reduction*	0.024 (0.02, 0.029) *12.0% reduction*	0.28 (0.23, 0.33) *13.1% reduction*	0.005 (0.004, 0.006) *11.8% reduction*	6.01 (7.70, 5.23) *0.4% reduction*
LMIC	2.83 (2.42, 3.29) *12.2% reduction*	0.31 (0.26, 0.35) *12.2% reduction*	3.07 (2.58, 3.57) *12.1% reduction*	0.09 (0.07, 0.10) *12.1% reduction*	119 (144, 103) *0.7% reduction*
UMIC	1.15 (1.01, 1.28) *11.6% reduction*	0.25 (0.22, 0.28) *10.6% reduction*	2.12 (1.83, 2.40) *11.3% reduction*	0.11 (0.10, 0.13) *10.5% reduction*	68.8 (69.5, 75.8) *0.1% reduction*
World region					
AFR	1.05 (0.92, 1.20) *13.3% reduction*	0.10 (0.09, 0.12) *13.3% reduction*	1.12 (0.97, 1.28) *13.2% reduction*	0.032 (0.028, 0.036) *13.3% reduction*	69.7 (77.3, 71.2) *0.97% reduction*
AMR	0.08 (0.07, 0.09) *9.4% reduction*	0.011 (0.009, 0.013) *10.3% reduction*	0.15 (0.13, 0.18) *9.4% reduction*	0.005 (0.004, 0.005) *10.2% reduction*	3.58 (4.45, 2.86) *0.04% reduction*
EMR	0.37 (0.31, 0.43) *14.1% reduction*	0.05 (0.04, 0.06) *14.2% reduction*	0.32 (0.27, 0.37) *13.8% reduction*	0.013 (0.01, 0.015) *14.1% reduction*	6.48 (8.72, 4.63) *0.2% reduction*
EUR	0.036 (0.032, 0.042) *8.5% reduction*	0.06 (0.05, 0.07) *8.4% reduction*	0.07 (0.06, 0.08) *8.8% reduction*	0.027 (0.023, 0.032) *8.7% reduction*	2.33 (2.73, 1.96) *0.04% reduction*
SEAR	2.08 (1.73, 2.43) *11.7% reduction*	0.22 (0.18, 0.25) *12% reduction*	2.46 (2.03, 2.86) *11.8% reduction*	0.07 (0.05, 0.08) *12.1% reduction*	88.8 (102, 81.0) *0.8% reduction*
WPR	0.76 (0.70, 0.84) *11.5% reduction*	0.14 (0.13, 0.16) *10.5% reduction*	1.34 (1.19, 1.52) *11.1% reduction*	0.065 (0.058, 0.074) *10.4% reduction*	23.2 (26.3, 22.2) *0.1% reduction*

[a] Costs include patient costs due to time lost for tuberculosis testing and treatment.

[b] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]

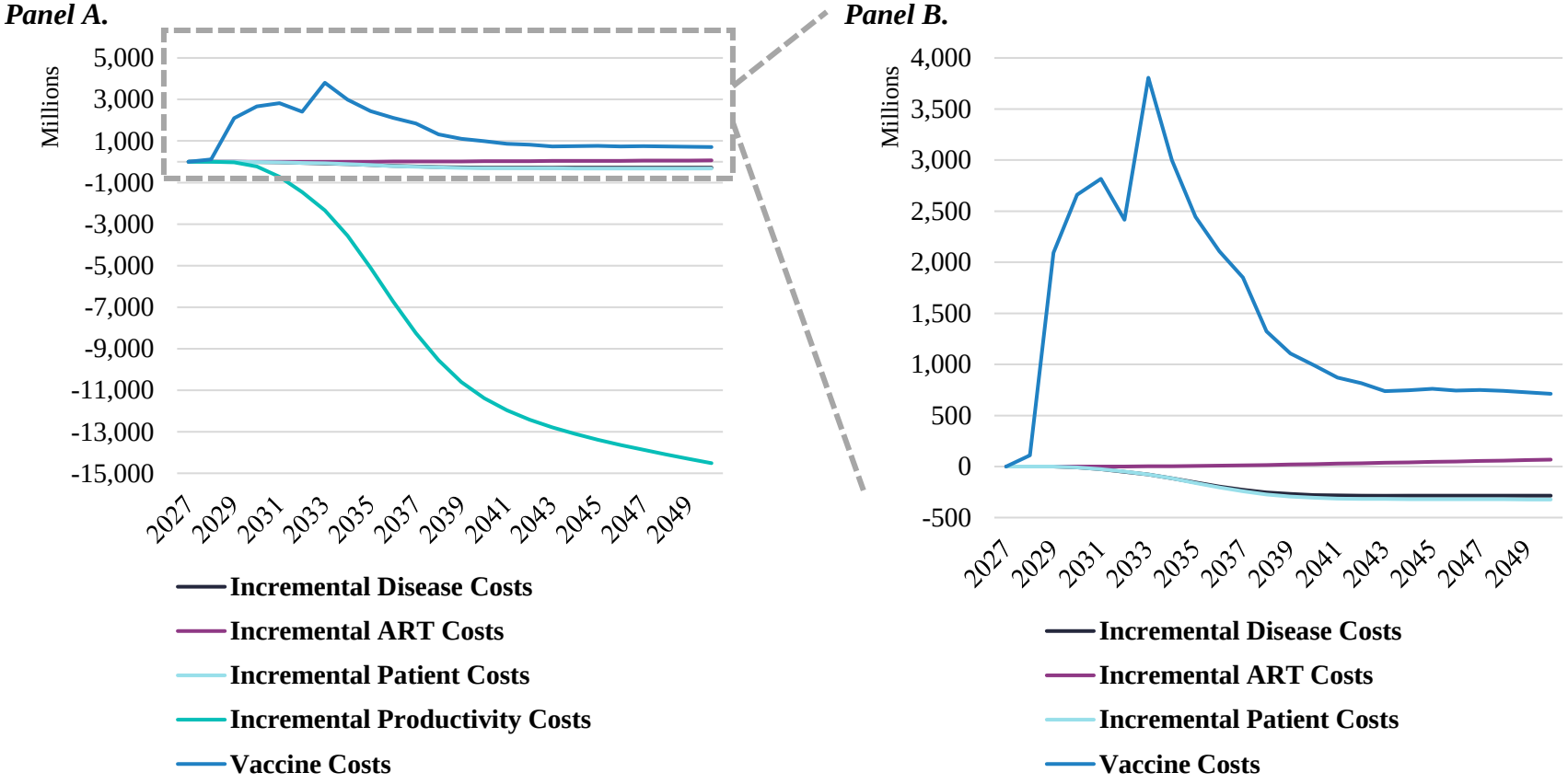
[c] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; TB = tuberculosis; UMIC = upper middle-income; WPR = Western Pacific region.

S8. Time trend of undiscounted costs (health system perspective) by programmatic area for infant tuberculosis vaccines: (A) including productivity costs; and (B) excluding productivity costs.



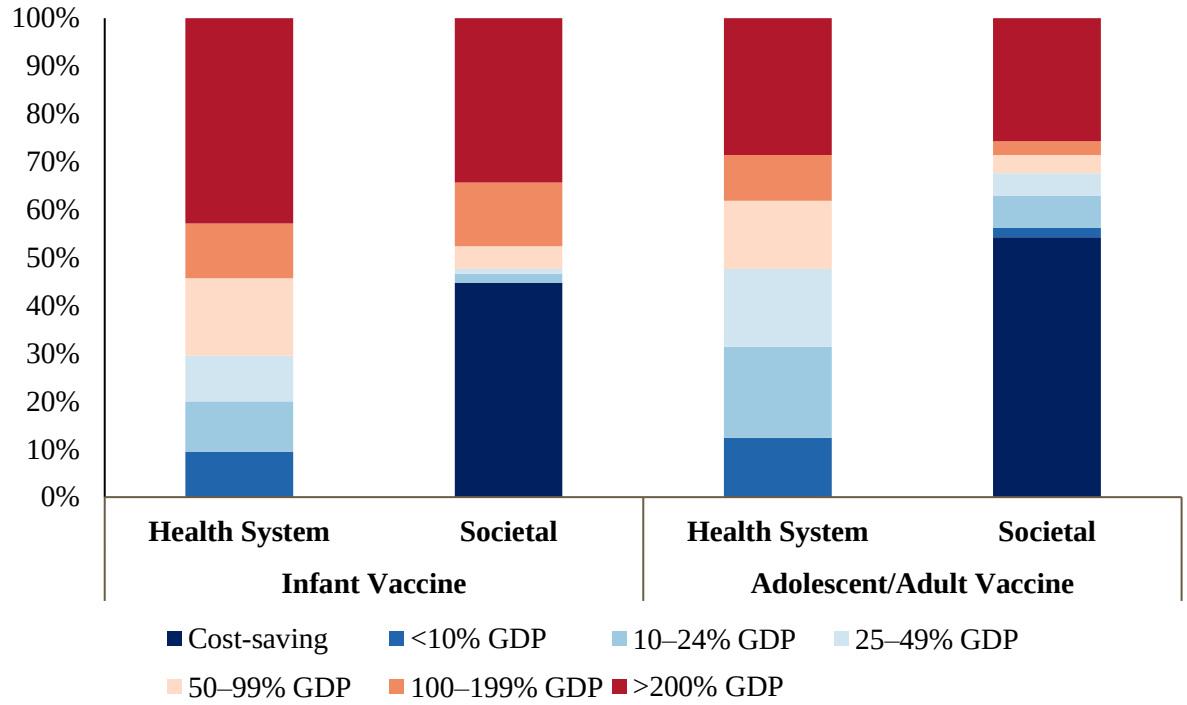
Note: ART = antiretroviral therapy; disease costs = tuberculosis testing and treatment costs from the health system perspective; patient costs = non-medical costs and productivity costs due to time lost for tuberculosis testing and treatment; productivity costs = productivity loss due to premature death.

S9. Time trend of undiscounted costs (health system perspective) by programmatic area for adolescent/adult tuberculosis vaccines: (A) including productivity costs; and (B) excluding productivity costs.



Note: ART = antiretroviral therapy; disease costs = tuberculosis testing and treatment costs from the health system perspective; patient costs = non-medical costs and productivity costs due to time lost for tuberculosis testing and treatment; productivity costs = productivity loss due to premature death.

S10. Percentage of countries where vaccination was cost-effective compared to percentage of GDP per capita thresholds, comparing health system and societal perspectives.



Note: Countries include 105 low- and middle-income countries analyzed. GDP estimates from 2020. GDP = gross domestic product per capita.

S11. Percentage of population in countries where vaccination was cost-effective compared to percentage of GDP per capita thresholds, comparing health system and societal perspectives.

	Perspective	Cost-saving	<10% GDP	10–24% GDP	25–49% GDP	50–99% GDP	100–199% GDP	>200% GDP
Infant Vaccine	Health System	0%	11%	29%	29%	10%	6%	14%
	Societal	78%	0%	2%	0%	5%	6%	10%
Adolescent/ Adult Vaccine	Health System	0%	13%	33%	34%	7%	4%	9%
	Societal	81%	0%	6%	3%	1%	0%	9%

Note: Countries include 105 low- and middle-income countries analyzed. Population includes vaccinated individuals 2028–2050. GDP estimates from 2020. GDP = gross domestic product per capita.

S12. Percentage of countries that were cost-effective compared to percentage of GDP per capita thresholds, comparing health system and societal perspectives, all countries weighted equally.

	Perspective	Cost-saving	<10% GDP	10–24% GDP	25–49% GDP	50–99% GDP	100–199% GDP	>200% GDP
Infant Vaccine	Health System	0%	10%	10%	10%	16%	11%	43%
	Societal	45%	0%	2%	1%	5%	13%	34%
Adolescent/ Adult Vaccine	Health System	0%	12%	19%	16%	14%	10%	29%
	Societal	54%	2%	7%	5%	4%	3%	26%

Note: Countries include 105 low- and middle-income countries analyzed. GDP estimates from 2020. GDP = gross domestic product per capita.

S13. Discounted costs, undiscounted disability-adjusted life-years (DALYs) averted, and cost-effectiveness of infant tuberculosis vaccines.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	6.61 (5.38, 9.23)	*-28.5* (*-33.6*, *-23.5*)	74.7 (64.7, 86.2)	89.0 (68.9, 126)	cost-saving[c]
High-TB burden[d]	4.43 (3.66, 6.18)	*-28.9* (*-33.9*, *-24.1*)	69.1 (59.1, 80.7)	64.6 (50.0, 92.3)	cost-saving[c]
High-TB/HIV burden[d]	3.13 (2.60, 4.23)	*-25.5* (*-30.5*, *-21.0*)	60.4 (50.8, 71.7)	52.2 (40.2, 72.7)	cost-saving[c]
High-MDR/RR-TB burden[d]	3.9 (3.18, 5.49)	*-27.2* (*-32.1*, *-22.4*)	61.0 (51.2, 72.2)	64.4 (48.9, 93.5)	cost-saving[c]
Income level[e]					
LIC	0.97 (0.83, 1.25)	*-0.25* (*-0.51*, 0.05)	8.39 (7.05, 10.2)	116 (89.9, 156)	cost-saving (cost-saving, 6.88)
LMIC	3.41 (2.84, 4.61)	*-23.8* (*-28.4*, *-19.5*)	61.8 (52.3, 73.3)	55.6 (42.9, 78.6)	cost-saving[c]
UMIC	2.22 (1.67, 3.52)	*-4.43* (*-6.48*, *-2.63*)	4.42 (3.34, 6.00)	515 (319, 841)	cost-saving[c]
World region					
AFR	2.09 (1.78, 2.73)	*-13.6* (*-17.3*, *-10.6*)	38.7 (32.1, 46.7)	54.5 (41.2, 73.9)	cost-saving[c]
AMR	0.59 (0.44, 0.92)	0.20 (0.04, 0.54)	0.25 (0.21, 0.30)	2390 (1670, 3740)	840 (133, 2190)
EMR	0.90 (0.74, 1.23)	*-0.70* (*-1.39*, *-0.11*)	6.65 (4.58, 9.16)	141 (89.9, 216)	cost-saving[c]
EUR	0.37 (0.26, 0.62)	0.15 (0.04, 0.39)	0.15 (0.13, 0.18)	2440 (1640, 4130)	1020 (233, 2660)
SEAR	1.38 (1.13, 1.89)	*-10.2* (*-13.3*, *-7.73*)	23.2 (17.4, 30.9)	60.6 (40.9, 93.3)	cost-saving[c]
WPR	1.28 (0.99, 2.00)	*-4.27* (*-5.97*, *-2.88*)	5.68 (4.12, 7.95)	231 (145, 378)	cost-saving[c]

[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.

[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

S14. Discounted costs, undiscounted disability-adjusted life-years (DALYs) averted, and cost-effectiveness of adolescent/adult tuberculosis vaccines.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	Incremental DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	24.5 (18.1, 37.1)	*-108* (*-122*, *-92.1*)	226 (205, 250)	109 (77.4, 164)	cost-saving[c]
High-TB burden[d]	17.5 (12.8, 26.8)	*-106* (*-119*, *-91.0*)	207 (185, 229)	84.8 (59.4, 128)	cost-saving[c]
High-TB/HIV burden[d]	10.7 (8.00, 15.6)	*-97.5* (*-110*, *-84.8*)	185 (165, 208)	58.1 (41.4, 85)	cost-saving[c]
High-MDR/RR-TB burden[d]	16.0 (11.5, 25.0)	*-99.4* (*-113*, *-85.4*)	183 (162, 205)	87.9 (59.9, 136)	cost-saving[c]
Income level[e]					
LIC	2.64 (2.1, 3.53)	*-1.63* (*-2.43*, *-0.62*)	23.5 (20.8, 26.5)	113 (85.4, 155)	cost-saving[c]
LMIC	11.6 (8.8, 16.6)	*-89.3* (*-100*, *-78.3*)	188 (168, 211)	61.8 (44.7, 89.2)	cost-saving[c]
UMIC	10.22 (6.7, 18.1)	*-17.2* (*-24.0*, *-7.69*)	14.2 (11.4, 18.2)	730 (434, 1390)	cost-saving[c]
World region					
AFR	4.93 (3.93, 6.64)	*-41.7* (*-49.6*, *-35.2*)	97.6 (86.4, 110)	50.7 (38.4, 70.8)	cost-saving
AMR	2.55 (1.73, 4.37)	*-0.09* (*-1.00*, 1.81)	1.29 (1.15, 1.44)	1980 (1310, 3420)	cost-saving (cost-saving, 1420)
EMR	2.80 (2.19, 3.87)	*-1.91* (*-3.25*, *-0.49*)	15.9 (12.2, 20.0)	179 (124, 264)	cost-saving
EUR	1.37 (0.92, 2.35)	*-0.40* (*-0.90*, 0.56)	0.92 (0.82, 1.02)	1490 (977, 2610)	cost-saving (cost-saving, 638)
SEAR	6.22 (4.63, 9.07)	*-53.2* (*-62.0*, *-44.5*)	96.9 (81.3, 115)	64.8 (44.2, 98.1)	cost-saving
WPR	6.58 (4.31, 11.6)	*-10.8* (*-13.9*, *-5.45*)	13.5 (11.6, 15.6)	489 (311, 884)	cost-saving

[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]

[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

S15. Incremental net monetary benefit (societal perspective, billions) of novel tuberculosis vaccines in countries where vaccine is cost-saving or cost-effective, comparing alternative willingness-to-pay thresholds.

Threshold	Infant Vaccine			Adolescent/Adult Vaccine		
	Cost-saving	Cost-effective	No. cost-effective	Cost-saving	Cost-effective	No. cost-effective
1x per-capita GDP (base-case)	50.8 (32.6, 74.6)	50.8 (32.6, 74.7)	55	341 (258, 444)	343 (258, 447)	75
0.5x per-capita GDP	30.8 (18.7, 46.7)	30.8 (19.0, 46.7)	50	261 (193, 344)	262 (194, 346)	71
1.6x per-capita GDP	74.7 (49.1, 108)	74.8 (49.1, 109)	67	437 (334, 564)	441 (336, 570)	78
2.3x per-capita GDP	103 (68.1, 148)	103 (68.2, 149)	69	550 (424, 705)	555 (427, 713)	81
Woods	24.7 (14.2, 38.4)	24.8 (15.4, 38.4)	51	233 (170, 310)	235 (170, 312)	68
Ochalek	22.0 (12.4, 34.7)	22.1 (13.0, 34.8)	55	227 (165, 302)	229 (166, 306)	72
Best Buy ($100)	12.6 (5.40, 22.0)	13.6 (7.60, 22.4)	47	188 (134, 252)	188 (136, 253)	58

Note: GDP = gross domestic product; No. countries = number of countries where vaccine is cost-effective at specified threshold. Values in parentheses represent equal-tailed 95% credible intervals.

S16. Market (millions) across 2028–2050 for infant tuberculosis vaccines (societal perspective)

	Vaccinated population where TB vaccine is cost-saving	Vaccinated population where TB vaccine is cost-effective (1x GDP per capita)
All countries	1186 (1176, 1196)	1257 (1246, 1268)
High-TB burden[a]	1032 (1025, 1039)	1075 (1068, 1083)
High-TB/HIV burden[a]	744 (740, 746)	776 (772, 780)
High-MDR/RR-TB burden[a]	918 (912, 925)	929 (923, 936)
Income level[b]		
LIC	148 (146, 150)	159 (156, 160)
LMIC	764 (760, 766)	781 (778, 784)
UMIC	274 (270, 280)	317 (312, 323)
World region		
AFR	436 (432, 438)	446 (442, 448)

AMR	12.6 (12.3, 12.9)	56.7 (55.7, 58.2)
EMR	106 (105, 107)	106 (105, 107)
EUR	28.0 (27.1, 28.7)	28.6 (27.8, 29.3)
SEAR	354 (352, 355)	358 (357, 359)
WPR	250 (247, 255)	261 (258, 266)

[a] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]

[b] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).

Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; GDP = gross domestic product; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; TB = tuberculosis; UMIC = upper middle-income; WPR = Western Pacific region.

S17. Market (millions) across 2028–2050 for adolescent/adult tuberculosis vaccines (societal perspective)

	Vaccinated population where TB vaccine is cost-saving	Vaccinated population where TB vaccine is cost-effective (1x GDP per capita)
All countries	3224 (3222, 3226)	3602 (3599, 3604)
High-TB burden[a]	2782 (2781, 2783)	2900 (2898, 2901)
High-TB/HIV burden[a]	1806 (1804, 1807)	1923 (1922, 1924)
High-MDR/RR-TB burden[a]	2632 (2631, 2634)	2669 (2668, 2671)
Income level[b]		
LIC	297.6 (297.3, 297.7)	299.6 (299.4, 299.8)
LMIC	1927 (1926, 1928)	1977 (1976, 1978)
UMIC	999.8 (999.3, 1000.3)	1325 (1324, 1327)
World region		
AFR	750 (749, 751)	770 (769, 771)
AMR	63.2 (63.0, 63.4)	332.7 (332.0, 333.5)
EMR	226.9 (226.7, 227.0)	260.1 (259.9, 260.2)
EUR	100.0 (99.9, 100.1)	142.0 (141.9, 142.3)
SEAR	1158.6 (1157.9, 1159.1)	1171 (1170, 1172)
WPR	925.8 (925.4, 926.1)	925.8 (925.4, 926.1)

[a] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]

[b] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).

Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; GDP = gross domestic product; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; TB = tuberculosis; UMIC = upper middle-income; WPR = Western Pacific region.

S18. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of infant tuberculosis vaccines: low-coverage scenario.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	6.24 (5.07, 8.69)	*-24.7* (*-29.3*, *-20.2*)	16.0 (13.8, 18.5)	393 (303, 560)	cost-saving[c]
High-TB burden[d]	4.18 (3.44, 5.82)	*-25.2* (*-29.7*, *-20.9*)	14.8 (12.6, 17.3)	285 (220, 407)	cost-saving[c]
High-TB/HIV burden[d]	2.94 (2.45, 3.98)	*-22.3* (*-26.8*, *-18.3*)	12.9 (10.8, 15.3)	230 (177, 323)	cost-saving[c]
High-MDR/RR-TB burden[d]	3.68 (3.01, 5.15)	*-23.8* (*-28.2*, *-19.5*)	13.1 (11.0, 15.5)	284 (215, 413)	cost-saving[c]
Income level[e]					
LIC	0.91 (0.78, 1.17)	*-0.16* (*-0.40*, 0.12)	1.78 (1.49, 2.16)	517 (397, 686)	cost-saving (cost-saving, 73.1)
LMIC	3.21 (2.68, 4.33)	*-20.8* (*-24.9*, *-16.9*)	13.2 (11.2, 15.7)	245 (190, 343)	cost-saving[c]
UMIC	2.12 (1.59, 3.37)	*-3.73* (*-5.55*, *-2.10*)	0.98 (0.74, 1.32)	2215 (1379, 3626)	cost-saving[c]
World region					
AFR	1.96 (1.67, 2.56)	*-11.9* (*-15.2*, *-9.24*)	8.26 (6.81, 10.0)	240 (180, 326)	cost-saving[c]
AMR	0.56 (0.42, 0.88)	0.22 (0.07, 0.54)	0.055 (0.046, 0.065)	10300 (7260, 16200)	4170 (1090, 10100)
EMR	0.86 (0.70, 1.16)	*-0.56* (*-1.18*, *-0.03*)	1.46 (1.02, 2.00)	606 (393, 933)	cost-saving[c]
EUR	0.35 (0.25, 0.59)	0.16 (0.05, 0.40)	0.03 (0.03, 0.04)	10800 (7310, 18300)	5000 (1520, 12600)
SEAR	1.29 (1.06, 1.77)	*-8.94* (*-11.6*, *-6.70*)	4.88 (3.69, 6.49)	270 (184, 412)	cost-saving[c]
WPR	1.22 (0.94, 1.89)	*-3.68* (*-5.19*, *-2.46*)	1.26 (0.92, 1.73)	990 (628, 1620)	cost-saving[c]

[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

S19. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of adolescent/adult tuberculosis vaccines: low-coverage scenario.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	20.6 (15.2, 31.2)	*-89.8* (*-102*, *-76.3*)	58 (52.6, 63.8)	356 (256, 541)	cost-saving[c]
High-TB burden[d]	14.7 (10.8, 22.4)	*-87.9* (*-99.2*, *-75.6*)	53 (47.7, 58.8)	278 (196, 424)	cost-saving[c]
High-TB/HIV burden[d]	9.10 (6.80, 13.2)	*-81.1* (*-91.9*, *-70.5*)	47.3 (42.4, 52.8)	192 (137, 281)	cost-saving[c]
High-MDR/RR-TB burden[d]	13.5 (9.70, 20.9)	*-82.7* (*-94.2*, *-70.8*)	47.1 (41.9, 52.4)	287 (198, 443)	cost-saving[c]
Income level[e]					
LIC	2.25 (1.79, 3.01)	*-1.31* (*-1.99*, *-0.45*)	5.87 (5.16, 6.61)	385 (291, 526)	cost-saving[c]
LMIC	9.80 (7.45, 14.0)	*-74.4* (*-83.7*, *-65.1*)	48.0 (43.1, 53.4)	205 (149, 296)	cost-saving[c]
UMIC	8.53 (5.59, 15.1)	*-14.1* (*-19.8*, *-6.19*)	4.15 (3.39, 5.20)	2080 (1250, 3940)	cost-saving[c]
World region					
AFR	4.22 (3.38, 5.70)	*-34.9* (*-41.5*, *-29.3*)	24.3 (21.7, 27.3)	174 (134, 243)	cost-saving[c]
AMR	2.14 (1.45, 3.66)	*-0.02* (*-0.78*, 1.58)	0.40 (0.36, 0.45)	5330 (3540, 9150)	cost-saving (cost-saving, 3880)
EMR	2.38 (1.86, 3.28)	*-1.56* (*-2.68*, *-0.36*)	4.11 (3.22, 5.15)	586 (410, 865)	cost-saving[c]
EUR	1.15 (0.77, 1.96)	*-0.29* (*-0.71*, 0.52)	0.28 (0.25, 0.31)	4100 (2700, 7190)	cost-saving (cost-saving, 1920)
SEAR	5.21 (3.88, 7.59)	*-44.1* (*-51.6*, *-36.7*)	25.0 (21.3, 29.4)	210 (145, 317)	cost-saving[c]
WPR	5.48 (3.59, 9.61)	*-8.89* (*-11.6*, *-4.47*)	3.84 (3.31, 4.41)	1440 (918, 2560)	cost-saving[c]

[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

S20. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of infant tuberculosis vaccines: high-coverage scenario.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	6.17 (5.00, 8.65)	*-33.1* (*-38.8*, *-27.7*)	20.2 (17.6, 23.4)	306 (235, 437)	cost-saving[c]
High-TB burden[d]	4.11 (3.37, 5.75)	*-33.2* (*-38.7*, *-27.9*)	18.7 (16.1, 21.8)	221 (170, 317)	cost-saving[c]
High-TB/HIV burden[d]	2.88 (2.38, 3.91)	*-29.1* (*-34.7*, *-24.2*)	16.3 (13.7, 19.4)	178 (136, 249)	cost-saving[c]
High-MDR/RR-TB burden[d]	3.62 (2.94, 5.09)	*-31.2* (*-36.6*, *-26.0*)	16.5 (13.9, 19.6)	221 (166, 323)	cost-saving[c]
Income level[e]					
LIC	0.91 (0.79, 1.18)	*-0.45* (*-0.74*, *-0.15*)	2.27 (1.90, 2.75)	407 (313, 542)	cost-saving[c]
LMIC	3.15 (2.61, 4.26)	*-27.3* (*-32.5*, *-22.5*)	16.7 (14.2, 19.8)	190 (146, 267)	cost-saving[c]
UMIC	2.11 (1.58, 3.35)	*-5.39* (*-7.65*, *-3.45*)	1.25 (0.95, 1.68)	1720 (1070, 2810)	cost-saving[c]
World region					
AFR	1.94 (1.64, 2.53)	*-15.7* (-19.7, *-12.3*)	10.5 (8.68, 12.6)	187 (141, 254)	cost-saving[c]
AMR	0.56 (0.42, 0.87)	0.12 (*-0.04*, 0.44)	0.07 (0.06, 0.08)	7980 (5610, 12400)	1810 (cost-saving, 6330)
EMR	0.85 (0.69, 1.15)	*-0.95* (*-1.70*, -0.31)	1.85 (1.29, 2.53)	473 (303, 731)	cost-saving[c]
EUR	0.35 (0.24, 0.59)	0.10 (*-0.01*, 0.33)	0.04 (0.04, 0.05)	8190 (5520, 14000)	2390 (cost-saving, 8150)
SEAR	1.27 (1.03, 1.76)	*-11.7* (*-15.2*, *-8.97*)	6.20 (4.69, 8.23)	209 (141, 321)	cost-saving[c]
WPR	1.21 (0.93, 1.89)	*-5.01* (*-6.89*, *-3.52*)	1.60 (1.17, 2.19)	777 (491, 1280)	cost-saving[c]

[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

S21. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of adolescent/adult tuberculosis vaccines: high-coverage scenario.

Country grouping	Health system perspective[a]	Societal perspective[b]	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted

	incremental cost (USD billions)	incremental cost (USD billions)			
All countries	27.0 (19.9, 41.1)	*-124* (*-140*, *-106*)	79.2 (72.0, 86.9)	342 (245, 520)	cost-saving[c]
High-TB burden[d]	19.3 (14.1, 29.7)	*-121* (*-136*, *-104*)	72.3 (65.2, 79.8)	268 (188, 411)	cost-saving[c]
High-TB/HIV burden[d]	11.8 (8.80, 17.2)	*-111* (*-125*, *-96.9*)	64.5 (57.9, 71.7)	184 (131, 269)	cost-saving[c]
High-MDR/RR-TB burden[d]	17.7 (12.7, 27.7)	*-113* (*-129*, *-97.7*)	64.3 (57.4, 71.5)	277 (191, 430)	cost-saving[c]
Income level[e]					
LIC	2.88 (2.29, 3.85)	*-1.97* (*-2.86*, *-0.85*)	8.01 (7.05, 8.99)	361 (274, 493.6)	cost-saving[c]
LMIC	12.7 (9.65, 18.3)	*-102* (*-114*, *-89.4*)	65.4 (58.9, 72.5)	196 (142, 282)	cost-saving[c]
UMIC	11.4 (7.44, 20.2)	*-20.0* (*-27.7*, *-9.40*)	5.75 (4.70, 7.17)	2000 (1200, 3800)	cost-saving[c]
World region					
AFR	5.35 (4.25, 7.19)	*-47.6* (*-56.4*, *-40.2*)	33.0 (29.5, 36.7)	163 (125, 226)	cost-saving[c]
AMR	2.83 (1.91, 4.84)	*-0.20* (*-1.21*, 1.91)	0.57 (0.51, 0.63)	5010 (3320, 8590)	cost-saving (cost-saving, 3350)
EMR	3.06 (2.38, 4.23)	*-2.29* (*-3.79*, *-0.70*)	5.58 (4.39, 6.97)	556 (387, 818)	cost-saving[c]
EUR	1.52 (1.02, 2.60)	*-0.52* (*-1.08*, 0.56)	0.40 (0.35, 0.44)	3830 (2520, 6750)	cost-saving (cost-saving, 1480)
SEAR	6.90 (5.13, 10.1)	*-60.7* (*-70.6*, *-50.9*)	34.4 (29.3, 40.2)	202 (139, 305)	cost-saving[c]
WPR	7.35 (4.80, 12.9)	*-12.4* (*-16.0*, *-6.47*)	5.26 (4.54, 6.04)	1400 (894, 2500)	cost-saving[c]

[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

S22. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of infant tuberculosis vaccines: accelerated scale-up scenario.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	7.80 (6.22, 11.0)	*-78.3* (*-90.9*, *-66.9*)	45.2 (39.3, 52.4)	173 (131, 253)	cost-saving[c]

High-TB burden[d]	4.84 (3.84, 6.91)	*-75.5* (*-88.2*, *-64.5*)	40.8 (35.0, 48.1)	119 (88.9, 175)	cost-saving[c]
High-TB/HIV burden[d]	3.46 (2.75, 4.84)	*-66.8* (*-79.7*, *-55.7*)	35.9 (29.9, 43.1)	97.0 (71.4, 142)	cost-saving[c]
High-MDR/RR-TB burden[d]	4.25 (3.32, 6.13)	*-71.0* (*-83.6*, *-60.3*)	36.3 (30.5, 43.5)	118 (85.3, 177)	cost-saving[c]
Income level[e]					
LIC	1.38 (1.17, 1.80)	*-1.86* (*-2.42*, *-1.33*)	5.41 (4.68, 6.34)	257 (200, 338)	cost-saving[c]
LMIC	4.04 (3.20, 5.63)	*-66.7* (*-79.5*, *-56.0*)	37.8 (31.9, 44.8)	108 (78.9, 158)	cost-saving[c]
UMIC	2.38 (1.78, 3.82)	*-9.74* (*-13.0*, *-7.15*)	2.03 (1.58, 2.66)	1200 (766, 2000)	cost-saving[c]
World region					
AFR	2.61 (2.19, 3.43)	*-29.4* (*-36.6*, *-23.9*)	20.5 (17.3, 24.5)	129 (96.8, 178)	cost-saving[c]
AMR	0.70 (0.53, 1.09)	*-0.25* (*-0.49*, 0.15)	0.16 (0.14, 0.19)	4420 (3150, 6900)	cost-saving (cost-saving, 887)
EMR	1.10 (0.88, 1.51)	*-2.30* (*-3.61*, *-1.20*)	3.52 (2.50, 4.67)	321 (208, 493)	cost-saving[c]
EUR	0.44 (0.31, 0.73)	*-0.12* (*-0.27*, 0.16)	0.16 (0.13, 0.18)	2850 (1910, 4800)	cost-saving (cost-saving, 1110)
SEAR	1.61 (1.21, 2.37)	*-37.0* (*-47.1*, *-29.1*)	18.1 (13.7, 23.7)	91.2 (57.2, 149)	cost-saving[c]
WPR	1.33 (1.01, 2.07)	*-9.16* (*-11.9*, *-7.03*)	2.88 (2.23, 3.74)	470 (308, 769)	cost-saving[c]

[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

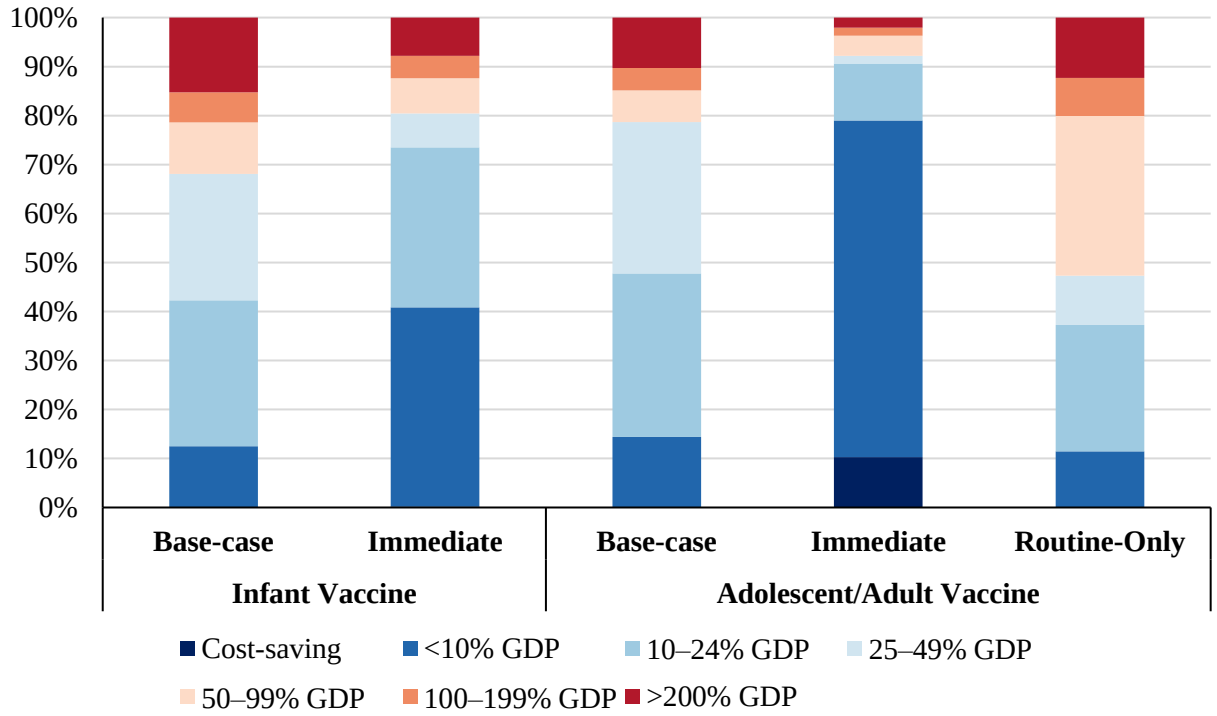
S23. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of adolescent/adult tuberculosis vaccines: accelerated scale-up scenario.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	4.93 (1.79, 9.43)	*-285* (*-312*, *-259*)	153 (139, 168)	32.4 (11.7, 62.2)	cost-saving[c]
High-TB burden[d]	2.29 (*-0.22*, 5.52)	*-263* (*-290*, *-238*)	137 (123, 152)	16.8 (cost-saving, 40.9)	cost-saving[c]

High-TB/HIV burden[d]	1.30 (*-0.57*, 3.44)	*-232* (*-259*, *-207*)	122 (109, 136)	10.7 (cost-saving, 28.4)	cost-saving[c]
High-MDR/RR-TB burden[d]	1.43 (*-1.00*, 4.53)	*-249* (*-275*, *-224*)	123 (109, 137)	11.7 (cost-saving, 36.9)	cost-saving[c]
Income level[e]					
LIC	1.44 (1.10, 2.00)	*-7.96* (*-9.13*, *-6.83*)	15.7 (14.0, 17.4)	92.3 (69.3, 129.8)	cost-saving[c]
LMIC	1.47 (*-0.52*, 3.77)	*-227* (*-252*, *-204*)	128 (114, 142)	11.6 (cost-saving, 30.1)	cost-saving[c]
UMIC	2.02 (0.93, 4.13)	*-50.1* (*-59.4*, *-42.7*)	9.36 (7.86, 11.4)	217 (94.4, 480)	cost-saving[c]
World region					
AFR	2.41 (1.70, 3.41)	*-85.9* (*-99.4*, *-74.6*)	57.4 (51.7, 63.6)	42.2 (29.8, 62.01)	cost-saving[c]
AMR	0.76 (0.48, 1.35)	*-5.36* (*-6.03*, *-4.58*)	1.16 (1.04, 1.28)	660 (410, 1189)	cost-saving[c]
EMR	0.97 (0.65, 1.47)	*-8.46* (*-10.7*, *-6.45*)	9.77 (7.75, 12.2)	101 (60, 161)	cost-saving[c]
EUR	0.17 (0.01, 0.46)	*-4.06* (*-4.50*, *-3.51*)	1.01 (0.91, 1.13)	167 (15.7, 474)	cost-saving[c]
SEAR	*-0.23* (*-1.50*, 1.06)	*-148* (*-171*, *-128*)	74.0 (63.1, 86.5)	cost-saving (cost-saving, 14.6)	cost-saving[c]
WPR	0.84 (0.11, 2.11)	*-33.3* (*-37.1*, *-29.6*)	9.28 (8.1, 10.61)	91 (12.5, 232)	cost-saving[c]

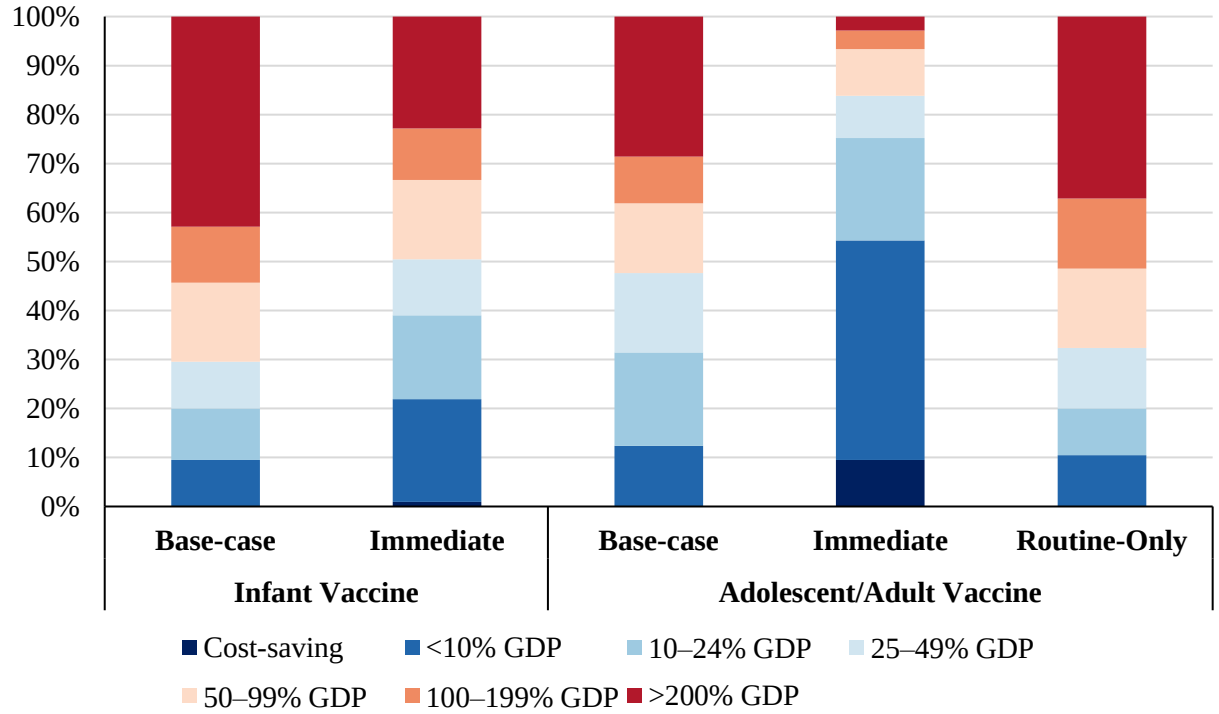
[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

S24. Percentage of population that live in countries where vaccination was cost-effective from the health system perspective compared to percentage of GDP per capita thresholds, comparing alternative scale-up scenarios.



Note: Countries include 105 low- and middle-income countries analyzed. Population includes vaccinated individuals 2028–2050. GDP estimates from 2020. GDP = gross domestic product per capita.

S25. Percentage of countries where vaccination was cost-effective from the health system perspective compared to percentage of GDP per capita thresholds, comparing alternative scale-up scenarios.



Note: Countries include 105 low- and middle-income countries analyzed. GDP estimates from 2020. GDP = gross domestic product per capita.

S26. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of adolescent tuberculosis vaccines: routine-only scale-up scenario.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	7.96 (6.06, 11.7)	*-32.9* (*-39.8*, *-25.9*)	21.2 (18.4, 24.8)	378 (266, 562)	cost-saving[c]
High-TB burden[d]	5.61 (4.24, 8.21)	*-33.2* (*-40.0*, *-26.8*)	19.7 (16.8, 23.3)	287 (198, 430)	cost-saving[c]
High-TB/HIV burden[d]	3.85 (2.96, 5.44)	*-30.8* (*-37.3*, *-25.3*)	17.6 (14.8, 21.3)	220 (153, 323)	cost-saving[c]
High-MDR/RR-TB burden[d]	4.95 (3.68, 7.42)	*-31.4* (*-38.2*, *-25.1*)	17.5 (14.6, 21.1)	287 (191, 441)	cost-saving[c]
Income level[e]					

LIC	1.15 (0.92, 1.53)	*-0.20* (*-0.55*, 0.23)	2.21 (1.88, 2.63)	521 (389, 729)	cost-saving (cost-saving, 115)
LMIC	4.11 (3.19, 5.76)	*-28.7* (*-35.4*, *-23.6*)	17.8 (15.0, 21.4)	233 (165, 339)	cost-saving[c]
UMIC	2.70 (1.81, 4.72)	*-3.96* (*-6.46*, *-1.32*)	1.18 (0.88, 1.61)	2350 (1310, 4530)	cost-saving[c]
World region					
AFR	2.33 (1.88, 3.10)	*-14.7* (*-19.2*, *-11.1*)	10.2 (8.42, 12.6)	231 (162, 330)	cost-saving[c]
AMR	0.73 (0.50, 1.24)	0.29 (0.05, 0.83)	0.07 (0.06, 0.09)	10100 (6520, 17500)	4090 (561, 11600)
EMR	1.06 (0.84, 1.45)	*-0.51* (*-1.13*, 0.08)	1.66 (1.21, 2.22)	652 (431, 989)	cost-saving (cost-saving, 57.0)
EUR	0.37 (0.26, 0.63)	0.13 (0.01, 0.37)	0.05 (0.04, 0.05)	8020 (5330, 14200)	2860 (249, 8950)
SEAR	1.82 (1.38, 2.61)	*-14.6* (*-18.8*, *-11.1*)	7.79 (5.94, 10.2)	238 (155, 378)	cost-saving[c]
WPR	1.65 (1.11, 2.84)	*-3.48* (*-4.76*, *-2.09*)	1.43 (1.13, 1.80)	1170 (708, 2070)	cost-saving[c]

[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

S27. Undiscounted vaccination costs (billions) of infant tuberculosis vaccines across 2028–2050 by vaccine price scenario.

Country grouping	Base-case	Half-price	Double-price	High-middle-tier-price
Global	9.71 (7.88, 13.9)	6.53 (4.63, 10.9)	17.5 (15.6, 21.9)	14.6 (12.7, 19.0)
High-TB burden[a]	6.59 (5.48, 9.26)	4.13 (3.01, 6.79)	11.6 (10.4, 14.2)	9.29 (8.17, 12.0)
High-TB/HIV burden[a]	4.74 (3.97, 6.48)	3.08 (2.28, 4.91)	8.76 (7.95, 10.6)	5.85 (5.05, 7.69)
High-MDR/RR-TB burden[a]	5.83 (4.81, 8.29)	3.84 (2.78, 6.42)	10.7 (9.61, 13.3)	8.89 (7.82, 11.5)
Income level[b]				
LIC	1.44 (1.23, 1.88)	0.93 (0.71, 1.40)	2.69 (2.46, 3.16)	1.51 (1.29, 1.98)
LMIC	4.79 (4.39, 7.11)	3.12 (2.33, 4.88)	8.84 (8.05, 10.6)	5.67 (4.88, 7.43)
UMIC	3.47 (2.26, 4.92)	2.49 (1.59, 4.66)	5.96 (5.05, 8.13)	7.41 (6.50, 9.58)
World region				
AFR	3.10 (2.62, 4.16)	2.01 (1.51, 3.12)	5.72 (5.21, 6.83)	3.37 (2.87, 4.48)

AMR	0.81 (0.61, 1.27)	0.58 (0.37, 1.06)	1.37 (1.16, 1.86)	1.65 (1.44, 2.14)
EMR	1.35 (1.11, 1.85)	0.91 (0.66, 1.44)	2.42 (2.17, 2.95)	2.07 (1.81, 2.60)
EUR	0.51 (0.36, 0.88)	0.39 (0.23, 0.77)	0.84 (0.67, 1.21)	0.93 (0.76, 1.31)
SEAR	2.16 (1.81, 2.95)	1.40 (1.04, 2.23)	4.00 (3.63, 4.83)	2.31 (1.95, 3.14)
WPR	1.79 (1.38, 2.80)	1.24 (0.83, 2.31)	3.14 (2.72, 4.20)	4.26 (3.84, 5.33)

[a] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]

[b] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).

Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; TB = tuberculosis; UMIC = upper middle-income; WPR = Western Pacific region.

S28. Undiscounted vaccination costs (billions) of adolescent/adult tuberculosis vaccines across 2028–2050 by vaccine price scenario.

Country grouping	Base-case	Half-price	Double-price	High-middle-tier-price
Global	32.7 (24.7, 49.1)	24.7 (16.2, 41.9)	53.7 (45.2, 70.9)	48.7 (40.3, 65.9)
High-TB burden[a]	23.7 (17.9, 35.3)	16.9 (11.2, 28.4)	36.7 (31.0, 48.3)	33.0 (27.3, 44.5)
High-TB/HIV burden[a]	15.4 (12.1, 21.8)	11.5 (8.03, 18.2)	25.5 (22.0, 32.2)	18.8 (15.3, 25.5)
High-MDR/RR-TB burden[a]	21.9 (16.6, 33.0)	16.6 (10.9, 28.2)	36.0 (30.3, 47.6)	32.7 (27.0, 44.3)
Income level[b]				
LIC	3.66 (2.89, 4.83)	2.70 (1.94, 3.99)	6.11 (5.35, 7.40)	3.83 (3.07, 5.13)
LMIC	15.3 (13.6, 23.2)	11.4 (8.25, 17.0)	25.3 (22.2, 30.9)	17.6 (14.5, 23.2)
UMIC	13.8 (8.18, 21.1)	10.6 (6.06, 20.9)	22.2 (17.7, 32.6)	27.3 (22.7, 37.6)
World region				
AFR	6.88 (5.49, 9.32)	5.10 (3.65, 7.66)	11.4 (10.0, 14.0)	7.49 (6.04, 10.1)
AMR	3.05 (2.09, 5.23)	2.33 (1.33, 4.61)	4.89 (3.89, 7.17)	5.71 (4.71, 7.99)
EMR	3.76 (2.97, 5.22)	2.80 (1.98, 4.33)	6.22 (5.40, 7.75)	5.56 (4.74, 7.09)
EUR	1.76 (1.24, 2.96)	1.35 (0.80, 2.60)	2.85 (2.30, 4.11)	3.15 (2.60, 4.41)
SEAR	9.32 (7.43, 12.8)	6.96 (4.97, 10.6)	15.4 (13.5, 19.1)	9.99 (8.01, 13.6)
WPR	7.96 (5.47, 13.6)	6.12 (3.51, 12.1)	12.8 (10.2, 18.8)	16.8 (14.2, 22.8)

[a] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]

[b] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; TB = tuberculosis; UMIC = upper middle-income; WPR = Western Pacific region.

S29. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of infant tuberculosis vaccines: half-price scenario.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	4.11 (2.88, 6.73)	*-31.0* (*-36.1*, *-26.0*)	18.1 (15.7, 20.9)	229 (154, 376)	cost-saving[c]
High-TB burden[d]	2.64 (1.86, 4.38)	*-30.6* (*-35.7*, *-25.9*)	16.7 (14.3, 19.5)	159 (108, 269)	cost-saving[c]
High-TB/HIV burden[d]	1.83 (1.31, 2.94)	*-26.7* (*-31.8*, *-22.3*)	14.6 (12.2, 17.3)	127 (86, 206)	cost-saving[c]
High-MDR/RR-TB burden[d]	2.33 (1.61, 3.91)	*-28.8* (*-33.7*, *-24.0*)	14.8 (12.4, 17.6)	159 (105, 275)	cost-saving[c]
Income level[e]					
LIC	0.58 (0.45, 0.86)	*-0.64* (*-0.90*, *-0.33*)	2.02 (1.69, 2.45)	291 (207, 434)	cost-saving[c]
LMIC	2.01 (1.44, 3.21)	*-25.2* (*-29.8*, *-20.9*)	14.9 (12.7, 17.7)	136 (92.3, 221)	cost-saving[c]
UMIC	1.52 (0.96, 2.82)	*-5.14* (*-7.19*, *-3.34*)	1.11 (0.84, 1.5)	1390 (763, 2680)	cost-saving[c]
World region					
AFR	1.25 (0.94, 1.89)	*-14.5* (*-18.1*, *-11.5*)	9.36 (7.73, 11.3)	135 (92.9, 210)	cost-saving[c]
AMR	0.40 (0.26, 0.74)	0.02 (*-0.15*, 0.35)	0.06 (0.05, 0.07)	6530 (3950, 11800)	353 (cost-saving, 5590)
EMR	0.56 (0.39, 0.88)	*-1.04* (*-1.73*, *-0.45*)	1.65 (1.15, 2.26)	352 (207, 606)	cost-saving[c]
EUR	0.27 (0.16, 0.52)	0.05 (*-0.06*, 0.29)	0.04 (0.03, 0.04)	7180 (4060, 14000)	1390 (cost-saving, 8130)
SEAR	0.79 (0.55, 1.31)	*-10.8* (*-13.9*, -8.31)	5.54 (4.18, 7.36)	146 (88.7, 259)	cost-saving[c]
WPR	0.83 (0.53, 1.55)	*-4.72* (*-6.42*, *-3.33*)	1.43 (1.04, 1.95)	597 (327, 1140)	cost-saving[c]

[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).

Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

S30. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of adolescent/adult tuberculosis vaccines: half-price scenario.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	16.8 (10.4, 29.4)	*-116* (*-130*, *-100*)	69.7 (63.3, 76.5)	242 (146, 419)	cost-saving[c]
High-TB burden[d]	11.8 (7.10, 21.2)	*-111* (*-125*, *-96.6*)	63.6 (57.3, 70.4)	187 (111, 327)	cost-saving[c]
High-TB/HIV burden[d]	7.08 (4.39, 12.0)	*-101* (*-114*, *-88.5*)	56.8 (51.0, 63.2)	125 (75, 213)	cost-saving[c]
High-MDR/RR-TB burden[d]	10.8 (6.30, 19.8)	*-105* (*-118*, *-90.6*)	56.6 (50.5, 62.9)	192 (110, 348)	cost-saving[c]
Income level[e]					
LIC	1.82 (1.28, 2.71)	*-2.45* (*-3.25*, *-1.44*)	7.05 (6.20, 7.92)	259 (177, 390)	cost-saving[c]
LMIC	7.63 (4.83, 12.6)	*-93.2* (*-104*, *-82.3*)	57.6 (51.8, 64.0)	133 (81, 222)	cost-saving[c]
UMIC	7.35 (3.83, 15.3)	*-20.1* (*-26.9*, *-10.6*)	5.03 (4.11, 6.29)	1480 (733, 3320)	cost-saving[c]
World region					
AFR	3.35 (2.36, 5.06)	*-43.3* (*-51.1*, *-36.8*)	29.1 (26.0, 32.4)	116 (77.9, 180)	cost-saving[c]
AMR	1.85 (1.03, 3.67)	*-0.79* (*-1.70*, 1.11)	0.49 (0.44, 0.55)	3770 (2070, 7500)	cost-saving (cost-saving, 2240)
EMR	1.92 (1.31, 2.99)	*-2.79* (*-4.13*, *-1.37*)	4.92 (3.86, 6.16)	396 (249, 648)	cost-saving[c]
EUR	0.97 (0.52, 1.94)	*-0.80* (*-1.31*, 0.16)	0.35 (0.31, 0.38)	2810 (1490, 5750)	cost-saving (cost-saving, 481)
SEAR	4.03 (2.44, 6.88)	*-55.4* (*-64.2*, *-46.6*)	30.2 (25.7, 35.3)	135 (75.6, 234)	cost-saving[c]
WPR	4.67 (2.40, 9.64)	*-12.7* (*-15.8*, *-7.36*)	4.62 (3.99, 5.3)	1020 (515, 2120)	cost-saving[c]

[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

S31. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of infant tuberculosis vaccines: double-price scenario.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	11.6 (10.4, 14.2)	*-23.5* (*-28.6*, *-18.5*)	18.1 (15.7, 20.9)	646 (536, 812)	cost-saving[c]
High-TB burden[d]	8.02 (7.24, 9.77)	*-25.3* (*-30.3*, *-20.5*)	16.7 (14.3, 19.5)	482 (396, 602)	cost-saving[c]
High-TB/HIV burden[d]	5.72 (5.19, 6.82)	*-22.9* (*-27.9*, *-18.4*)	14.6 (12.2, 17.3)	395 (320, 502)	cost-saving[c]
High-MDR/RR-TB burden[d]	7.04 (6.33, 8.64)	*-24.1* (*-29.0*, *-19.3*)	14.8 (12.4, 17.6)	480 (386, 610)	cost-saving[c]
Income level[e]					
LIC	1.74 (1.61, 2.02)	0.53 (0.26, 0.83)	2.02 (1.69, 2.45)	872 (701, 1081)	267 (110, 460)
LMIC	6.22 (5.65, 7.41)	*-21.0* (*-25.6*, *-16.7*)	14.9 (12.7, 17.7)	419 (338, 526)	cost-saving[c]
UMIC	3.64 (3.08, 4.94)	*-3.02* (*-5.06*, *-1.21*)	1.11 (0.84, 1.50)	3340 (2290, 4930)	cost-saving[c]
World region					
AFR	3.76 (3.45, 4.40)	*-12.0* (*-15.6*, *-8.97*)	9.36 (7.73, 11.3)	406 (320, 518)	cost-saving[c]
AMR	0.96 (0.82, 1.29)	0.57 (0.41, 0.91)	0.06 (0.05, 0.07)	15500 (11800, 21200)	9340 (5700, 15000)
EMR	1.59 (1.42, 1.91)	*-0.01* (*-0.71*, 0.58)	1.65 (1.15, 2.26)	996 (680, 1440)	cost-saving (cost-saving, 479)
EUR	0.57 (0.46, 0.82)	0.36 (0.24, 0.60)	0.04 (0.03, 0.04)	15400 (11800, 22700)	9630 (5990, 16900)
SEAR	2.54 (2.30, 3.05)	*-9.07* (*-12.1*, *-6.56*)	5.54 (4.18, 7.36)	468 (337, 648)	cost-saving[c]
WPR	2.18 (1.88, 2.90)	*-3.37* (*-5.07*, *-1.98*)	1.43 (1.04, 1.95)	1570 (1070, 2270)	cost-saving[c]

[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

S32. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of adolescent/adult tuberculosis vaccines: double-price scenario.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	39.8 (33.4, 52.4)	*-92.8* (*-107*, *-76.8*)	69.7 (63.3, 76.5)	572 (460, 759)	cost-saving[c]
High-TB burden[d]	28.7 (24.0, 38.0)	*-94.4* (*-108*, *-79.8*)	63.6 (57.3, 70.4)	453 (360, 602)	cost-saving[c]
High-TB/HIV burden[d]	18.0 (15.3, 22.9)	*-90.2* (*-103*, *-77.6*)	56.8 (51, 63.2)	318 (256, 409)	cost-saving[c]
High-MDR/RR-TB burden[d]	26.4 (21.9, 35.4)	*-89.0* (*-103*, *-75.0*)	56.6 (50.5, 62.9)	469 (367, 630)	cost-saving[c]
Income level[e]					
LIC	4.28 (3.74, 5.16)	0.01 (*-0.79*, 1.02)	7.05 (6.2, 7.92)	609 (501, 761)	3.05 (cost-saving, 151)
LMIC	19.6 (16.8, 24.5)	*-81.3* (*-92.3*, *-70.4*)	57.6 (51.8, 64)	341 (278, 432)	cost-saving[c]
UMIC	16.0 (12.4, 23.9)	*-11.5* (*-18.3*, *-1.96*)	5.03 (4.11, 6.29)	3209 (2220, 5171)	cost-saving[c]
World region					
AFR	8.08 (7.08, 9.79)	*-38.6* (*-46.4*, *-32.1*)	29.1 (26, 32.4)	279 (232, 350)	cost-saving[c]
AMR	3.95 (3.12, 5.76)	1.31 (0.39, 3.21)	0.49 (0.44, 0.55)	8026 (6088, 11776)	2670 (758, 6470)
EMR	4.56 (3.95, 5.64)	*-0.15* (*-1.48*, 1.27)	4.92 (3.86, 6.16)	941 (702, 1252)	cost-saving (cost-saving, 295)
EUR	2.18 (1.74, 3.16)	0.41 (*-0.09*, 1.38)	0.35 (0.31, 0.38)	6343 (4882, 9484)	1210 (cost-saving, 4250)
SEAR	10.6 (9.01, 13.5)	*-48.8* (*-57.7*, *-40.1*)	30.2 (25.7, 35.3)	354 (275, 474)	cost-saving[c]
WPR	10.4 (8.13, 15.4)	*-6.93* (*-10.1*, *-1.62*)	4.62 (3.99, 5.3)	2263 (1682, 3388)	cost-saving[c]

[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

S33. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of infant tuberculosis vaccines: high-middle-tier-price scenario.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	9.73 (8.51, 12.4)	*-25.3* (*-30.5*, *-20.4*)	18.1 (15.7, 20.9)	542 (443, 711)	cost-saving[c]
High-TB burden[d]	6.36 (5.58, 8.11)	*-26.9* (*-32.0*, *-22.2*)	16.7 (14.3, 19.5)	383 (310, 500)	cost-saving[c]
High-TB/HIV burden[d]	3.75 (3.22, 4.86)	*-24.8* (*-29.9*, *-20.4*)	14.6 (12.2, 17.3)	259 (203, 348)	cost-saving[c]
High-MDR/RR-TB burden[d]	5.88 (5.17, 7.49)	*-25.3* (*-30.2*, *-20.5*)	14.8 (12.4, 17.6)	401 (317, 527)	cost-saving[c]
Income level[e]					
LIC	0.97 (0.83, 1.25)	*-0.25* (*-0.51*, 0.05)	2.02 (1.69, 2.45)	485 (373, 645)	cost-saving (cost-saving, 28.3)
LMIC	3.98 (3.41, 5.17)	*-23.2* (*-27.9*, *-18.9*)	14.9 (12.7, 17.7)	268 (210, 364)	cost-saving[c]
UMIC	4.79 (4.23, 6.09)	*-1.87* (*-3.91*, *-0.05*)	1.11 (0.84, 1.50)	4400 (3090, 6220)	cost-saving[c]
World region					
AFR	2.18 (1.86, 2.82)	*-13.5* (*-17.2*, *-10.6*)	9.36 (7.73, 11.3)	235 (178, 317)	cost-saving[c]
AMR	1.16 (1.01, 1.49)	0.78 (0.61, 1.11)	0.06 (0.05, 0.07)	18800 (14600, 24700)	12600 (8470, 18400)
EMR	1.35 (1.18, 1.67)	*-0.25* (*-0.95*, 0.34)	1.65 (1.15, 2.26)	846 (571, 1253)	cost-saving (cost-saving, 276)
EUR	0.65 (0.53, 0.90)	0.43 (0.31, 0.67)	0.04 (0.03, 0.04)	17400 (13500, 24800)	11600 (7700, 18800)
SEAR	1.41 (1.16, 1.92)	*-10.2* (*-13.2*, *-7.70*)	5.54 (4.18, 7.36)	260 (178, 394)	cost-saving[c]
WPR	2.99 (2.69, 3.72)	*-2.55* (*-4.26*, *-1.17*)	1.43 (1.04, 1.95)	2150 (1490, 3020)	cost-saving[c]

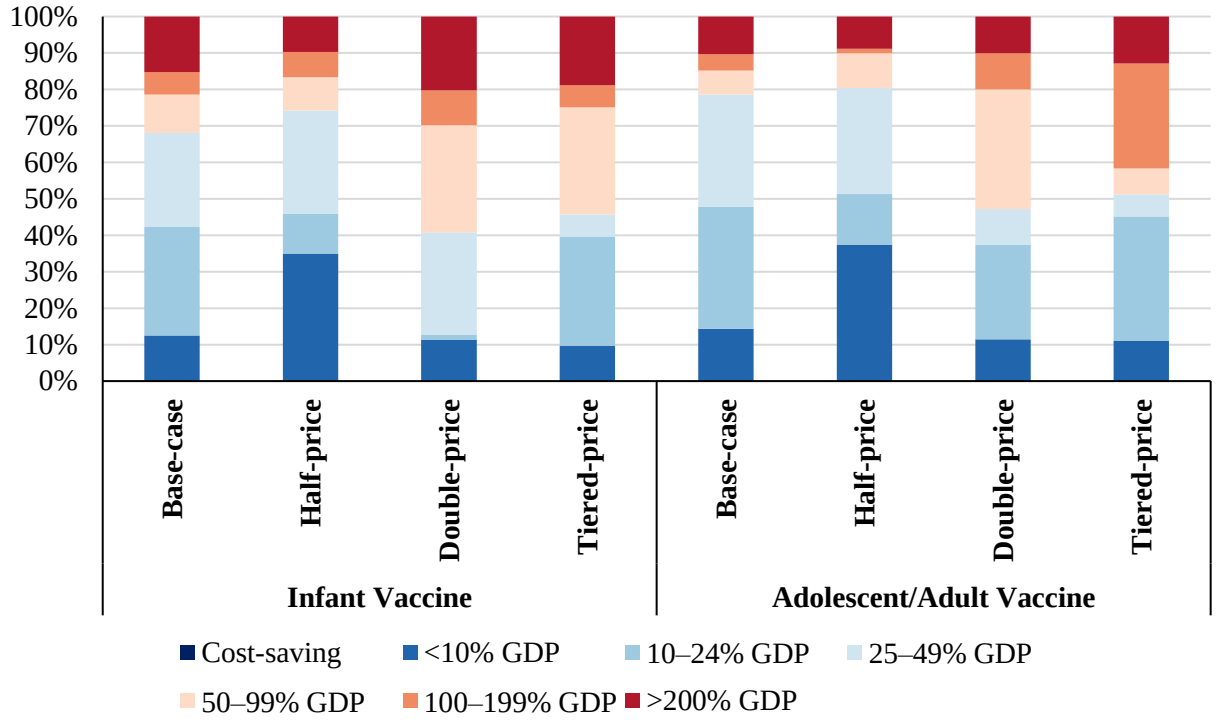
[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

S34. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of adolescent/adult tuberculosis vaccines: high-middle-tier-price scenario.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	36.6 (30.3, 49.3)	*-95.9* (*-110*, *-79.9*)	69.7 (63.3, 76.5)	527 (419, 711)	cost-saving[c]
High-TB burden[d]	25.7 (21.0, 35.0)	*-97.5* (*-111*, *-82.8*)	63.6 (57.3, 70.4)	404 (316, 553)	cost-saving[c]
High-TB/HIV burden[d]	12.9 (10.2, 17.8)	*-95.2* (*-108*, *-82.6*)	56.8 (51, 63.2)	229 (172, 317)	cost-saving[c]
High-MDR/RR-TB burden[d]	24.3 (19.8, 33.3)	*-91.1* (*-105*, *-77.1*)	56.6 (50.5, 62.9)	432 (333, 592)	cost-saving[c]
Income level[e]					
LIC	2.64 (2.1, 3.53)	*-1.63* (*-2.43*, *-0.62*)	7.05 (6.2, 7.92)	376 (285, 514)	cost-saving[c]
LMIC	13.3 (10.5, 18.3)	*-87.6* (*-98.6*, *-76.6*)	57.6 (51.8, 64)	232 (175, 322)	cost-saving[c]
UMIC	20.7 (17.2, 28.6)	*-6.71* (*-13.5*, 2.81)	5.03 (4.11, 6.29)	4170 (3020, 6180)	cost-saving (cost-saving, 584)
World region					
AFR	5.16 (4.17, 6.87)	*-41.5* (*-49.3*, *-35.0*)	29.1 (26, 32.4)	178 (138, 245)	cost-saving[c]
AMR	4.65 (3.82, 6.46)	2.01 (1.09, 3.91)	0.49 (0.44, 0.55)	9440 (7410, 13200)	4090 (2120, 7880)
EMR	4.07 (3.46, 5.15)	*-0.64* (*-1.97*, 0.78)	4.92 (3.86, 6.16)	840 (617, 1135)	cost-saving (cost-saving, 178)
EUR	2.46 (2.02, 3.44)	0.69 (0.19, 1.66)	0.35 (0.31, 0.38)	7160 (5670, 10300)	2020 (544, 5170)
SEAR	6.39 (4.8, 9.24)	*-53.0* (*-61.9*, *-44.3*)	30.2 (25.7, 35.3)	213 (149, 320)	cost-saving[c]
WPR	13.9 (11.6, 18.9)	*-3.43* (*-6.60*, 1.88)	4.62 (3.99, 5.3)	3030 (2360, 4160)	cost-saving (cost-saving, 412)

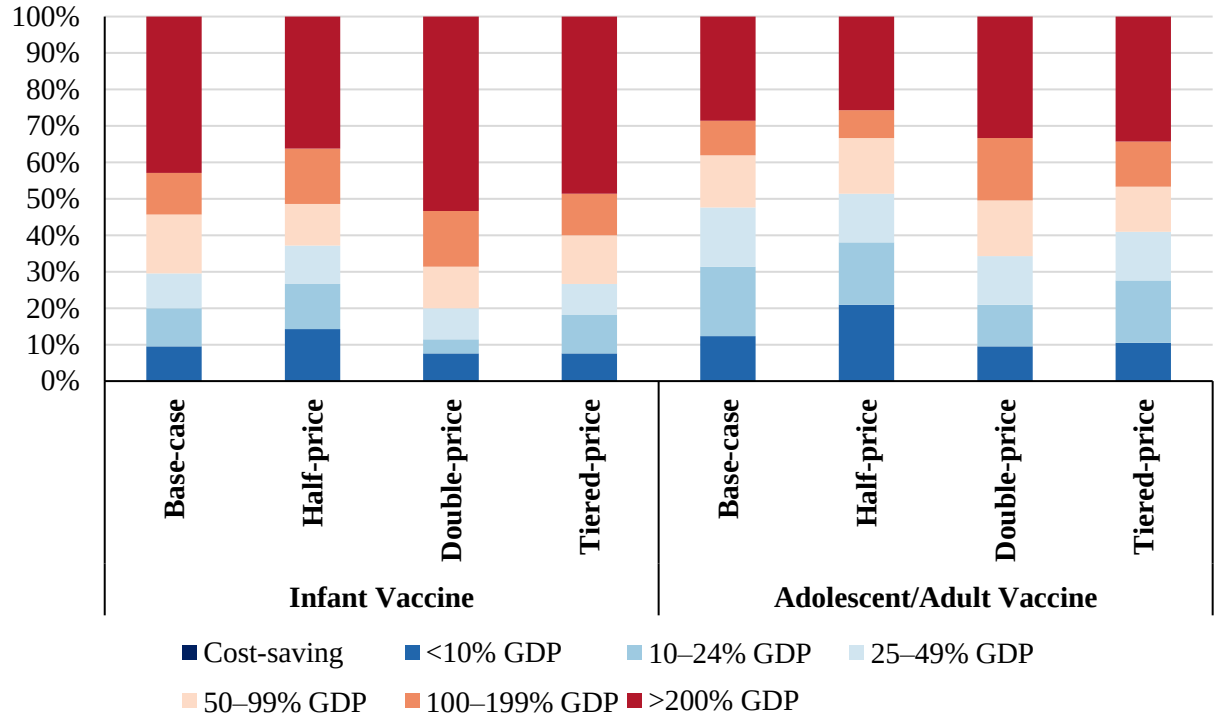
[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

S35. Percentage of population that live in countries where vaccination was cost-effective from the health system perspective compared to percentage of GDP per capita thresholds, comparing alternative vaccine price scenarios.



Note: Countries include 105 low- and middle-income countries analyzed. Population includes vaccinated individuals 2028–2050. GDP estimates from 2020. GDP = gross domestic product per capita.

S36. Percentage of countries where vaccination was cost-effective from the health system perspective compared to percentage of GDP per capita thresholds, comparing alternative vaccine price scenarios.



Note: Countries include 105 low- and middle-income countries analyzed. GDP estimates from 2020. GDP = gross domestic product per capita.

S37. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of infant tuberculosis vaccines: EndTB baseline scenario.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	7.01 (5.79, 9.60)	3.27 (0.08, 6.57)	1.73 (0.93, 3.21)	4510 (2000, 8220)	2310 (23.3, 5870)
High-TB burden[d]	4.79 (4.01, 6.56)	1.25 (*-1.98*, 3.83)	1.60 (0.80, 3.10)	3400 (1420, 6320)	1140 (cost-saving, 4080)
High-TB/HIV burden[d]	3.39 (2.88, 4.51)	0.40 (*-2.51*, 2.41)	1.36 (0.61, 2.77)	2910 (1170, 5710)	669 (cost-saving, 3470)
High-MDR/RR-TB burden[d]	4.24 (3.53, 5.89)	0.94 (*-2.21*, 3.43)	1.39 (0.62, 2.92)	3550 (1360, 7180)	1120 (cost-saving, 4550)
Income level[e]					

LIC	1.00 (0.86, 1.28)	0.88 (0.69, 1.17)	0.18 (0.08, 0.35)	6490 (2730, 13200)	5850 (2090, 12600)
LMIC	3.71 (3.15, 4.95)	1.32 (*-1.44*, 3.19)	1.33 (0.58, 2.87)	3290 (1230, 6630)	1480 (cost-saving, 4810)
UMIC	2.31 (1.74, 3.65)	1.07 (*-0.67*, 2.73)	0.22 (0.06, 0.51)	14400 (3760, 42500)	8660 (cost-saving, 35500)
World region					
AFR	2.18 (1.87, 2.84)	0.21 (*-2.44*, 1.63)	0.98 (0.41, 2.39)	2710 (860, 5450)	676 (cost-saving, 3550)
AMR	0.60 (0.46, 0.94)	0.57 (0.41, 0.91)	0.006 (0.002, 0.012)	113000 (47100, 266000)	107000 (40900, 259000)
EMR	0.96 (0.79, 1.29)	0.78 (0.25, 1.15)	0.17 (0.02, 0.61)	10800 (1510, 40300)	9730 (421, 38600)
EUR	0.38 (0.27, 0.64)	0.34 (0.21, 0.60)	0.006 (0.002, 0.014)	72700 (24300, 178000)	66500 (17100, 173000)
SEAR	1.52 (1.28, 2.05)	0.63 (*-0.64*, 1.45)	0.42 (0.11, 1.09)	5070 (1280, 15400)	2850 (cost-saving, 13100)
WPR	1.36 (1.06, 2.10)	0.74 (*-0.38*, 1.65)	0.15 (0.03, 0.49)	14200 (2570, 43800)	9670 (cost-saving, 38800)

[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

S38. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of adolescent/adult tuberculosis vaccines: EndTB baseline scenario.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	36.8 (27.9, 54.7)	*-2.83* (*-20.4*, 18.4)	19.5 (14.6, 27.2)	1940 (1220, 3080)	cost-saving (cost-saving, 1040)
High-TB burden[d]	26.9 (20.3, 40.0)	*-9.00* (*-24.9*, 7.70)	17.6 (12.7, 25.0)	1580 (960, 2590)	cost-saving (cost-saving, 496)
High-TB/HIV burden[d]	16.7 (13.1, 23.6)	*-13.9* (*-28.0*, *-2.60*)	15.3 (10.7, 22.6)	1140 (676, 1780)	cost-saving[c]
High-MDR/RR-TB burden[d]	25.0 (18.7, 37.9)	*-8.77* (*-24.7*, 8.00)	15.6 (11.0, 23.3)	1660 (968, 2790)	cost-saving (cost-saving, 572)
Income level[e]					
LIC	3.59 (2.89, 4.77)	2.46 (1.49, 3.66)	1.85 (1.29, 2.81)	2020 (1220, 3070)	1420 (564, 2450)
LMIC	18.2 (14.4, 25.1)	*-6.70* (*-19.8*, 3.46)	15.0 (10.4, 22.8)	1260 (750, 1930)	cost-saving (cost-saving, 272)

UMIC	15.0 (10.0, 26.3)	1.42 (*-8.68*, 13.9)	2.64 (1.77, 4.23)	5990 (2830, 11400)	816 (cost-saving, 6270)
World region					
AFR	6.83 (5.59, 9.03)	*-7.73* (*-18.2*, *-1.67*)	7.97 (5.49, 12.5)	900 (499, 1370)	cost-saving[c]
AMR	3.65 (2.49, 6.22)	2.53 (1.34, 5.19)	0.23 (0.19, 0.28)	16300 (10500, 29100)	11300 (5510, 24100)
EMR	4.03 (3.19, 5.54)	2.60 (0.39, 4.37)	1.43 (0.76, 3.24)	3210 (1140, 5790)	2220 (122, 4830)
EUR	2.05 (1.42, 3.45)	0.97 (0.03, 2.40)	0.20 (0.15, 0.29)	10400 (5910, 19000)	5100 (102, 13500)
SEAR	10.3 (8.06, 14.3)	*-4.71* (*-15.2*, 2.57)	8.01 (4.96, 14.0)	1380 (671, 2370)	cost-saving (cost-saving, 483)
WPR	9.95 (6.68, 17.1)	3.51 (*-2.09*, 11.5)	1.66 (1.08, 2.99)	6430 (2820, 12300)	2480 (cost-saving, 8390)

[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

S39. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of infant tuberculosis vaccines: lifelong duration of protection scenario.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	5.80 (4.65, 8.18)	*-47.8* (*-55.2*, *-40.8*)	27.5 (23.9, 31.6)	212 (162, 306)	cost-saving[c]
High-TB burden[d]	3.83 (3.10, 5.39)	*-47.0* (*-54.4*, *-40.1*)	25.4 (21.8, 29.6)	151 (115, 218)	cost-saving[c]
High-TB/HIV burden[d]	2.68 (2.18, 3.71)	*-41.1* (*-48.4*, *-34.6*)	22.3 (18.8, 26.3)	121 (92.3, 172)	cost-saving[c]
High-MDR/RR-TB burden[d]	3.35 (2.69, 4.77)	*-44.2* (*-51.3*, *-37.4*)	22.5 (19.0, 26.6)	150 (113, 223)	cost-saving[c]
Income level[e]					
LIC	0.87 (0.75, 1.13)	*-0.97* (*-1.32*, *-0.63*)	3.04 (2.55, 3.66)	289 (222, 385)	cost-saving[c]
LMIC	2.93 (2.38, 4.01)	*-38.2* (*-45.3*, *-32.1*)	22.7 (19.2, 26.8)	130 (98.9, 185)	cost-saving[c]
UMIC	2.00 (1.49, 3.23)	*-8.57* (*-11.8*, *-6.15*)	1.78 (1.35, 2.40)	1150 (713, 1900)	cost-saving[c]
World region					

AFR	1.84 (1.55, 2.42)	*-22.3* (*-27.6*, *-17.8*)	14.3 (11.8, 17.1)	130 (97.7, 180)	cost-saving[c]
AMR	0.54 (0.40, 0.84)	*-0.08* (*-0.26*, 0.23)	0.10 (0.08, 0.12)	5440 (3810, 8540)	cost-saving (cost-saving, 2460)
EMR	0.80 (0.64, 1.09)	*-1.61* (*-2.55*, *-0.82*)	2.48 (1.74, 3.39)	331 (211, 513)	cost-saving[c]
EUR	0.33 (0.23, 0.57)	*-0.02* (*-0.13*, 0.21)	0.06 (0.05, 0.07)	5700 (3800, 9710)	cost-saving (cost-saving, 3670)
SEAR	1.16 (0.92, 1.65)	*-16.4* (*-20.9*, *-12.6*)	8.38 (6.33, 11.1)	142 (94.8, 221)	cost-saving[c]
WPR	1.13 (0.86, 1.79)	*-7.44* (*-9.95*, *-5.46*)	2.20 (1.62, 2.98)	527 (332, 874)	cost-saving[c]

[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

S40. Discounted costs, disability-adjusted life-years (DALYs) averted, and cost-effectiveness of adolescent/adult tuberculosis vaccines: lifelong duration of protection scenario.

Country grouping	Health system perspective[a] incremental cost (USD billions)	Societal perspective[b] incremental cost (USD billions)	DALYs averted (millions)	Health system cost (USD) per DALY averted	Societal cost (USD) per DALY averted
All countries	20.9 (15.1, 32.7)	*-159* (*-177*, *-141*)	94.8 (86.7, 103)	221 (155, 341)	cost-saving[c]
High-TB burden[d]	14.7 (10.3, 23.3)	*-153* (*-170*, *-135*)	86.6 (78.6, 95.5)	170 (116, 265)	cost-saving[c]
High-TB/HIV burden[d]	8.82 (6.21, 13.2)	*-138* (*-154*, *-122*)	77.3 (69.8, 85.6)	114 (78.0, 173)	cost-saving[c]
High-MDR/RR-TB burden[d]	13.4 (9.2, 21.6)	*-143* (*-160*, *-127*)	76.9 (69.1, 85.3)	174 (114, 279)	cost-saving[c]
Income level[e]					
LIC	2.35 (1.86, 3.17)	*-3.40* (*-4.32*, *-2.38*)	9.51 (8.36, 10.7)	248 (188, 341)	cost-saving[c]
LMIC	9.58 (6.89, 14.1)	*-126* (*-140*, *-112*)	78.0 (70.5, 86.0)	123 (85.9, 183)	cost-saving[c]
UMIC	9.00 (5.76, 16.2)	*-30.4* (*-39.6*, *-20.3*)	7.31 (5.96, 9.14)	1250 (736, 2400)	cost-saving[c]
World region					
AFR	4.25 (3.31, 5.74)	*-60.0* (*-70.8*, *-51.1*)	39.8 (35.6, 44.0)	107 (81.6, 151)	cost-saving[c]
AMR	2.30 (1.54, 3.96)	*-1.45* (*-2.38*, 0.33)	0.71 (0.63, 0.79)	3270 (2150, 5650)	cost-saving (cost-saving, 477)

EMR	2.44 (1.88, 3.43)	*-4.01* (*-5.76*, *-2.41*)	6.72 (5.31, 8.39)	368 (253, 547)	cost-saving[c]
EUR	1.18 (0.77, 2.07)	*-1.36* (*-1.89*, *-0.42*)	0.49 (0.43, 0.54)	2440 (1570, 4400)	cost-saving[c]
SEAR	5.05 (3.48, 7.66)	*-74.2* (*-85.3*, *-63.1*)	40.7 (34.8, 47.2)	125 (80.0, 192)	cost-saving[c]
WPR	5.70 (3.60, 10.3)	*-18.4* (*-21.9*, *-13.5*)	6.41 (5.55, 7.37)	892 (553, 1630)	cost-saving[c]

[a] Costs from the health system perspective include vaccination costs, tuberculosis testing and treatment costs, and antiretroviral treatment costs.
[b] Costs from the societal perspective include health system perspective costs, as well as patient non-medical costs and productivity losses.
[c] Both the point estimate and the interval estimates were cost-saving.
[d] High-TB, high-TB/HIV (HIV-associated TB), and high-MDR/RR-TB (multidrug/rifampicin-resistant TB) burden countries as defined by the World Health Organization.[1]
[e] LIC: Gross national income (GNI) per capita of $1,025 or less; LMIC: GNI per capita of $1,026 to $3,995; UMIC: GNI per capita of $3,996 to $12,375 (World Bank 2019).
Note: All countries include 105 low- and middle-income countries analyzed. Values in parentheses represent equal-tailed 95% credible intervals. AFR = African region; AMR = Region of the Americas; EMR = Eastern Mediterranean region; EUR = European region; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

References

1. World Health Organization. WHO releases new global lists of high-burden countries for TB, HIV-associated TB and drug-resistant TB. Last updated: 17 June 2021. [Online] Accessed 1 July 2021. Available at: https://www.who.int/news/item/17-06-2021-who-releases-new-global-lists-of-high-burden-countries-for-tb-hiv-associated-tb-and-drug-resistant-tb.

Manuscript title:

The Full Value of Vaccine Assessments (FVVA): a framework to assess and communicate the value of vaccines for investment and introduction decision making

Author names:
Raymond C.W. Hutubessy[1*], PhD, Jeremy A. Lauer[2], PhD, Birgitte Giersing[1], PhD, So Yoon Sim,[1] MA, MSPH, Mark Jit[3,4,5], PhD, David C. Kaslow[6] ,MD. Siobhan Botwright[1] BA.

Author affiliations:
1. Department of Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland.
2. Department of Management Science, Strathclyde Business School, 199 Cathedral Street Glasgow, University of Strathclyde, Glasgow, UK.
3. London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK.
4. Modelling and Economics Unit, National Infections Service, Public Health England, London, UK.
5. School of Public Health, University of Hong Kong, Hong Kong, SAR, China.
6. Essential Medicines, PATH, Seattle, Washington, USA.

*** Corresponding author:**

Raymond C.W. Hutubessy, PhD
Value of Vaccines, Modeling and Economics
Department of Immunization, Vaccines and Biologicals
World Health Organization
Avenue Appia 20
CH-1211 Geneva 27, Switzerland
Mobile: +41227913253
Email: hutubessyr@who.int

Acknowledgements:
Geordan D. Shannon and Alec Morton acknowledged for helpful discussions. The views expressed are those of the authors and do not necessarily represent the views of their respective Organizations.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

Financing disclosure/funding statement:
None reported

Conflict of interest:
All authors declare no conflicts of interest in relation to this article.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

Abstract

Objectives
The optimal development, use and impact of vaccines can be hindered by a number of seemingly distinct, but interrelated obstacles, which need to be addressed with a single over-arching strategy encompassing all stakeholders.

Methods
We propose a framework on the Full Value of Vaccines Assessments (FVVA) to guide the assessment and communication of the value of vaccines, to facilitate alignment among key stakeholders, and to improve decision-making around investment in vaccine development, policy, procurement, and introduction, for vaccines intended for use in LMICs.

Results
The framework outlines three functions of FVVA that will facilitate the achievement of afore-mentioned objectives. First, existing methods and tools need to be adapted to include broader benefits of vaccines as well as opportunity costs borne by stakeholders (assessment). Second, the increasing focus on the agency of stakeholders and country ownership of decision-making and priority setting should be reflected in the deliberative FVVA process to ensure introduction, equitable vaccine access and coverage, and sustainable impact (decision making). Finally, FVVAs should facilitate communication about the full value of vaccines and enhance alignment and coordination across diverse stakeholders (communication).

Conclusions
The framework on FVVA serves to guide stakeholders in organizing global-level efforts to invest in vaccines that are priorities for LMICs, and overcome hurdles to expand sustainable and equitable impacts of vaccines and immunization programs.

Keywords
Vaccine, vaccination, immunization, research and development, decision making, priority setting, economic evaluations, health technology assessment, low and middle income countries.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

Manuscript text:

Problem statement *(Introduction)*

The optimal development, use, and impact of vaccines is hindered by a number of interrelated obstacles. While most of these obstacles are not new, many of them have been brought to the forefront of public debates around the urgent need to develop and deploy a safe, effective and affordable vaccine for COVID-19. Piot et al (2019) identify four major hurdles, or gaps, on the road to achieving population level vaccine impact: first, one between discovery and early clinical development (specifically, proof-of-clinical concept), also known as the translation gap; second, one between early development and licensure, sometimes referred to as the 2nd valley of death; third, one between licensure and subsequent introduction; and, fourth, one between scale-up of implementation and ensuring sustainable and equitable impact of immunization programs (Figure 1).[1] While these hurdles represent seemingly distinct problems faced by different stakeholders along the vaccine value chain, they are in fact components of a single over-arching strategy that need to be integrated from vaccine development through licensure, policy, introduction and sustainable use. Yet failure to consider these obstacles in a holistic way has hindered comprehensive progress and impact with vaccines, particularly in LMICs, but increasingly in other settings as well. Recent examples include vaccines for hepatitis E, tuberculosis, and group A streptococcus, each of which incurred one or more of the four major hurdles in the vaccine value chain.

Coordination and communication across multiple stakeholders can be enhanced through mechanisms for the integration of diverse sets of information and the harmonization of divergent incentives. Efforts so far typically have been categorized in terms of 'pull' and 'push' mechanisms.[2] In addition to financial 'pull' mechanisms, in the form of advanced market commitments, market guarantees or prize systems, the practice of providing systematic information on demand preferences or desired product characteristics has also helped to incentivize manufacturers and reduce the uncertainties in the development of products suitable for use in public immunization programmes in low- and middle-income countries (LMICs). WHO's Preferred Product Characteristics (PPC) and Target Product Profiles (TPP) describe the desired product attributes for vaccines to be used in LMICs, and are two examples of guidance that aims to address the translation gap by articulating the preferences of end-users or their agents, such as purchasers, insurers and donors in LMICs, although these do not usually take into account policy and economic considerations.[3] Another example of demand-preference signaling takes the form of official reference cases published by consumer representatives, such as Health Technology Assessment (HTA) Institutions,[4] which are usually conducted subsequent to vaccine licensure, in particular in LMICs. Alternatively, 'push' mechanisms in the form of financial incentives, such as grants, subsidies, co-financing arrangements, product-development partnerships, or in the form of technical assistance for country plan development, partner-coordination mechanisms, and social mobilization, have also helped stakeholders to reduce risks and share costs, thereby facilitating the development and uptake of vaccines.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

While these kinds of mechanism have improved coordination across stakeholders, there is a great diversity in approaches that countries take towards assessing the value of vaccines. WHO guidelines around economic evaluation of vaccines advocate that such assessments should consider broad population-level effects of vaccines (such as herd protection, reduction of antimicrobial resistance (AMR) and serotype replacement), as well as the effects that vaccines can have on long-term human capital development (figure 2b).[5] In addition, while many countries only consider 'narrow' benefits such as gains in health, reduced health-care costs, and increased care-related productivity,[6] others increasingly assess and quantify the broader benefits of vaccination by taking into consideration effects such as herd protection, educational outcomes, equity, financial and programme synergies, public-sector-budget impact, and macroeconomic consequences.[7] The broader approach implies a paradigm shift to account for such benefits in discussions on commercial, regulatory and implementation policy.[8] However, to facilitate this quantitative assessment of broader benefits there is a need for greater standardization both between countries and also between disease areas to facilitate international and cross-disease comparisons.

In addition to such benefits, the 'narrow' approach holds that costs are important, since economic theory proposes that social value can be defined as individuals' collective willingness to pay for benefits realized by individuals. On the basis of microeconomic principles, moreover, these benefits should be compared with "the opportunity cost of resources used to produce the improvement".[9] The broader approach is also based on opportunity costs, but goes beyond individual willingness to pay, to implicitly argue that a still more inclusive perspective to such costs are needed, one that goes beyond the perspective that many countries take in focusing solely on individual-level benefits, namely, one that considers also system-level emergent and ecological effects.[9] Thus, adopting a comprehensive framework that both takes an end-to-end view of the vaccine development-to-uptake continuum and accounts for the broader benefits of vaccines (Figure 1) should structure dialogue between stakeholders and foster coordination that lower the major hurdles and result in more sustainable and equitable vaccine development and introduction.

Solution *(Method)*

To this end, we propose here a framework for considering the Full Value of Vaccine Assessments (FVVA) to guide the assessment and communication of the value of vaccines and to facilitate alignment among key stakeholders. Such a framework would inform decision-making related to investment in vaccine development intended for use in LMICs, as well as country-level decision making related to introduction, especially in LMICs, by enabling greater cross-country and cross-disease comparability. The framework that is building on seminal publications and events that took place over the last decade (see Annex 1) introduces two concepts.

First, we argue that a number of adaptations are required in the individualist, welfarist methods of assessment that are still used in many countries to account for the evidence on broader impact. Second, we argue that the full value of vaccines derives not only from the results of assessments of benefits and costs (whether welfarist or broader in scope) but also rests on the robustness of the decision-making process itself. In other words, the assessment of the full value of vaccines must

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

take into account the agency and autonomy of end-users, or their representatives, as one of its primary guiding principles and not merely tacked on as an afterthought.[10] We observe that, too often, HTA decisions and processes in LMICs have been donor driven, explaining the prevalent focus on quantifying (donor) value for money and/or return on (donor) investments.[11,12] In contrast, the framework here aims to provide guiding principles that can promote country ownership of decision-making and priority setting. It is intended to address comprehensively, therefore, not only the hurdles hindering development, licensure, and introduction, but also those hindering equitable access and desired coverage required to achieve and sustain optimal population-level impact described in the Sustainable Development Goals (SDGs) and Immunization Agenda 2030 (IA2030). Consequently, FVVAs should not only facilitate communication about the full value of vaccines and enhance alignment and coordination across diverse stakeholders but also engage end-users or their representatives in a meaningful process focused on the co-creation of healthier lives for all and "leaving no one behind". In doing so, the framework will better integrate LMICs preferences and needs, while increasing the likelihood of achieving global goals for health and well-being. As a final preliminary remark, we demonstrate below that value propositions, investment cases, and business cases can all be seen as derivative use cases of FVVAs.

Two streams in Enlightenment ethics—which following convention we label here as consequentialism and proceduralism— have dominated discussions around assessment of health interventions, including immunisation programmes. Both are embodied in the FVVA framework. Consequentialism is "a philosophical view that actions should be judged by their outcomes, or consequences," based on which causal modeling can "capture and organize knowledge about states of the world in ways that are relevant to decision-making."[10] This is the view that primarily motivates both what we have called the narrow and broader approaches. On the other hand, proceduralism is "a rules-based conception of decision-making according to which decisions are only partially (if at all) justified with reference to the goals stakeholders may have regarding outcomes, but where it is held that descriptive modelling (e.g. 'deliberative discourse') should structure and make explicit the reasons for actors' preferred decisions, establishing the possibility of 'accountability for reasonableness.'"[10] This latter is the view motivating an increased attention on the decision-making process itself. These two views have typically been seen as mutually exclusive or even contradictory. However, modern commentators have argued that both are important components of just health policy and governance.[13] There is also a need to incorporate ethical systems that are not rooted mainly in Enlightenment thought, with its focus on the individual. This includes incorporating concerns in non-Western ethical systems such as communitarian values and relationships.

We assert that they can be harmonized, and that best-practice HTA and other initiatives that we discuss below provide the broad outlines of how to incorporate both ethical views in FVVAs. Specifically, in this paper we argue that (1) consequentialist frameworks should take a broader perspective and (2) that proceduralism must be integrated with consequentialist approaches, especially to ensure successful coordination and alignment of diverse stakeholders.

(Results)

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

Assessment: need to adapt existing methods and tools

To estimate the broader benefits of vaccination, existing methods and tools need to be adapted to include additional types of benefit for which empirical evidence has become available in recent years, as well as novel concepts of value that incorporate risk, uncertainty, and/or equity (e.g. financial risk protection provided by vaccination[14]). Figure 2a is a simple graphical metaphor of the added dimension of FVVAs in relation to PPCs and TPPs, which tend to focus more on direct, individual-level benefits as well as risks and costs. Our claim is that technologies cannot fully express characteristics that are valuable to stakeholders when this additional dimension (called here for illustration purposes "global health value") is ignored or underestimated by stakeholders and decision-makers. Similarly, Figure 2b demonstrates the narrower focus of TPPs, PPCs, economic evaluations, and HTA in relation to their potential scope. Appraisal of the evidence demonstrates that there is also a need for more experimental and observational studies to enhance the evidence base for the benefits of vaccination[7] broader than those included in existing conceptual frameworks.[6,15,16] Gessner et al. called for an inventory of evidence and the annual monitoring of progress on completeness.[8] Efforts to address this include the Value of Vaccination Research Network (VoVRN) which supports research that focuses on pathways, models, estimates and data needed to expand the evidence base and brings together interested stakeholders.[17]

Lauer et al. (2020) argue that a critical ontology of consequentialist economic evaluations can be articulated through the simple categorization of inputs and outcomes, as well as their associated costs, into market-traded and non-market-traded inputs and outcomes, on the one hand, and market or non-market prices, on the other.[10] Such an accounting framework serves as a theoretically grounded representation of methodological choices; however, it can be also mapped in terms of the usual names employed for diverse types of economic evaluations.[10] Moreover, the accounting framework explicitly disentangles inputs and outcomes from their respective prices, thereby making transparent the value judgements informing monetized summary indicators of benefits and/or costs.[10]

There are a number of existing guidelines for assessment methods as listed in Table 1. The FVVA framework, relying on the work of Lauer et al. (2020), provides a set of organizing principles for the consideration and selection of assessment approaches. Methodological and technical details belonging to the various approaches should be based on the recommendations of existing guidelines.

In all economic evaluations, stakeholders and decision contexts are important since they drive the choice of inputs, outcomes and assessment methods. It is important to identify the policy, business question or decision context that is relevant to each stakeholder (Table 1). The factors drive the choice of assessment methods, by use of which outcomes of vaccination are compared against distinct types of costs (market-traded and non-market-traded inputs) borne by each stakeholder. While it is possible to adopt a so-called societal perspective to describe expected benefits and costs regardless of incidence,[18] usually only the inputs and outcomes for vaccines and immunization programs that are relevant to the stakeholder concerned should be selected when a decision involves a resource constraint binding on that specific stakeholder.[9]

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

Decision making process: focus on the agency of stakeholders

Investment decisions need to draw from both consequentialist and proceduralist framework. In LMICs, economic evaluations of vaccines are often donor driven, and when so, decisions are usually rooted exclusively in consequentialism. Proceduralism, on the other hand, is based on a concern about the rules of action of autonomous agents. At a fundamental level, the primary value embraced in proceduralism is the agency itself of individuals.[10] In proceduralism, in other words, the means might be considered as more important than the ends, whereas the reverse is the case for consequentialism.

Multi-criteria decision analysis (MCDA) is one example of a decision-making method that is both proceduralist and consequentialist.[19] Deliberative processes, along with either a qualitative or quantitative MCDA framework, have provided additional advantages, such as enhanced consensus building, the revelation of evidence gaps, and the increased likelihood of acceptance and implementation of decisions.[20] Global-level prioritization processes such as Gavi's Vaccine Investment Strategy,[21] the Vaccine Innovation Prioritisation Strategy[22] or WHO's Value Attribution Framework for vaccines against AMR,[23] take a qualitative approach to MCDA and rely mainly on an evidence-informed deliberative process conducted by global decision makers and domain-specific experts.

A deliberative process is also a critical component of Health Technology Assessment (HTA), and forms part of the contextualization of evidence,[24] based on transparent, accountable and evidence-informed political and social judgement at the local level[25]. The importance of participatory dialogue is also emphasized in the WHO '3Ds' approach (Data, Dialogue and Decision) to priority setting for Universal Health Coverage.[26]

The importance of incorporating a proceduralist approach was highlighted during development of the WHO Country-led Assessment for Prioritisation on Immunisation (CAPACITI) project.[27] CAPACITI evolved from Total Systems Effectiveness (TSE), a consequentialist framework aimed at optimizing the trade-offs between defined benefit and cost criteria through a quantitative MCDA model. The overall goal of the project was to support immunisation programmes to prioritise among existing vaccine products, and to communicate preferences and priorities for vaccine innovations still under development. Through iterative piloting and consultations across twelve LMICs, the primary gap for decision-making was not an outcomes-based framework to structure decisions, but instead a process-based framework that supports the articulation of different stakeholder perspectives and allows national and regional committees to come to a consensus on priority immunisation products, strategies and services, both now and in future.[28,29] For immunisation programmes, the proceduralist approach allows incorporation of national and local values and programme context for country-owned decisions; f, tor research and development, a focus on the deliberative process allows LMICs to communicate a consensus view to product developers, strengthening the business case for investment. The country ownership of decision-making contributes to ensuring introduction, equitable vaccine access and coverage, and sustainable impact for Immunization Agenda 2030.[30]

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

Communication: using FVVAs for value propositions, investment cases and business cases

Both consequentialist and proceduralist approaches adopt the perspective of specific stakeholders or decision makers. An unaddressed question is: how do we facilitate dialogue *across* stakeholders that focus on different parts of the vaccine value chain, to overcome hurdles to maximize the impact of vaccines?

There is a growing number of so-called "value propositions", "investment cases", or "business cases" in the field of vaccines and immunization programs.[31] The Full Public Health Value Propositions for Vaccines (FPVHP), the predecessor of the FVVA framework, was among the first global proposals to attempt to harmonize such work through development of a comprehensive framework that outlines the components of evidence needed to describe the full value of vaccines, with the goal of incentivizing vaccine development for LMIC markets. The concept was presented to WHO's Strategic Advisory Group of Experts (SAGE) on Immunization in 2018, and development of the approach was encouraged with strong consideration and representation of the end-user (country) perspective.[32,33] Value propositions, investment cases, and business cases all are designed to facilitate the identification of data needed for decisions at each stage of development and, through strategic alignment tools such as PPCs and TPPs, the generation of relevant evidence from clinical trials, implementation and market studies to guide funding and policy decisions as well as risk assessment.[34] They are intended to engage and align stakeholders more effectively along the continuum towards implementation.

A model that explicitly embeds stakeholders in the decision-making process, such as CAPACITI, will further enhance global dialogue. While the eventual creation of a feedback loop from end-users to R&D stakeholders is reflective of the 'pull' mechanism mentioned above, CAPACITI's approach is intended to enable countries to articulate value propositions specific to local contexts and to communicate their needs in a more formalized, iterative process.

While the stated objectives of value propositions, investment cases, and business cases are typically to provide information for decision-making, in fact, they have other, often unstated, objectives, including advocacy to convince a specific target audience to undertake a course of action (e.g., to invest in the development of vaccines). In practice, this advocacy function can become untethered from the requirements of scientific objectivity or even of the evidence considered. Assessments and decision aids intended to promote optimal outcomes both within and beyond the health sector should be by design unconstrained by this advocacy function, though as we have seen they can contain other biases. To mitigate these risks, the remit of the FVVA should always be aligned with the standard reference cases so as to avoid the appearance of "special pleading" for particular vaccines and to avoid explicit or hidden donor-driven agendas that are not aligned with country needs.[35,36] While outcomes from FVVA-based approaches can be synthesized to support the development of value propositions, investment cases, and business cases for vaccines, the interpretation of the arguments and their application to a decision context will ultimately be at the discretion of the target audience. Comparing multiple arguments from different stakeholders can provide insights on how incentives might be aligned and where and when mediation should happen, although such appraisals require strong technical capacity on the part of the decision-maker. The FVVA framework elucidates the aspects relevant to communication about

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

the value of vaccines separately from the assessment of value and the priority-setting process so that the latter can be aligned with standard practices and broader global health goals, such as SDGs and IA2030, in support of achieving Universal Health Coverage.

Within the CAPACITI project, the FVVA approach has been welcomed by immunisation programme stakeholders as a means to incorporate a broad range of considerations into decision-making beyond criteria like safety, efficacy, disease burden and cost-effectiveness, including supply availability, government liability, local manufacture, and duration of fixed pricing agreements. The combination of both consequentialist and proceduralist approach allowed Indonesia to convene discussions between the national immunisation technical advisory group (NITAG), national immunisation programme, and Ministry of Health planning department on joint priorities for new vaccine introduction, strengthening strategic planning.[37] In Mali, it allowed the NITAG to demonstrate a rigorous process for vaccine product choice that had been driven by national level experts.[38] Above all, CAPACITI pilots illustrated the importance of complementing data collection and analysis with a robust process for stakeholder dialogue. For successful implementation, such processes for evidence-informed decision-making will need to be institutionalized within national decision-making, underpinned by strong legal frameworks.

(Discussion)

The Full of Value of Vaccines Assessment Framework and COVID-19 vaccines

The implications of the FVVA concept for the development and implementation of vaccines for COVID-19 can be illustrated by addressing the extent to which (1) the broader assessment has been applied, (2) stakeholder dialogue has been considered, and (3) coordination across stakeholders has occurred.

(1) Broader assessment of COVID-19 vaccines

Activities on the pathway to vaccine development, implementation, and impact are being de-risked by financial commitments and incentives and coordinated expeditiously by global stakeholders, through initiatives such as the COVAX facility as part of the Access to COVID-19 Tools (ACT) Accelerator.[39] There thus seems to be a consensus on the part of virtually all stakeholders regarding the need, if not the means, to capture the full value of COVID-19 vaccine candidates, and the typical vaccine hurdles are therefore being effectively addressed. Specifically by considering investments as an economic impetus to get society "back to normal"[40] has resulted in an unprecedented number of candidates in development since the sequencing of the SARS-CoV-2 genome in beginning of 2020, with over 250 candidate antigens being developed, nearly 200 in early clinical trials and over 80 in late-stage development.[41] Many of these candidate vaccines are based on novel methods of antigen presentation, manufacturing, or delivery, which could be a major catalyst for the accelerated development and access of vaccines or technologies for other pathogens. It seems to us that if the lessons concerning the need for a robust infrastructure supporting vaccine development can be capitalized going forward, then that infrastructure will be an unequivocal win for the full value of vaccines.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

(2) Stakeholder dialogue

Vaccines, like other health interventions, have their opponents as well as proponents, and decisions that might be made for the sake of an emergency response taken *purely on welfarist grounds* can have permanent implications if adverse consequences, real or perceived, lead to loss of confidence in vaccines or health decision makers. This can clearly have durable long-term negative consequences for the full value of vaccines. Given the levels of resistance that have been witnessed to non-pharmaceutical interventions (NPIs) in some settings,[42] active resistance to vaccines for COVID-19 seems likely regardless of the empirically derived risk-benefit profiles. As we argue here in the general case, likewise in the case of COVID-19 vaccines, it will also be *at least as important* to include the views of end-users and their representatives in a participatory decision-making process regarding implementation as well as tackling the scientific, manufacturing, regulatory, policy, financing, and logistical problems associated with immunization against COVID-19. In light of the unprecedented emergency, however, such efforts should likewise be undertaken in an integrated fashion, and prospectively, rather than only at the point when decisions need to be made about the introduction of vaccines for COVID-19. Failing this, the second through fourth vaccine hurdles are likely to prove daunting to address for COVID-19 vaccines.

(3) Coordination across stakeholders

Now that the first COVID-19 vaccines have received regulatory approval and policy recommendations for their widespread use, there is the issue of how equitable access can be assured both between and within countries.[43] A technocratic approach to allocation needs to be integrated with participatory decision-making processes that incorporate technical, ethical, legal, regulatory, and policy perspectives to facilitate global dialogue on fair and equitable allocation of vaccines.[44] These processes should be based on both consequentialist and proceduralist principles and should be initiated concurrently with the ongoing development of COVID-19 vaccines. Strategic alignment tools to assist include Preferred Product Characteristics/Target Product Profiles, strategic R&D Roadmaps, integrated product development plans and Preferred Policy Profiles/Target Policy Profiles. All of these take into consideration the different perspectives of stakeholders, as well as the different decision-making criteria along the product development-policy-financing continuum.

Conclusion

The FVVA framework represents a set of coherent, organizing principles guiding the adoption of consequentialist tools while putting the autonomy and agency of stakeholders at the center of decision-making. In addition, FVVAs facilitate the determination of and communication about the full value of vaccines, addressing information gaps and enhancing coordination across stakeholders. Global-level efforts can be organized based on these three functions—assessment, stakeholder alignment and decision-making, and communication—of the FVVA framework with the clear objective of overcoming hurdles to expand sustainable and equitable impacts of vaccines and immunization programs.

(Word count: 3732)

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

References

1. Piot P, Larson HJ, O'Brien KL, et al. Immunization: vital progress, unfinished agenda. *Nature*. 2019;575(7781):119-129. doi:10.1038/s41586-019-1656-7
2. Wynia* MK. Markets and Public Health: Pushing and Pulling Vaccines into Production. *Am J Bioeth*. 2006;6(3):3-6. doi:10.1080/15265160600781504
3. World Health Organization. WHO's Preferred Product Characteristics (PPCs) and Target Product Profiles (TPPs).
4. Wilkinson T, Sculpher MJ, Claxton K, et al. The International Decision Support Initiative Reference Case for Economic Evaluation: An Aid to Thought. *Value Heal*. 2016;19(8):921-928. doi:https://doi.org/10.1016/j.jval.2016.04.015
5. World Health Organization, ed. *WHO Guide for Standardization of Economic Evaluations of Immunization Programmes, 2nd Edition.* Licence: C. Geneva; 2019.
6. Bärnighausen T, Bloom DE, Canning D, et al. Rethinking the benefits and costs of childhood vaccination: The example of the Haemophilus influenzae type b vaccine. *Vaccine*. 2011;29(13):2371-2380. doi:https://doi.org/10.1016/j.vaccine.2010.11.090
7. Jit M, Hutubessy R, Png ME, et al. The broader economic impact of vaccination: reviewing and appraising the strength of evidence. *BMC Med*. 2015;13(1):209. doi:10.1186/s12916-015-0446-9
8. Gessner BD, Kaslow D, Louis J, et al. Estimating the full public health value of vaccination. *Vaccine*. 2017;35(46):6255-6263. doi:https://doi.org/10.1016/j.vaccine.2017.09.048
9. Garrison LP, Pauly M V, Willke RJ, Neumann PJ. An Overview of Value, Perspective, and Decision Context—A Health Economics Approach: An ISPOR Special Task Force Report [2]. *Value Heal*. 2018;21(2):124-130. doi:https://doi.org/10.1016/j.jval.2017.12.006
10. Lauer, JA; Morton, A; Culyer, AJ; Chalkidou K. *What Counts in Economic Evaluations in Health? Benefit-Cost Analysis Compared to Other Forms of Economic Evaluations. (Health Systems Financing and Governance, Working Paper No. 14).* Geneva; 2020.
11. O'Brien N, Li R, Isaranuwatchai W, et al. How can we make better health decisions a Best Buy for all?: Commentary based on discussions at iDSI roundtable on 2 (nd) May 2019 London, UK. *Gates open Res*. 2019;3:1543. doi:10.12688/gatesopenres.13063.2
12. Haakenstad A, Birger M, Singh L, et al. Vaccine Assistance To Low- And Middle-Income Countries Increased To $3.6 Billion In 2014. *Health Aff (Millwood)*. 2016;35(2):242-249. doi:10.1377/hlthaff.2015.1080
13. Ruger JP. Global health justice and governance. *Am J Bioeth*. 2012;12(12):35-54. doi:10.1080/15265161.2012.733060
14. Verguet S, Kim JJ, Jamison DT. Extended Cost-Effectiveness Analysis for Health Policy Assessment: A Tutorial. *Pharmacoeconomics*. 2016;34(9):913-923. doi:10.1007/s40273-016-0414-z
15. Deogaonkar R, Hutubessy R, van der Putten I, Evers S, Jit M. Systematic review of studies evaluating the broader economic impact of vaccination in low and middle income countries. *BMC Public Health*. 2012;12(1):878. doi:10.1186/1471-2458-12-878
16. Ozawa S, Mirelman A, Stack ML, Walker DG, Levine OS. Cost-effectiveness and

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

economic benefits of vaccines in low- and middle-income countries: A systematic review. *Vaccine*. 2012;31(1):96-108. doi:https://doi.org/10.1016/j.vaccine.2012.10.103
17. Value of Vaccination Research network. Value of Vaccination.
18. Carias C, Chesson HW, Grosse SD, et al. Recommendations of the Second Panel on Cost Effectiveness in Health and Medicine: A Reference, Not a Rule Book. *Am J Prev Med*. 2018;54(4):600-602. doi:10.1016/j.amepre.2017.11.013
19. Thokala P, Devlin N, Marsh K, et al. Multiple Criteria Decision Analysis for Health Care Decision Making - An Introduction: Report 1 of the ISPOR MCDA Emerging Good Practices Task Force. *Value Heal*. 2016;19(1):1-13. doi:10.1016/j.jval.2015.12.003
20. Culyer, J, Lomas J. Deliberative processes and evidence-informed decision making in healthcare: do they work and how might we know? *Evid Policy A J Res Debate Pract*. 2006;2(3):357-371.
21. Gavi the Vaccine Alliance. Vaccine Investment Strategy.
22. Gavi the Vaccine Alliance. *VIPS- Vaccine Innovation Prioritisation Strategy (Focusing on Vaccine Product Attributes)*. Geneva
23. Hasso-Agopsowicz, Mateusz; Vekemans J. *Vaccines against AMR, Summary of Work and Progress Report*.; 2020.
24. Kristensen FB, Husereau D, Huić M, et al. Identifying the Need for Good Practices in Health Technology Assessment: Summary of the ISPOR HTA Council Working Group Report on Good Practices in HTA. *Value Heal*. 2019;22(1):13-20. doi:https://doi.org/10.1016/j.jval.2018.08.010
25. Chalkidou K, Li R, Culyer AJ, Glassman A, Hofman KJ, Teerawattananon Y. Health Technology Assessment: Global Advocacy and Local Realities; Comment on "Priority Setting for Universal Health Coverage: We Need Evidence-Informed Deliberative Processes, Not Just More Evidence on Cost-Effectiveness." *Int J Heal Policy Manag*. 2017;6(4):233-236. doi:10.15171/ijhpm.2016.118
26. Organization WH. *Strategizing National Health in the 21st Century: A Handbook*. Geneva PP - Geneva: World Health Organization
27. Botwright et al. *Country-Led Assessment for Prioritisation on Immunisation (CAPACITI): A Novel Approach to Support Systematic Decision-Making in Low and Middle Income Country Immunization Programmes*.; 2020.
28. Botwright et al. *Supporting Decision-Making from Product Development to Uptake for Immunisation in Low and Middle Income Countries: The Experience of Total Systems Effectiveness (TSE)*.; 2020.
29. Rattanavipapong W, Kapoor R, Teerawattananon Y, et al. Comparing 3 Approaches for Making Vaccine Adoption Decisions in Thailand. *Int J Heal Policy Manag*. 2020.
30. World Health Organization. Immunization Agenda 2030: a global strategy to leave no one behind - Draft Four.
31. Sim SY, Jit M, Constenla D, Peters DH, Hutubessy RCW. A Scoping Review of Investment Cases for Vaccines and Immunization Programs. *Value Heal*. 2019;22(8):942-952. doi:https://doi.org/10.1016/j.jval.2019.04.002
32. World Health Organization. *Full Public Health Value Propositions for Vaccines: Executive Summary*.; 2018.
33. World Health Organization. WHO full public health value proposition (FPHVP) for vaccines - draft template. 2018.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

34. World Health Organization. *Meeting of the Strategic Advisory Group of Experts on Immunization, April 2018 – Conclusions and Recommendations*.; 2018.
35. Jit M, Hutubessy R. Methodological Challenges to Economic Evaluations of Vaccines: Is a Common Approach Still Possible? *Appl Health Econ Health Policy*. 2016;14(3):245-252. doi:10.1007/s40258-016-0224-7
36. Beutels P, Scuffham PA, MacIntyre CR. Funding of drugs: do vaccines warrant a different approach? *Lancet Infect Dis*. 2008;8(11):727-733. doi:10.1016/S1473-3099(08)70258-5
37. Botwright S, Kahn A-L, Hutubessy R, et al. How can we evaluate the potential of innovative vaccine products and technologies in resource constrained settings? A total systems effectiveness (TSE) approach to decision-making. *Vaccine X*. 2020;6:100078. doi:10.1016/j.jvacx.2020.100078
38. Abdoul Karim, S. Ibrahima D. Total Systems Effectiveness: Experience in Mali. *Wkly Epidemiol Rec*. 2019;94(2019):617-618.
39. World Health Organization. The Access to COVID-19 Tools (ACT) Accelerator. https://www.who.int/initiatives/act-accelerator.
40. Calmak, Cem, Demiralp, Selva, Kalemli-Özcan, Sebnem, Yesiltas, Sevcan, Yidrim MA. *The Economic Case for Global Vaccinations: An Epidemiological Model with International Production Networks*.; 2021. https://iccwbo.org/publication/the-economic-case-for-global-vaccinations/.
41. World Health Organization. Draft landscape and tracker of COVID-19 candidate vaccines. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. Accessed March 24, 2021.
42. World Health Organization. *Calibrating Long-Term Non-Pharmaceutical Interventions for COVID-19: Principles and Facilitation Tools.*
43. Eccleston-Turner M, Upton H. International Collaboration to Ensure Equitable Access to Vaccines for COVID-19: The ACT-Accelerator and the COVAX Facility. *Milbank Q*. March 2021. doi:10.1111/1468-0009.12503
44. UNICEF. COVID-19 Vaccine Market Dashboard. https://www.unicef.org/supply/covid-19-vaccine-market-dashboard. Accessed March 31, 2021.
45. Bärnighausen T, Berkley S, Bhutta ZA, et al. Reassessing the value of vaccines. *Lancet Glob Heal*. 2014;2(5). doi:10.1016/S2214-109X(13)70170-0
46. Deogaonkar R, Hutubessy R, Van Der Putten I, Evers S, Jit M. Systematic review of studies evaluating the broader economic impact of vaccination in low and middle income countries. *BMC Public Health*. 2012;12(1). doi:10.1186/1471-2458-12-878
47. Kaslow DC, Black S, Bloom DE, Datla M, Salisbury D, Rappuoli R. Vaccine candidates for poor nations are going to waste. *Nature*. 2018;564(7736):337-339. doi:10.1038/d41586-018-07758-3
48. Gebreselassie N, Hutubessy R, Vekemans J, den Boon S, Kasaeva T, Zignol M. The case for assessing the full value of new tuberculosis vaccines. *Eur Respir J*. 2020;55(3). doi:10.1183/13993003.02414-2019
49. Organization WH, Baltussen RMPM, Adam T, et al. Making choices in health : WHO guide to cost-effectiveness analysis / edited by T. Tan-Torres Edejer ... [et al].
50. Robinson, Lisa A.; Hammitt, James K.; Cecchini, Michele; Chalkidou, Kalipso; Claxton, Karl; Cropper M, Hoang-Vu Eozenou, Patrick; de Ferranti, David; Deolalikar, Anil B.; Guanais, Frederico; Jamison, Dean T.; Kwon, Soonman; Lauer, Jeremy A.;O'Keeffe,

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

Lucy; Walker, Damian; Whittington, Dale; Wilkinson, Thomas; Wilson, David ; Wong B. *Reference Case Guidelines for Benefit-Cost Analysis in Global Health and Development*.; 2019.

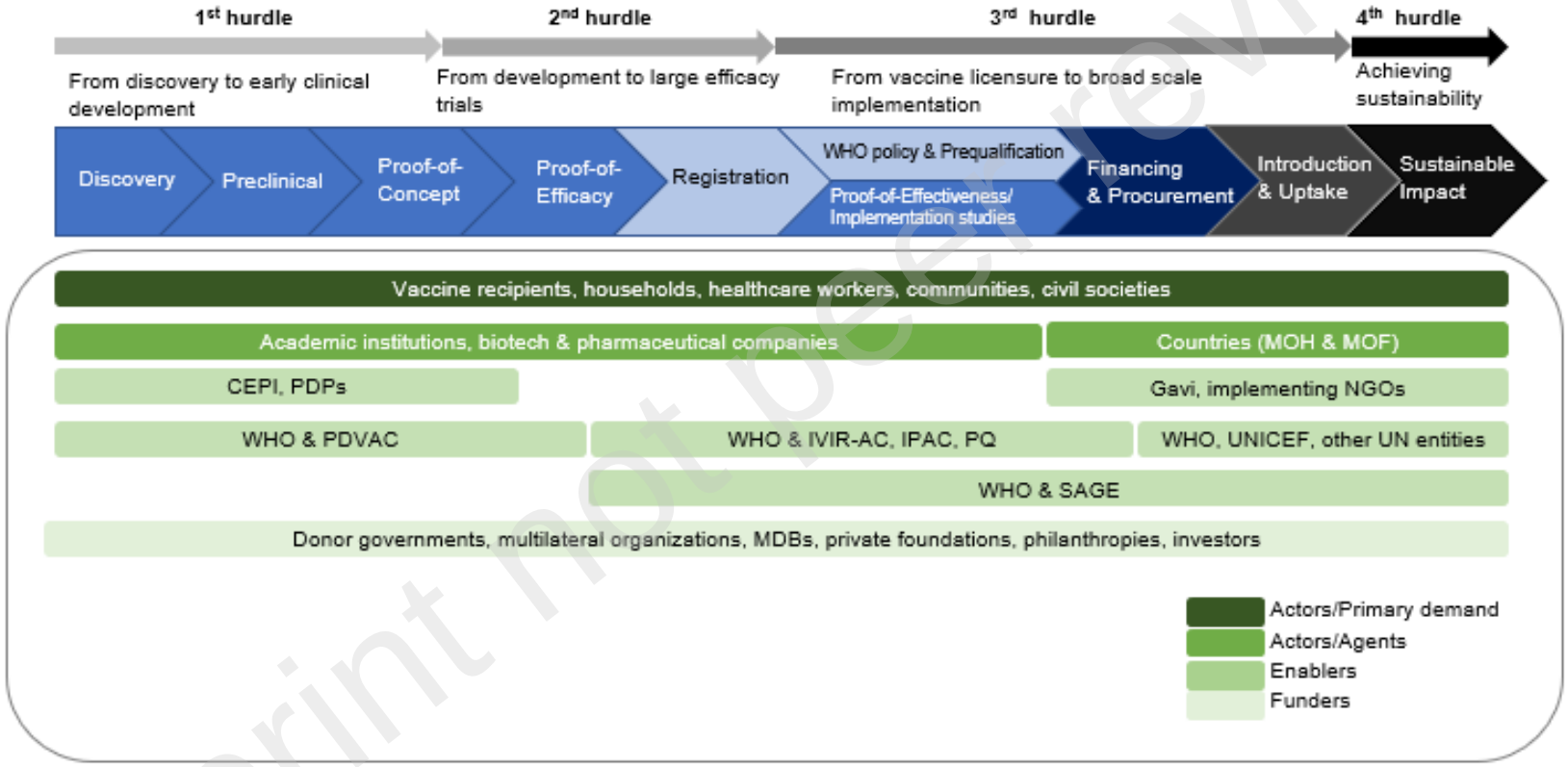
51. Herlihy N, Hutubessy R, Jit M. Current global pricing for human papillomavirus vaccines brings the greatest economic benefits to rich countries. *Health Aff*. 2016;35(2). doi:10.1377/hlthaff.2015.1411
52. Sullivan SD, Mauskopf JA, Augustovski F, et al. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Heal J Int Soc Pharmacoeconomics Outcomes Res*. 2014;17(1):5-14. doi:10.1016/j.jval.2013.08.2291
53. Carvalho N, Jit M, Cox S, Yoong J, Hutubessy RCW. Capturing Budget Impact Considerations Within Economic Evaluations: A Systematic Review of Economic Evaluations of Rotavirus Vaccine in Low- and Middle-Income Countries and a Proposed Assessment Framework. *Pharmacoeconomics*. 2017. doi:10.1007/s40273-017-0569-2

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

Figures and tables

Figure 1. The "full value of vaccines" continuum: pathway, hurdles and stakeholders



Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

CEPI: The Coalition for Epidemic Preparedness Innovations (CEPI)[1]
PDP: Product Development Partnerships (PDPs)
PDVAC: Product Development for Vaccines Advisory Committee[2]
IVIR-AC: Immunization- and Vaccine-related Implementation Research Advisory Committee[3]
IPAC: Immunization Practices Advisory Committee[4]
SAGE: Strategic Advisory Group of Experts on Immunization[5]
MDB: Multilateral Development Bank

[1] https://cepi.net/
[2] https://www.who.int/immunization/research/meetings_workshops/pdvac_2020/en/
[3] https://www.who.int/immunization/research/committees/ivir_ac/en/
[4] https://www.who.int/immunization/programmes_systems/policies_strategies/ipac/en/
[5] https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/members

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

Figure 2. Current approach vs. proposed approach
(Note: Figures need to be updated to be in line with text)

Figure 2a. Addition of global health value

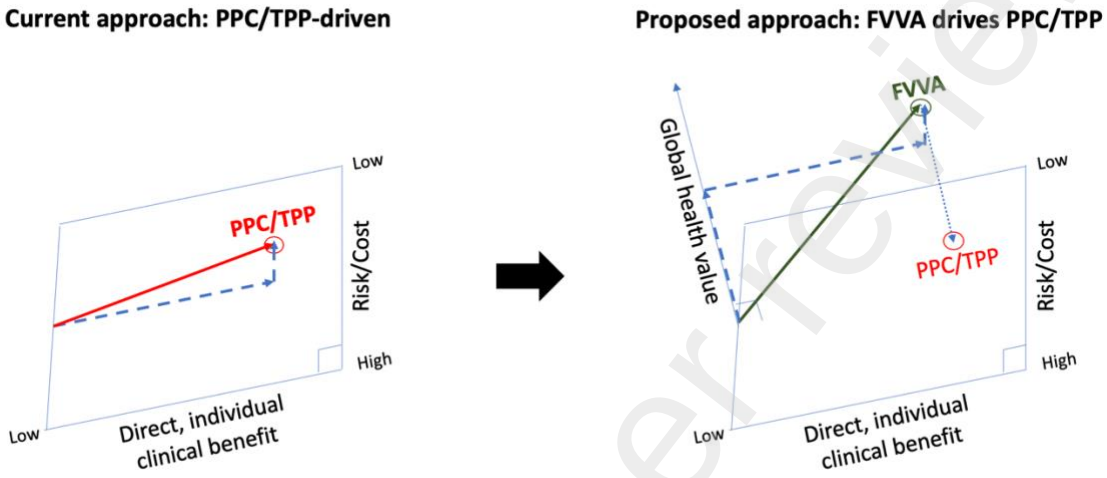
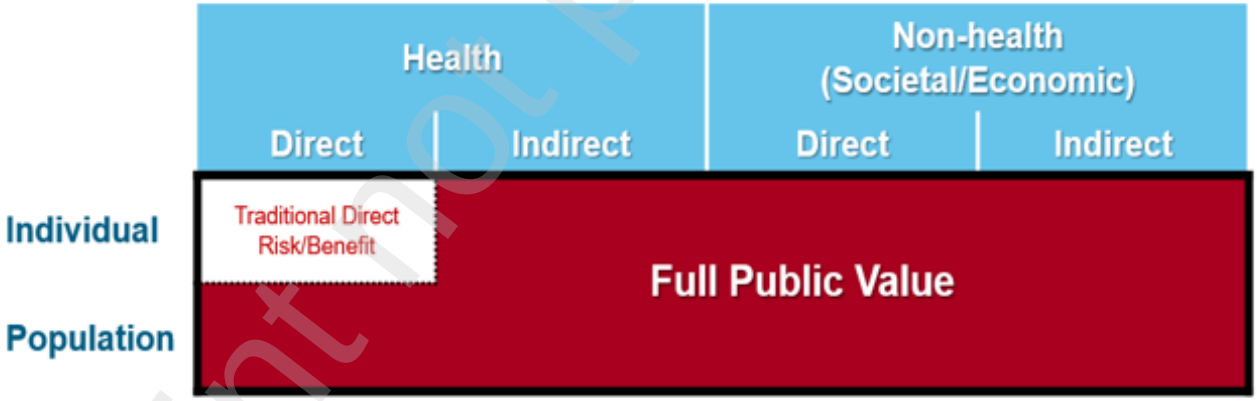


Figure 2b. Traditional direct risk/benefit vs. full public value of vaccines



Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

Table 1. Evidence based assessment methods driven by policy questions and decision contexts

Assessment method	Policy question	Summary measure	Guidelines/examples
Effectiveness study*	How effective is vaccine in improving health outcome?	• Efficacy/effectiveness outcomes • Health outcomes	• FDA GCP/Clinical Trial Guidance documents[6] • Reporting guidelines for main study types[7]
Vaccine impact modeling study*	How effective is vaccine in improving health outcome?	• Children vaccinated/immunized • Cases/deaths averted • QALY gained/DALY averted • Bed days/outpatient visits averted	• ISPOR-SMDM Modeling Good Research Practices Task Force Report[8] • Review articles on mathematical models for epidemiology of infectious diseases[9][10]
Costing study	What is the financial value of resources consumed to develop/introduce a new vaccine?	• Cost per dose; per infant; per fully immunized child	• Consensus statement on vaccine delivery cost[11] • How to cost immunization programs: a practical guide on

[6] Selected FDA GCP/Clinical Trial Guidance Documents. https://www.fda.gov/science-research/guidance-documents-including-information-sheets-and-notices/selected-fda-gcpclinical-trial-guidance-documents

[7] Enhancing the Quality and Transparency of Health Research (Equator) network. https://www.equator-network.org/reporting-guidelines/

[8] Pitman R, Fisman D, Zaric GS, et al. Dynamic Transmission Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group–5. *Medical Decision Making*. 2012;32(5):712-721. doi:10.1177/0272989X12454578

[9] Grassly, N., Fraser, C. Mathematical models of infectious disease transmission. *Nat Rev Microbiol* **6,** 477–487 (2008). https://doi.org/10.1038/nrmicro1845

[10] Jit, M., Brisson, M. Modelling the Epidemiology of Infectious Diseases for Decision Analysis. *Pharmacoeconomics* **29,** 371–386 (2011). https://doi.org/10.2165/11539960-000000000-00000

[11] WHO Consensus statement on vaccine delivery cost (forthcoming)

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

			primary data collection and analysis (EPIC project)[12]
Cost of Illness study (COI)	What is the economic burden that vaccine preventable diseases impose on the society?	• Total direct and indirect cost of a case due to a vaccine preventable disease	• WHO manual for estimating the economic burden of seasonal influenza[13] • Methodological considerations for COI studies of Enteric Fever[14]
Cost-effectiveness analysis (CEA)/Cost-Utility analysis (CUA)	Is a vaccine or immunization program economically justified according to the opportunity cost of health care spending?	• Incremental cost-effectiveness ratio (ICER) using natural units or QALYs, DALYs	• The iDSI Reference Case for Economic Evaluation [15] • Economic analysis of vaccination programs: ISPOR Good practices for Outcomes Research Task Force report[16] • WHO guide to cost-effectiveness analysis[17]
Extended cost-effectiveness analysis (ECEA)	With given cost, what is the effect of a vaccine on financial risk protection, health gains, and averted private expenditures across income quintiles?	• Financial protection afforded by expenditure, distributional aspects of outcomes	• Example: Extended Cost-Effectiveness Analysis for Health Policy Assessment: A Tutorial[18]

[12] Resch SC, Menzies NA, **Portnoy A**, Clarke-Deelder E, Suharlim C, O'Keefe L, Brenzel L. "How to cost immunization programs: A practical guide on primary data collection and analysis." EPIC Project. Immunization Economics Community of Practice. Last updated: 23 December 2020. Available at: http://immunizationeconomics.org/methods

[13] World Health Organization. *WHO Manual for Estimating the Economic Burden of Seasonal Influenza*. Geneva: 2016.

[14] Nelly Mejia, Enusa Ramani, Sarah W Pallas, Dayoung Song, Taiwo Abimbola, Vittal Mogasale, Methodological Considerations for Cost of Illness Studies of Enteric Fever, *Clinical Infectious Diseases*, Volume 71, Issue Supplement_2, 15 August 2020, Pages S111-S119.

[15] Wilkinson T, Sculpher MJ, Claxton K, et al. The International Decision Support Initiative Reference Case for Economic Evaluation: An Aid to Thought. *Value Heal*. 2016;19(8):921-928. doi:https://doi.org/10.1016/j.jval.2016.04.015

[16] Mauskopf J, Standaert B, Connolly MP, et al. Economic analysis of vaccination programs: an ISPOR Good Practices for Outcomes Research Task Force Report. Value Health. 2018; 21(10):1133-1149.

[17] World Health Organization. Baltussen RMPM, Adam T, et al. Making choices in health : WHO guide to cost-effectiveness analysis / edited by T. Tan-Torres Edejer. [49]

[18] Verguet, S., Kim, J.J. & Jamison, D.T. Extended Cost-Effectiveness Analysis for Health Policy Assessment: A Tutorial. *PharmacoEconomics* **34,** 913–923 (2016). https://doi.org/10.1007/s40273-016-0414-z[14]

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

Benefit-Cost analysis	Is vaccine purchase economically justified according to individuals' willingness to pay for health gains? What is the return on investment for a vaccine from the perspective of a vaccine manufacturer, funder or immunization program?	• Benefit-cost ratio (BCR) • Positive net benefits • Return on investment (ROI), Net present value (NPV), Internal rate of investment (IRR)	• Reference Case Guidelines for Benefit-Cost Analysis in Global Health and Development[19]
Investment/business case case/value proposition	What type of evidence is needed to inform decisions or advocacy for development and introduction of vaccines as well as sustainable implementation of immunization programs?	• • Disease burden • Cost of investment • Impact of investment • Considerations for implementation	• Systematic review of existing examples[20]
Economic surplus analysis	How is global welfare in dollar terms generated by the uptake of vaccines distributed between vaccine producers vs. purchasers? Between HIC vs. LMICs? Across countries?	• Consumer surplus • Producer surplus • Total economic surplus	• Example: economic surplus analysis for HPV vaccines[21]
Budget Impact Analysis (BIA)	What will be the impact of adding a new vaccine on the budget of a stakeholder (i.e. annual budget of the Ministry of Health)?	• Difference in health system costs (with vs. without the intervention	• Budget Impact Analysis—Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Taskforce[22]
Optimization modelling	Given a constrained budget, what is the best possible set of interventions including vaccine that maximizes/minimizes the target outcome?	• Minimization/maximization of outcome variable(s) of interest	• Economic analysis of vaccination programs: An ISPOR Good Practices for

[19] Robinson, Lisa A.; Hammitt, James K.; Cecchini, Michele; Chalkidou, Kalipso; Claxton, Karl; Cropper M, Hoang-Vu Eozenou, Patrick; de Ferranti, David; Deolalikar, Anil B.; Guanais, Frederico; Jamison, Dean T.; Kwon, Soonman; Lauer, Jeremy A.;O'Keeffe, Lucy; Walker, Damian; Whittington, Dale; Wilkinson, Thomas; Wilson, David ; Wong B. *Reference Case Guidelines for Benefit-Cost Analysis in Global Health and Development*.; 2019 [50]

[20] Sim SY, Jit M, Constenla D, Peters DH, Hutubessy RCW. A Scoping Review of Investment Cases for Vaccines and Immunization Programs. *Value Health*. 2019;22(8):942-952. doi:10.1016/j.jval.2019.04.002

[21] Herlihy, Niamh; Hutubessy, Raymond; Jit, Mark (2016) *Current Global Pricing For Human Papillomavirus Vaccines Brings The Greatest Economic Benefits To Rich Countries*. Health affairs (Project Hope), 35 (2). pp. 227-234.[51]

[22]Sullivan et al. (2014) Budget Impact Analysis—Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Taskforce.[52] Carvalho et al. 2018 [53]

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

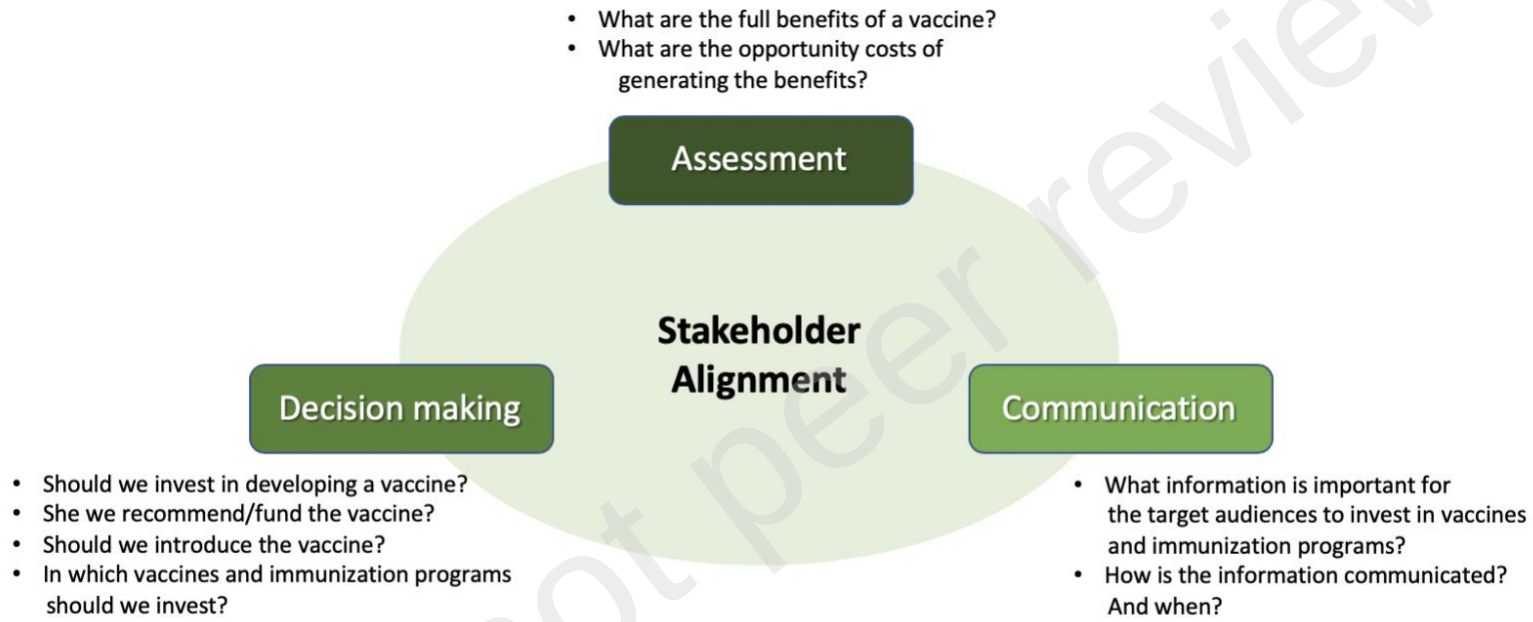
			Outcomes Research Task Force Report[23]
Fiscal impact modeling	What is the change in tax revenue and transfer payments attributable to changes in mortality and morbidity caused by a vaccine?	• Net present value (NPV) • Return on investment (ROI) • Benefit-cost ratio (BCR)	• Economic analysis of vaccination programs: An ISPOR Good Practices for Outcomes Research Task Force Report[24]

[23] Mauskopf, et al. (2018). Economic analysis of vaccination programs: An ISPOR Good Practices for Outcomes Research Task Force Report
[24] Ibid.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

Figure 3. A framework on Full Value of Vaccines Assessments (FVVA): three functions



Annex 1: Development of the FVVA (could be a text box)

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

The development of the FVVA framework has been inspired by seminal papers and events over the last decade.
- In their paper in 2008 Beutels and colleagues[36] stated that vaccines need to be on a level playing field with other interventions. In particular features that are related to herd immunity, quality of life in young children, parental case and work loss, time preference, macroeconomics and tiered pricing relevant to decision making for vaccines, or for pharmaceuticals in general should be considered when assessing their cost-effectiveness.
- In early 2010s work on the broader economic impact of vaccines proposed a broader perspective in evaluations in different generic and vaccine preventable disease specific framework (e.g. by Barnighausen & Bloom[6,45], reviews by Ozawa et al.[16], Deogaonkar et al. ,Jit et al.[7,46])
- Between 2015 and 2017 several meetings took place at the Fondation Mérieux place whereby Gessner and colleagues[8] eventually proposed to go beyond the therapeutic paradigm applied to the evaluation of prophylactic vaccines that focuses on individual benefit-risk assessment. By contrast they propose a public health paradigm instead that considered population impact and community benefits against a range of outcomes. Follow up articles by David Kaslow and colleagues[47] raised issues around problems in financing vaccine development relevant to LMICs.
- Subsequent statements from WHO's advisory committees, including PDVAC, IVIR-AC and SAGE asking for clarity in this area (add refs).
- Funding of investment cases in GBS, GAS, Shigella, MR-MAP and TB[48] which take a broader perspective.
- Gavi VIS criteria that have broader criteria: https://www.gavi.org/our-alliance/strategy/vaccine-investment-strateg
- WHO AMR framework leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance: An Action Framework: https://cdn.who.int/media/docs/default-source/immunization/product-and-delivery-research/action-framework-final.pdf?sfvrsn=13c119f3_5&download=true
- Possibly we could also mention the relevance to COVID-19 vaccines where a pure health sector perspective alone is clearly too narrow to capture all the benefits that society is interested in, and where WHO SAGE has explicitly laid down ethical principles for vaccine prioritisation.
- In preparation of the IA2030 global strategy the full benefits of vaccines to everyone contributing to good health and well-being play a prominent role.

Annex 2. Glossary of terms and definitions

2.1 Terms

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

CAPACITI: Country-led Assessment for Prioritization of Immunisation
CEPI: The Coalition for Epidemic Preparedness Innovations
FPVHP: Full Public Health Value Propositions for Vaccines
FVVA: Full Value of Vaccines Assessment
HTA: Health Technology Assessment
IVIR-AC: Immunization- and Vaccine-related Implementation Research Advisory Committee
IPAC: Immunization Practices Advisory Committee
PDP: Product Development Partnerships (PDPs)
PDVAC: Product Development for Vaccines Advisory Committee
PPC: Preferred Product Characteristics
SAGE: Strategic Advisory Group of Experts on Immunization
TPP: Target Product Profiles
TSE: Total Systems Effectiveness
MDB: Multilateral Development Bank

2.2 Definitions

Terms	Definitions
Preferred Product Characteristics (PPC)	PPCs are developed by WHO IVB and provide guidance as to WHO's preferences for new vaccines in priority disease areas. The objective is to promote the development of vaccines with optimal effectiveness and suitability, for use in LMICs, thereby maximizing global vaccine impact.
Target Product Profiles (TPP)	The TPPs are pathogen rather than product specific and define a mandatory set of product attribute. The intent of WHO TPPs is to provide early technical guidance into the various product-specific vaccine TPPs that are developed by individual vaccine manufacturers
Health Technology Assessment (HTA)	A multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

Investment cases, business cases, value propositions	A body of work, as a compilation of outcomes from existing analyses and studies, that aims to provide information needed for decisions around technical or financial support for vaccine introduction by donors and country stakeholders, or investment decisions on vaccine development made by donors or private investors. Some aim to advocate for specific goals or agenda related to disease control and immunization programs.
Full Value of Vaccines Assessment (FVVA)	A framework that guides assessment and communication of the value of vaccines and informs decision making around vaccine development and introduction as well as sustainable implementation of immunization programs.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3841999

The case for assessing the full value of new tuberculosis vaccines

Nebiat Gebreselassie[1], Raymond Hutubessy[2], Johan Vekemans[2], Saskia den Boon[2], Tereza Kasaeva[1] and Matteo Zignol[1]

Affiliations: [1]Global TB Programme, World Health Organization, Geneva, Switzerland. [2]Dept of Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland.

Correspondence: Nebiat Gebreselassie, World Health Organization, Global TB Programme, Avenue Appia 20, Geneva 1211, Switzerland. E-mail: gebreselassien@who.int

@ERSpublications
A multidisciplinary framework is needed to guide the research needed for making economic and health impact arguments for tuberculosis vaccine development and uptake http://bit.ly/2stNDok

Cite this article as: Gebreselassie N, Hutubessy R, Vekemans J, *et al*. The case for assessing the full value of new tuberculosis vaccines. *Eur Respir J* 2020; 55: 1902414 [https://doi.org/10.1183/13993003.02414-2019].

Tuberculosis (TB) ranks as the leading cause of death among infectious diseases in human history, claiming over a billion lives in the past two centuries alone [1, 2]. Although a number of important advances have been made to control TB in the past decade, an estimated 10 million people fell ill with TB and 1.5 million died from the disease in 2018 alone [1]. The only licensed TB vaccine, bacille Calmette–Guérin (BCG), provides partial protection against severe forms of TB in infants and young children (averting thousands of paediatric deaths annually), but fails to stop transmission of pulmonary tuberculosis in adults [3, 4]. The World Health Organization (WHO)'s End TB Strategy stipulates that more effective vaccines are needed to end the TB epidemic, which will subsequently bolster efforts to achieve broader global health ambitions under universal health coverage, and a number of other sustainable development goal targets, particularly the targets focused on eradicating poverty in all its forms, ending the AIDS epidemic, strengthening health systems, and reducing premature mortality among women and children [5, 6]. By preventing TB disease, an effective vaccine would also reduce the need for antibiotics, an essential step for curbing antimicrobial resistance. Recognising this, member states during the United Nations General Assembly high level meeting on TB, held in New York in 2018, have committed to increase investment in and accelerate research for the development of more effective TB vaccines that are affordable and accessible by all countries that need them [7].

To accelerate efforts, WHO, through a wide consensus-generating consultation, has developed preferred product characteristics for new TB vaccines, to articulate attributes of products suitable for end users, and to guide scientists, funding agencies and industry groups developing TB vaccine candidates intended for WHO prequalification and policy recommendations [8, 9]. There are several challenges to developing more effective TB vaccines. From a scientific perspective, significant challenges include a lack of validated, predictive animal models of TB infection and disease; a lack of validated biomarkers that can act as prospective signatures of the risk of developing TB or as correlates of protection; and an incomplete understanding of the nature of protective immunity to TB. From a developer perspective, market uncertainties, as well as the long and expensive research timeline, make TB vaccine development challenging. There is also the impending challenge of developing a product that is affordable to low-and-middle income countries; acceptable to communities; and feasible to sustainably implement

Received: 16 Dec 2019 | Accepted after revision: 7 Jan 2020

Copyright ©ERS 2020

under low resource settings. Despite these difficulties, there is cause for optimism. Recently, an experimental TB vaccine candidate ($M72/AS01_E$) was found to be significantly protective against pulmonary TB in a phase IIb trial conducted in Kenya, South Africa and Zambia, in individuals with latent TB infection [10, 11]. An increasing number of signatures that predict risk of disease progression are also emerging [12]. At least 14 other vaccine candidates are being tested for prevention of infection; prevention of TB disease (in persons with or without evidence of past exposure); or as an immunotherapeutic agent for shortening TB treatment or reducing the risk of recurrence following treatment completion [1, 5].

Further development and validation of candidate vaccines in the clinical pipeline is conditional on collaboration between research funders, governments, public private partnerships, international agencies, affected communities and the pharmaceutical industry. Partnerships are particularly important in order to finance multi-country clinical trials needed to gather evidence for licensure. Beyond clinical trials, broader research in areas of social, economic, and population health impact are also needed to guide vaccine introduction and implementation [13]. Recognising this complexity, countries weigh in different factors before adding a vaccine to their national immunisation programmes that oftentimes involves a trade off with investing in other vaccines or alternative strategies [14]. These include 1) the disease burden and its political priority at national and global platforms; 2) relative effectiveness of alternative strategies; 3) safety, efficacy, and equity impact of the vaccine; 4) sufficient vaccine supply; 5) the vaccine's economic and financial attributes (cost, affordability, and cost-effectiveness); and 6) the capacity of the immunisation programme and underlying health system to successfully introduce and sustainably deliver the vaccine. For TB, additional evidence needs include studies on how to align vaccine implementation with ongoing TB prevention efforts (particularly among populations eligible for TB preventive therapy), and how to use the vaccine among vulnerable groups such as children, diabetics, people living with HIV, and pregnant women. Because future TB vaccines will likely target adults and adolescents who are not part of traditional

TABLE 1 Framework for assessing the full value of new tuberculosis (TB) vaccines

Category	Needs
Health gains	Estimated potential impact of new TB vaccines on disease burden and transmission (including drug-resistant TB (DR-TB) and co-infection with HIV), as measured by incidence, mortality and morbidity (in the context of alternative strategies)
Value for money	Estimated societal cost-effectiveness/cost-utility and return on investment for new TB vaccines from the perspective of both the healthcare payer and society
Equity and financial risk protection impact	Estimated impact of a new TB vaccine on equity (in the context of health gains by income distribution and vulnerability) and reduced household financial vulnerability (catastrophic costs and impoverishment)
Economic impact	Estimated impact of new TB vaccines on medical and other expenses, as well as on gross domestic product and its rate of growth; estimated impact of new TB vaccines on government expenditure (including expenditure through the HIV response, as applicable) and on sustainability of financing over the long term
Global health security impact	An estimated impact of a new TB vaccine on antimicrobial stewardship (reducing antibiotic use, mitigating the reduced effectiveness of antimicrobials from continued use, reducing DR-TB disease incidence, reducing human and programmatic costs of DR-TB management, and improving health outcomes)
Market	Estimated potential demand for new TB vaccines
Vaccine characteristics and implementation scenario assumptions	The various parameters above should be evaluated under different vaccine characteristics and implementation scenario assumptions (target population, geographical scope and vaccine characteristics) In addition, the interaction between a new vaccine and alternative strategies (optimal use of current and future alternative interventions) on key outputs should be considered

immunisation programmes, programme innovation will also be needed to achieve acceptable coverage and equity in these populations [8].

Considering these broad areas of need, a framework would be helpful to guide research and evidence necessary for making economic and health impact arguments for TB vaccine development and uptake (table 1). Evidence aligned to such a framework can help boost investments by vaccine developers, traditional health institutions, such as ministries of health or GAVI, the Vaccine Alliance, and ministries of finance or their equivalent [15, 16]. Preliminary modelling works have already shown that new TB vaccines will be highly cost-effective, and will offer substantial cost savings to healthcare systems and society [17]. In addition, mathematical modelling using data from 183 countries suggests that a new TB vaccine for prevention of disease that is 60% efficacious and delivered to just 20% of adolescents and adults globally could avert 25–35 million cases in its first 20 years of use [18]. A significantly improved infant vaccine (relative to BCG) would avert about an additional 4–6 million new cases of TB over the same period. Expanding on this work by modelling additional disease dynamics and scenarios, as outlined above, will help resolve complexities around late stage research needs and provide better understanding of the demand around TB vaccines, for stakeholders engaged in vaccine development, production and implementation.

Conflict of interest: None declared.

References

1 World Health Organization. Global Tuberculosis Report. Geneva, World Health Organization, 2019.
2 Paulson T. Epidemiology: a mortal foe. *Nature* 2013; 502: S2–S3.
3 Dockrell HM, Smith SG. What have we learnt about BCG vaccination in the last 20 years? *Front Immunol* 2017; 8: 1134.
4 Dara M, Acosta CD, Rusovich V, *et al.* Bacille Calmette-Guerin vaccination: the current situation in Europe. *Eur Respir J* 2014; 43: 24–35.
5 World Health Organization. End TB Strategy: Global Strategy and Targets for Tuberculosis Prevention, Care and Control after 2015. Geneva, World Health Organization, 2014.
6 World Health Organization. Immunization Agenda 2030: A Global Strategy to Leave No One Behind. Geneva, World Health Organization.
7 United Nations General Assembly. Political Declaration of the High-Level Meeting of the General Assembly on the Fight against Tuberculosis [73/3]. New York, United Nations General Assembly, 2018.
8 World Health Organization. WHO Preferred Product Characteristics for New Tuberculosis Vaccines. Geneva, World Health Organization, 2018.
9 World Health Organization. Preferred Product Characteristics for Therapeutic Vaccines to Improve Tuberculosis. Geneva, World Health Organization, 2019.
10 Van Der Meeren O, Hatherill M, Nduba V, *et al.* Phase 2b controlled trial of M72/AS01$_E$ vaccine to prevent tuberculosis. *N Engl J Med* 2018; 379: 1621–1634.
11 Tait DR, Hatherill M, Van Der Meeren O, *et al.* Final analysis of a trial of M72/AS01$_E$ vaccine to prevent tuberculosis. *N Engl J Med* 2019; 381: 2429–2439.
12 Duffy FJ, Weiner J III, Hansen S, *et al.* Immunometabolic signatures predict risk of progression to active tuberculosis and disease outcome. *Front Immunol* 2019; 10: 527.
13 Jit M, Hutubessy R, Png ME, *et al.* The broader economic impact of vaccination: reviewing and appraising the strength of evidence. *BMC Med* 2015; 13: 209.
14 World Health Organization. Principles and Considerations for Adding a Vaccine to a National Immunization Programme. Geneva, World Health Organization, 2014.
15 Bloom DE, Canning D. Policy forum: public health. The health and wealth of nations. *Science* 2000; 287: 1207–1209.
16 GAVI. Evaluation Criteria for Vaccines for Endemic Disease Prevention through Routine Immunisation for Vaccines. Geneva, GAVI, 2019. Available from: www.gavi.org/about/strategy/vis/evaluation-criteria-for-vaccines-for-endemic-disease-prevention-through-routine-immunisation/
17 Harris RC, Sumner T, Knight GM, *et al.* Systematic review of mathematical models exploring the epidemiological impact of future TB vaccines. *Hum Vaccin Immunother* 2016; 12: 2813–2832.
18 Aeras, TBVI. TB Vaccine Research and Development: A Business Case for Investment. Rockville, Aeras, 2014.

The impact of alternative delivery strategies for novel tuberculosis vaccines in low- and middle-income countries: a modelling study

Authors

Rebecca A. Clark, MSc[1-3], Christinah Mukandavire, PhD[1-3], Allison Portnoy, ScD[4], Chathika K. Weerasuriya, PhD[1-3], Arminder Deol, PhD[1-3], Danny Scarponi, PhD[1-3], Andrew Iskauskas, PhD[5], Roel Bakker, PhD[1-3,6], Matthew Quaife, PhD[1-3], Shelly Malhotra, PhD[7], Nebiat Gebreselassie, PhD[8], Matteo Zignol, MD[8], Raymond C.W. Hutubessy, PhD[9], Birgitte Giersing, PhD[10], Mark Jit, PhD[2,3], Rebecca C. Harris, PhD[1-3,11], Nicolas A. Menzies, PhD[4,12], Richard G. White, PhD[1-3]

Affiliations

[1] TB Modelling Group and TB Centre, London School of Hygiene and Tropical Medicine, London UK

[2] Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, London UK

[3] Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London UK

[4] Center for Health Decision Science, Harvard T.H. Chan School of Public Health, Boston MA, USA

[5] Department of Mathematical Sciences, Durham University, Durham UK

[6] KNCV Tuberculosis Foundation, The Hague, Netherlands

[7] Global Access, IAVI, New York NY, USA

[8] Global TB Programme, World Health Organization, Geneva, Switzerland

[9] Department of Immunization, Vaccines and Biologicals (IVB), World Health Organization, Geneva, Switzerland

[10] The Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

[11] Sanofi Pasteur, Singapore

[12] Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston MA, USA

Corresponding author information

Rebecca A. Clark, MSc

Rebecca.Clark@lshtm.ac.uk

Tel: +44 (0)7543 360240

London School of Hygiene and Tropical Medicine

Keppel Street

London

WC1E 7HT

United Kingdom

Main text word count 3485 /3500

Abstract

Background

Tuberculosis is a leading infectious cause of death worldwide. Novel vaccines will be required to reach global targets and reverse setbacks from the COVID-19 pandemic. We estimated the impact of novel tuberculosis vaccines in low- and middle-income countries (LMICs), under alternative delivery scenarios.

Methods

We calibrated a tuberculosis model to 105 LMICs (93% of global incidence). Vaccine scenarios were implemented as *Basecase*: routine vaccination of 9-year-olds and a one-time vaccination campaign for ages ≥10 with country-specific introduction between 2028–2047 and 5-year scale-up to target coverage; *Accelerated Scale-up*: as *Basecase*, but all countries introducing in 2025 with instant scale-up; and *Routine Only*: as *Basecase*, but routine vaccination only. Vaccines protected against disease for 10-years, with 50% efficacy.

Findings

The *Basecase* scenario reduced tuberculosis incidence (19·5% [95% uncertainty range=18·3–21·6%]) and mortality (20·6% [19·2–23·4%]) rates in 2050 and prevented 3·6 (3·3–3·9) million deaths before 2050, including 1·6 million in the WHO South-East Asian region. The *Accelerated Scale-up* scenario reduced tuberculosis incidence (25·2% [23·9–27·5%]), mortality (26·7% [25·2–29·9%]), and prevented 7·9 (7·3–8·5) million deaths. The *Routine Only* scenario reduced tuberculosis incidence (9·9% [9·0–11·6%]), mortality (9·9% [8·9–12·3%]), and prevented 1·1 (0·9–1·2) million deaths.

Interpretations

Novel tuberculosis vaccines could have substantial impact, which will vary depending on delivery strategy. Including a campaign will be crucial for rapid impact. Accelerated introduction similar to the pace of COVID-19 vaccines could approximately double the lives saved before 2050. Investment is required to support vaccine development, manufacturing, prompt introduction and scale-up.

Funding

WHO (2020/985800-0)

Research in Context

Evidence before this study

Two systematic reviews in the previous five years have highlighted the benefits that novel tuberculosis vaccines could have on reducing the tuberculosis burden globally, and that they are likely crucial to achieve elimination. The impact of novel tuberculosis vaccines will depend on the characteristics of the setting, the vaccine, and the delivery strategy. No modelling studies have estimated the potential impact of the WHO Preferred Product Characteristics for New Tuberculosis Vaccines (PPCs) in low- and middle-income countries (LMICs), and existing literature remains limited in terms of how realistic the modelled vaccine introduction and scale-up scenarios are.

Added value of this study

We estimated the potential health impacts of infant and adolescent/adult vaccines meeting the WHO PPCs in 105 low- and middle-income countries, accounting for 93% of the global tuberculosis incidence and mortality in 2019. We evaluated more complex and realistic *Basecase* vaccine delivery scenarios than previously modelled by introducing in country-specific introduction years between 2028 and 2047, and scaling-up to target vaccine coverage over five years upon initial country introduction. We compared to an *Accelerated* introduction and scale-up in all countries in 2025, more similar to the pace of COVID-19 vaccine introduction, to estimate the implications of failing to meet the End TB target to develop and licence an adolescent/adult vaccine by 2025 and scale up quickly. We also compared to a less ambitious *Routine Only* introduction. We grouped countries by WHO region, income group, and TB burden to identify where the largest impacts of a novel vaccine may be realised and identified the key implications of these findings.

We found novel tuberculosis vaccines meeting the WHO PPCs could have a substantial impact, which will vary depending on delivery and vaccine characteristics. Inclusion of a vaccination campaign will be crucial for rapid impact. Most lives may be saved in the WHO South-East Asian region and African region, and higher rate reductions may be seen in low-income countries. Failing to meet the End TB target to develop and licence an adolescent/adult vaccine by 2025 and quickly scale-up in all countries could lead to around four million more deaths in LMICs, whereas

introduction at the pace of COVID-19 vaccines may approximately double the lives saved before 2050.

Implications of all the available evidence

Our new evidence can support investment decisions in vaccine development, manufacturing, and delivery. We show that millions of additional deaths could be averted with rapid development and licensing of novel tuberculosis vaccines, and preparations should be made for their prompt introduction, including in campaigns, ideally at the pace that COVID-19 vaccines have been introduced.

Background

Tuberculosis is one of the leading causes of infectious disease death worldwide, second only to COVID-19 in 2020.[1] The negative impact of COVID-19 on tuberculosis-related health services, such as delays in diagnosis, treatment, and neonatal vaccination has paused and reversed previous slowly declining trends in mortality.[1,2]

The WHO established the "End TB Strategy" in 2015, with the goal of reducing disease incidence, deaths, and costs worldwide from tuberculosis.[3] Targets for 2025 and 2035 include reductions in the absolute number of tuberculosis deaths by 75% and 95% and the tuberculosis incidence rate by 50% and 90%, respectively, compared to 2015 levels.[3] However, the majority of countries are not on track to achieve these targets.[1,4]

The 2035 End TB targets explicitly assumed the introduction of new tools, including a novel tuberculosis vaccine, in 2025.[3] The WHO has proposed Preferred Product Characteristics for New Tuberculosis Vaccines (WHO PPCs) developed through a highly consultative process, including regulators and policy makers from high burden countries.[5] While progress has been made, it is unlikely that the 2025 target for novel tuberculosis vaccine introduction will be achieved.

A phase 2b trial of the M72/AS01$_E$ candidate vaccine demonstrated an efficacy of 49·7% (95% confidence interval: 2·1–74·2) for preventing disease in adults positive by interferon-gamma release assay (IGRA+) from South Africa, Zambia, and Kenya after three years follow-up,[6] and a trial of BCG-revaccination appeared efficacious at preventing sustained infection in a cohort of IGRA negative (IGRA-) adolescents in South Africa with an efficacy of 45·4% (6·4–68·1).[7] Unfortunately, the phase 3 trial of M72/AS01$_E$ has not started, and therefore the realistic licensure date, should a positive result be found, may not be for a number of years. Policy changes on BCG-revaccination in adolescents could happen sooner in settings such as South Africa, as the trial is likely to be completed in 2024/2025, but BCG-revaccination has not been tested in infected individuals–a population shown previously to be epidemiologically important for rapid population-level vaccine impact.[8]

This raises critical questions for global and country decision-makers, including: How many lives will be lost if we fail to roll out a novel tuberculosis vaccine by 2025? What is the potential impact if instead vaccines are introduced and rolled out following more traditional timelines, and how do we best prepare for that? And how would these impacts vary by WHO region, income level, and TB burden?

We estimated the potential impact of vaccines meeting the technical specifications of the WHO Preferred Product Characteristics for New Tuberculosis Vaccines in low- and middle-income countries (LMICs), in a range of introduction and scale-up scenarios.

Methods

Model Development and Calibration

To estimate the impact of novel tuberculosis vaccines, we developed a compartmental age-stratified dynamic *Mycobacterium tuberculosis* (*Mtb)* transmission model (Figure 1), by adapting features of earlier models.[8,9] In our model, tuberculosis natural history is represented using eight compartments, allowing for *Mtb* infection along a spectrum from uninfected to active clinical disease.[10,11] A detailed description of the structure can be found in Supplementary Material section 1, with parameterisation in Supplementary Material section 2.

We incorporated an access-to-care structure to represent the systematic differences in tuberculosis burden and healthcare access by income.[12] The access-to-care structure contains high-access-to-care, representing the top three income quintiles (60% of the population) and low-access-to-care, representing the bottom two income quintiles (40% of the population). We assumed no transition between the high- and low-access-to-care classes, and random mixing between them.

To account for the influences of human immunodeficiency virus (HIV) and antiretroviral therapy (ART) on the risk of infection and progression to disease,[13,14] we included an HIV structure for countries if the proportion of tuberculosis cases among people living with HIV (PLHIV) was at least 15%, and the HIV prevalence was greater than 1% (countries listed in the Supplementary Material Table S5.3). The HIV structure included HIV uninfected, HIV infected and not on ART, and HIV infected and on ART. The tuberculosis mortality rate and risk of progression is increased in both HIV compartments, with greater increases in those not on ART compared to on ART.

We calibrated the model to epidemiologic data in each country separately using history matching with emulation through the *hmer* R package,[15] generating at least 1000 fitted parameter sets per country. We used the distribution of results produced by these parameter sets to quantify estimation uncertainty.[16] The model for each country was fit to nine calibration targets in 2019: the tuberculosis incidence rate (overall and by age), tuberculosis case notification rate (overall and by age), tuberculosis mortality rate (overall), the fraction of subclinical tuberculosis among active tuberculosis, and the risk ratio of active tuberculosis in the low-access-to-care group relative to

high-access-to-care. Models for countries with the HIV structure were fit to four additional all age HIV targets in 2019: HIV prevalence, ART coverage, tuberculosis incidence rate in PLHIV, and tuberculosis mortality rate in PLHIV.

Policy Scenarios

i. Status Quo No-New-Vaccine Baseline

For each country, separately, a primary baseline with no novel vaccine introduction was simulated, assuming that non-vaccine tuberculosis interventions continue at current levels ('*Status Quo No-New-Vaccine'* baseline). As reported country-level data includes the high coverage of neonatal BCG vaccination,[17] this was not explicitly modelled. We assumed that BCG vaccination would not be discontinued over the model time horizon.

ii. Novel Vaccine Scenarios

Aligning with the product characteristics described in the WHO PPC, we evaluated a novel adolescent/adult and a novel infant vaccine.[5] Vaccines were assumed to prevent progression to disease and confer 10-years duration of protection on average, with exponential waning. We assumed the adolescent/adult vaccine would "take" in individuals in any infection state at the time of vaccination aside from active tuberculosis disease (i.e., a "pre- and post-infection" vaccine), with 50% vaccine efficacy. We assumed the infant vaccine would "take" in individuals who were uninfected at the time of vaccination (i.e., a "pre-infection" vaccine), with 80% efficacy. Further details are in Supplementary Material section 7.1.

The infant vaccine was implemented in two scenarios, and, separately, the adolescent/adult vaccine was implemented in three scenarios, with assumptions confirmed through consultation with a range of global tuberculosis vaccine stakeholders. The *Basecase* and *Accelerated Scale-up* scenarios included routine neonatal vaccination for the infant vaccine (85% coverage), and routine vaccination of 9-year-olds (80% coverage) with a one-time vaccination campaign for ages ten and older (70% coverage) for the adolescent/adult vaccine. The *Routine Only* scenario (adolescent/adult vaccine only) was introduced through routine vaccination of 9-year-olds (i.e., no campaign).

We evaluated vaccine delivery scenarios by varying the introduction year and scale-up trends between scenarios and countries (Table 1). In the *Basecase* and *Routine Only* scenarios, based on data from historical vaccine introduction, vaccines were introduced in country-specific years and linearly scaled-up to coverage targets over five years once introduced. To estimate introduction years, countries were divided into 'procuring with Gavi support' and 'self-procuring'. Factors influencing the likely timing of vaccine introduction were identified through expert consultation, and included disease burden, prior early adopter status, timelines for Gavi processes, capacity for immunisation, country-specific registration timelines, and commercial prioritisation. A scoring system was applied to each factor, and countries were assigned an aggregate score ranking their likely introduction position. The number of countries introducing the vaccine per year was informed by pneumococcal vaccine scale-up.[18] See Supplementary Material section 7.2 for details. In the *Accelerated Scale-up* scenarios, to more resemble the pace of COVID-19 vaccine introduction, vaccines were introduced in 2025 in all countries with vaccine coverage targets reached instantly.

Health impact indicators

We calculated tuberculosis incidence and mortality rate reductions in 2050 for each vaccine scenario compared to the *Status Quo No-New-Vaccine* baseline and calculated the cumulative numbers of tuberculosis treatments, deaths, and cases averted between vaccine introduction and 2050. Incidence rates in 2035 for each vaccine scenario were also estimated to investigate the feasibility of meeting the 2035 End TB target. Results are presented as the median and 95% uncertainty range for all countries modelled, WHO region, World Bank income group,[19] and WHO tuberculosis burden level.[22]

Additional scenario analyses

We conducted scenario analyses to evaluate alternative assumptions regarding the *Status Quo No-New-Vaccine* baseline, vaccine characteristics, and delivery. We simulated vaccine scenarios with lifelong duration of protection for both vaccines, as well as scenarios with adolescent/adult vaccine efficacy increased to 75%. For each scenario, low- and high-coverage targets for five years post-introduction were compared to the medium-coverage targets used for the main analyses. We also explored an alternative baseline: the *2025 End TB No-New-Vaccine* baseline, which assumed

strengthening of non-vaccine tuberculosis interventions to meet the 2025 End TB incidence target,[3] providing an alternative estimate of impact assuming existing measures would be deployed more effectively (Supplementary Material section 6.2).

Role of the funding source

The funder was involved in the development of the research question, study design, and provided comments on the manuscript draft, but had no role in the collection, analysis, and interpretation of the data, or writing of the report. All authors had the opportunity to access and verify the data, and all authors were responsible for the decision to submit the manuscript for publication.

Results

Model calibration and vaccine introduction year

Epidemiologic and demographic data were available to model 115 of 135 LMICs. We successfully calibrated 105 of 115 countries, accounting for 93·3% of global tuberculosis cases and 93·6% of deaths in 2019. Calibrated model incidence and mortality rate trends for WHO regions, WHO TB burden levels, and World Bank income groups are given in Supplementary Material section 9.3. Country-specific vaccine introduction years (used in *Basecase* and *Routine Only* scenarios) ranged between 2028 and 2047 (Supplementary Material Table S8.1), with the earliest Gavi-supported country introducing following a two-year delay compared to the earliest self-procuring. Figure 2 demonstrates the cumulative number of countries introducing per year between 2028 and 2047, with 50% of countries introducing the vaccine by 2034.

Health impact for the adolescent/adult vaccine

Our findings suggest that introducing a 50% efficacy adolescent/adult vaccine with 10-years protection in the *Basecase* scenario would reduce tuberculosis incidence and mortality rates in 2050 by 19·5% (95% uncertainty range=18·3–21·6%) and 20·6% (19·2–23·4%), respectively, compared to the *Status Quo No-New-Vaccine* baseline (Table 2). The incidence reduction ranged from 11·2% in the WHO Region of the Americas (AMR) to 21·1% in the African (AFR) and Eastern-Mediterranean (EMR) regions (Table 2, Figure 3). The tuberculosis mortality rate was reduced by 12·4% in AMR to 21·9% in EMR. By income group, relative impact was slightly higher in low-income countries compared to lower middle-income countries and upper middle-income countries (Table 2, Figure 3).

The adolescent/adult vaccine *Basecase* scenario was predicted to avert approximately 31·5 (26·9–36·9) million cases for all countries compared to the *Status Quo No-New-Vaccine* baseline by 2050, including 21·8 (18·0–26·0) million cases in lower middle-income countries (Table 2, Figure 3). High numbers of cases could be averted in both AFR and the WHO South-East Asian (SEAR) regions, which contribute the highest number to the global total. By 2050, 3·6 (3·3–3·9) million deaths could be averted for all countries, including 1·6 million in SEAR, 1·5 million in AFR, and 2·7 million in lower middle-income countries (Table 2, Figure 3). By 2050, 17·5 (15·6–19·2)

million treatments could be averted, with 8·2 (7·1–9·5) million averted treatments in SEAR alone. In the 27 countries categorised by WHO as high-TB-burden of the 105 modelled, 28·6 (24·4–33·4) million cases, 15·9 (14·1–17·5) million treatments, and 3·3 (3·0–3·6) million deaths could be averted by 2050; around ten times higher than those averted in all other countries combined (Table 2, Figure 3).

Health impact for the infant vaccine

For both the *Basecase* and *Accelerated Scale-up* scenarios, lower impact was estimated for the infant vaccine compared to the adolescent/adult vaccine before 2050, including 0·5–0·6 times incidence and mortality rate reductions by 2050 and 0·2–0·3 times the number of cases, treatments, and deaths averted (Table 2).

Health impact by delivery scenario

With the *Accelerated Scale-up* scenario, a 50% efficacy adolescent/adult vaccine could prevent 7·9 (7·3–8·5) million deaths–4·3 million more deaths than the *Basecase* delivery–and avert 65·7 (55·8–76·2) million cases and 38·6 (34·4–42·3) million treatments (Table 2, Figure 3). In contrast, by only routinely vaccinating 9-year-olds (*Routine Only* scenario), 8·8 (7·7–10·1) million cases, 4·1 (3·7–4·6) million treatments, and 1·1 (0·9–1·2) million deaths would be averted (Table 2, Figure 3).

Comparing to the 2035 End TB target

Assuming non-vaccine interventions do not improve in the future (*Status Quo No-New-Vaccine* baseline), the *Basecase* and *Accelerated Scale-up* scenarios of the adolescent/adult vaccine suggest we would reach 29% and 41% of the 2035 global target for reduction in tuberculosis cases, respectively. Assuming the 2025 End TB targets are met before vaccine roll out (*2025 End TB No-New-Vaccine* baseline), progress is increased, with the *Accelerated Scale-up* scenario reaching 82% of the target.

Additional scenario analyses

Impact results from scenarios with lifelong duration of protection, 75% efficacy, and low- and high-coverage targets are provided in the Supplementary Material section 10. Assuming lower

coverage targets or the *2025 End TB No-New-Vaccine* baseline led to reduced health impact, and higher coverage targets, 75% efficacy, or lifelong duration of protection vaccines led to an increased health impact compared to the *Status Quo No-New-Vaccine* baseline, a medium-coverage target, 50% efficacy vaccine, or vaccine with only ten-years protection.

Discussion

Our results suggest that novel tuberculosis vaccines could substantially reduce the tuberculosis burden in the coming decades. The *Basecase* scenario, in which a 50% efficacy adolescent/adult vaccine was introduced over 20 years, could reduce tuberculosis incidence (19·5%) and mortality (20·6%) rates in 2050, and prevent 3·6 million deaths before 2050, including 1·6 million in the WHO South-East Asian region and 1·5 million in the African region. The more ambitious *Accelerated Scale-up* scenario could reduce tuberculosis incidence (25·2%) and mortality (26·7%) rates in 2050 and prevent over double (7·9 million) the number of deaths before 2050. The less ambitious *Routine Only* scenario could reduce tuberculosis incidence (9·9%) and mortality (9·9%) rates in 2050 and prevent around a third (1·1 million) of the deaths before 2050.

Impact estimates for vaccine introduction varied by region. While incidence and mortality rate reductions achievable by 2050 were similar between high-TB-burden countries and all other countries, the number of cases, treatments, and deaths averted were around ten times higher than those averted in all other countries, emphasising the need to focus on high-burden countries to maximise health impact. Particularly large numbers of averted cases, treatments, and deaths were predicted in Africa and South-East Asia, and in lower-middle-income countries, arguably populations in the greatest need.

Vaccination campaigns will be important to expedite health gains from vaccination. The *Basecase* and *Routine Only* scenarios offer a direct comparison of implementing with and without a campaign. The *Basecase* scenario averted around four times as many cases, deaths, and treatments as the *Routine Only* scenario, supporting the need to include a campaign in any future delivery strategy to maximise health impact.

A new vaccine will be an important tool to accelerate progress towards 2035 End TB targets. Conservatively assuming non-vaccine intervention coverage and quality does not improve in the future (*Status Quo No-New-Vaccine* baseline) and roll out from 2028 in line with previous vaccines (before COVID-19) the *Basecase* scenario suggests we could reach around a third of the 2035 global target. More optimistic assumptions, that assume 2025 End TB targets are met before

vaccine roll out (*2025 End TB No-New-Vaccine* baseline), combined with the *Accelerated Scale-up* scenario, suggests over 80% of the global 2035 target could be met.

Two recent systematic reviews have highlighted potential health impacts of novel tuberculosis vaccines.[20,21] Our study expands on the findings of these reviews and addresses some identified gaps. We showed that the adolescent/adult vaccine would have greater and more rapid health impacts than an infant vaccine before 2050. The largest burden of pulmonary tuberculosis disease is most often found in adults,[1] and the adolescent/adult vaccine targets the age ranges with the highest burden of tuberculosis, compared to the infant vaccine. However, as the health outcomes are measured in 2050, the maximum follow-up time between vaccine delivery and impact calculation is 25 years. Therefore, even with duration of protection increased, it is unlikely that the infant vaccine would be protecting those at highest risk of progressing to active disease in most countries during the time period of our analyses.

Meeting the End TB target to develop and licence an adolescent/adult vaccine by 2025 and introducing at the pace of COVID-19 vaccines (*Accelerated Scale-up*) could approximately double the lives saved before 2050, compared to introduction at a historical pace (*Basecase*). The pace of COVID-19 vaccine introduction in LMICs, albeit slower than in high-income countries, has been much faster. At the time of writing, over 10% of the population in at least 75% (102/135) of LMICs have been fully vaccinated in the two years since COVID-19 vaccines have been available, showing that faster vaccine introduction in LMICs is possible with high political will and financial resources.[22] This is more similar to our *Accelerated Scale-up* scenario, which averted up to 4·3 million more deaths than our *Basecase* scenario, and while the benefits of rolling out a vaccine from 2028 at pre-COVID-19 pace are predicted to be large, the increase in deaths demonstrate the health consequences from failing to rapidly introduce a vaccine. Unlike COVID-19, tuberculosis is a disease of the poor, which does not have the associated novelty, nor the same impact on high-income countries. Therefore, tuberculosis vaccines need concerted, sustained policy attention to overcome these barriers.

Our study has limitations. We successfully calibrated 105 of the 135 LMICs, representing 93% of global tuberculosis incidence, due in part to missing data from 20 countries that prevented

calibration from being attempted. Excluding 30 countries will slightly underestimate the number of cases, deaths, and treatments averted, and may bias the generalizability of the relative impact results.

Aligning with the WHO PPC, we assumed the adolescent/adult vaccine would be efficacious ("take") in both infected and uninfected individuals. However, the majority of previous and current trials have only enrolled either IGRA+ or IGRA- individuals.[6,7] Ideally, novel vaccines will be safe and effective in both infected and uninfected individuals, as it would be costly and logistically difficult to include testing for tuberculosis infection before vaccine administration. If the realised vaccine will only be efficacious in either IGRA+ or IGRA-, our results will be overestimates of impact, as show in previous work.[8] We also assumed that vaccine efficacy was equivalent in PLHIV and HIV-naïve. However, vaccines are not always as efficacious in immunocompromised individuals,[23,24] which would reduce the vaccine impact in countries incorporating the HIV structure.

We evaluated three vaccine scenarios for the adolescent/adult vaccine and two vaccine scenarios for the infant vaccine to provide estimates of vaccine impact under more and less ambitious introduction years and scale-up trends. Our more ambitious scenario, (*Accelerated Scale-up*), is less realistic, as it assumes a vaccine candidate would be ready for licensure, the supply exists, and that countries are positioned to make an introduction decision resulting in immediate uptake, all within the next 3 years. No specific risk groups were vaccinated in our model, however, initial delivery of novel tuberculosis vaccines within countries is likely to be through a targeted approach–a strategy shown to have a large population impact per vaccinated individual.[25–29] Countries may decide to initially target groups at the highest risk of developing tuberculosis disease or that contribute the most to transmission, while others may focus on vaccinating vulnerable age groups. Understanding how a new tuberculosis vaccine may be introduced in different settings is an important area for future research.

There are remaining gaps that modelling can help to address to provide evidence for investing in tuberculosis vaccine development and delivery to inform the Full Value of Vaccine Assessment.[30] Estimates of the cost-effectiveness, budget impact, and wider benefits of specific tuberculosis

vaccine candidates would support research investment decision making. Future modelling research can help to better understand potential vaccine effectiveness considering a variety of factors, such as age, gender, duration of vaccine protection, and specific risk groups. We included an access-to-care structure in the model to account for differences in tuberculosis burden and healthcare access, which could be used to investigate vaccine targeting by income. Additionally, to maximise the potential evidence available to individual countries, it would be beneficial to create more detailed individual country models to inform vaccine introduction decision making.

Novel tuberculosis vaccines could have a substantial impact, which will vary depending on vaccine and delivery characteristics. Vaccination campaigns will be crucial for rapid impact and accelerated introduction similar to the pace of COVID-19 vaccine introduction may approximately double the lives saved before 2050. The COVID-19 pandemic has demonstrated the advantage that billions of dollars of investment can have on vaccine research and development, and this provides an illustration of what is possible to achieve with novel tuberculosis vaccines. Continued investment in tuberculosis vaccine research is required to strengthen vaccine development, trials, and manufacturing, and to support prompt introduction and scale-up.

Data sharing statement

No individual level participant data was used for this modelling study. Epidemiologic data used are available from the *World Health Organization Global TB Report CSV files to download* (https://www.who.int/teams/global-tuberculosis-programme/data) and summarised in the Supplementary Material section 9.2.1. Population estimates and projections are available from the *United Nations Department of Economic and Social Affairs World Population Prospects 2019* (https://population.un.org/wpp/Download/Standard/Population/). Analytic code will be made available at https://doi.org/10.5281/zenodo.6421372 immediately following publication indefinitely for anyone who wishes to access the data for any purpose.

Acknowledgements

We are grateful for the support of the World Health Organization for funding this research (2020/985800-0). We thank all the attendees at the WHO meetings on the Full Value Assessment of TB Vaccines for insightful advice and direction. We thank Philippe Glaziou (WHO) for reviewing and providing helpful suggestions on the paper.

Author contributions

Conception: RGW, NAM, MJ, RCH, CKW

Data acquisition and preparation: AD, RAC, CM, CKW, DS, AP, SM

Data analysis: RAC, CM, DS, CKW

Interpretation of results: RAC, RGW, NAM, CKW, CM, AP

Manuscript drafting and revisions: RAC, RGW, AP, NAM, CKW, CM, RCH, MJ, SM, DS, RB, NG, MZ, RCWH, BG, MQ, AD, AI

Declaration of interests

RCH reports employment by Sanofi Pasteur, unrelated to tuberculosis and outside the submitted work. All other authors declare no conflicts of interest.

References

1 World Health Organization. Global tuberculosis report 2021. Geneva: World Health Organization, 2021 https://apps.who.int/iris/handle/10665/346387 (accessed Jan 7, 2022).

2 McQuaid CF, Vassall A, Cohen T, Fiekert K, White RG. The impact of COVID-19 on TB: a review of the data. *Int J Tuberc Lung Dis* 2021; **25**: 436–46.

3 World Health Organization. WHO | WHO End TB Strategy. 2015.

4 New data shows COVID-19 combined with funding shortfalls are devastating efforts to end TB by 2030. http://www.stoptb.org/news/stories/2021/ns21_035.html (accessed Oct 4, 2021).

5 World Health Organization. WHO Preferred Product Characteristics for New Tuberculosis Vaccines. 2018 DOI:CC BY-NC-SA 3.0 IGO.

6 Tait DR, Hatherill M, Van Der Meeren O, *et al.* Final Analysis of a Trial of M72/AS01E Vaccine to Prevent Tuberculosis. *N Engl J Med* 2019; **381**: 2429–39.

7 Nemes E, Geldenhuys H, Rozot V, al E. Prevention of M. tuberculosis Infection with H4:1C31 Vaccine or BCG Revaccination. *N Engl J Med* 2018; **379**: 138–49.

8 Harris RC, Sumner T, Knight GM, Zhang H, White RG. Potential impact of tuberculosis vaccines in China, South Africa, and India. *Sci Transl Med* 2020; **12**: eaax4607.

9 Knight GM, Griffiths UK, Sumner T, *et al.* Impact and cost-effectiveness of new tuberculosis vaccines in low- and middle-income countries. *Proc Natl Acad Sci* 2014; **111**: 15520–5.

10 Richards AS, Sossen B, Emery JC, *et al.* The natural history of TB disease-a synthesis of data to quantify progression and regression across the spectrum. Epidemiology, 2021 DOI:10.1101/2021.09.13.21263499.

11 Emery J. Subclinical TB disease: lessons and questions from field to lab. *Present TB Sci* 2020.

12 Siroka A, Law I, Macinko J, *et al.* The effect of household poverty on tuberculosis. *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis* 2016; **20**: 1603–8.

13 Kwan CK, Ernst JD. HIV and Tuberculosis: a Deadly Human Syndemic. *Clin Microbiol Rev* 2011; **24**: 351–76.

14 Suthar AB, Lawn SD, del Amo J, *et al.* Antiretroviral Therapy for Prevention of Tuberculosis in Adults with HIV: A Systematic Review and Meta-Analysis. *PLoS Med* 2012; **9**: e1001270.

15 Iskauskas A. hmer: History Matching and Emulation Package. 2022 https://CRAN.R-project.org/package=hmer (accessed April 14, 2022).

16 Briggs AH, Weinstein MC, Fenwick EAL, *et al.* Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6. *Med Decis Mak Int J Soc Med Decis Mak* 2012; **32**: 722–32.

17 GHO | By category | BCG - Data by WHO region. WHO. https://apps.who.int/gho/data/view.main.81500?lang=en (accessed Jan 8, 2022).

18 Vaccination and Immunization Statistics. UNICEF DATA. https://data.unicef.org/topic/child-health/immunization/ (accessed March 7, 2022).

19 World Bank. World Bank Country and Lending Groups. Washington, DC: The World Bank. 2019 https://blogs.worldbank.org/opendata/new-country-classifications-income-level-2019-2020. (accessed Dec 4, 2020).

20 Harris RC, Sumner T, Knight GM, White RG. Systematic review of mathematical models exploring the epidemiological impact of future TB vaccines. *Hum Vaccines Immunother* 2016; **12**: 2813–32.

21 Weerasuriya CK, Clark RA, White RG, Harris RC. New tuberculosis vaccines: advances in clinical development and modelling. *J Intern Med* 2020; **288**: 661–81.

22 Our World in Data. Coronavirus (COVID-19) Vaccinations. *Our World Data* 2020. https://ourworldindata.org/covid-vaccinations (accessed March 7, 2022).

23 Nicolini LA, Giacobbe DR, Di Biagio A, Viscoli C. Insights on common vaccinations in HIV-infection: efficacy and safety. *J Prev Med Hyg* 2015; **56**: E28–32.

24 Kumarasamy N, Poongulali S, Beulah FE, *et al.* Long-term safety and immunogenicity of the M72/AS01E candidate tuberculosis vaccine in HIV-positive and -negative Indian adults. *Medicine (Baltimore)* 2018; **97**: e13120.

25 Shrestha S, Chihota V, White RG, Grant AD, Churchyard GJ, Dowdy DW. Impact of Targeted Tuberculosis Vaccination Among a Mining Population in South Africa: A Model-Based Study. *Am J Epidemiol* 2017; **186**: 1362–9.

26 Shrestha S, Chatterjee S, Rao KD, Dowdy DW. Potential impact of spatially targeted adult tuberculosis vaccine in Gujarat, India. *J R Soc Interface* 2016; **13**: 20151016.

27 Awad SF, Critchley JA, Abu-Raddad LJ. Epidemiological impact of targeted interventions for people with diabetes mellitus on tuberculosis transmission in India: Modelling based predictions. *Epidemics* 2020; **30**: 100381.

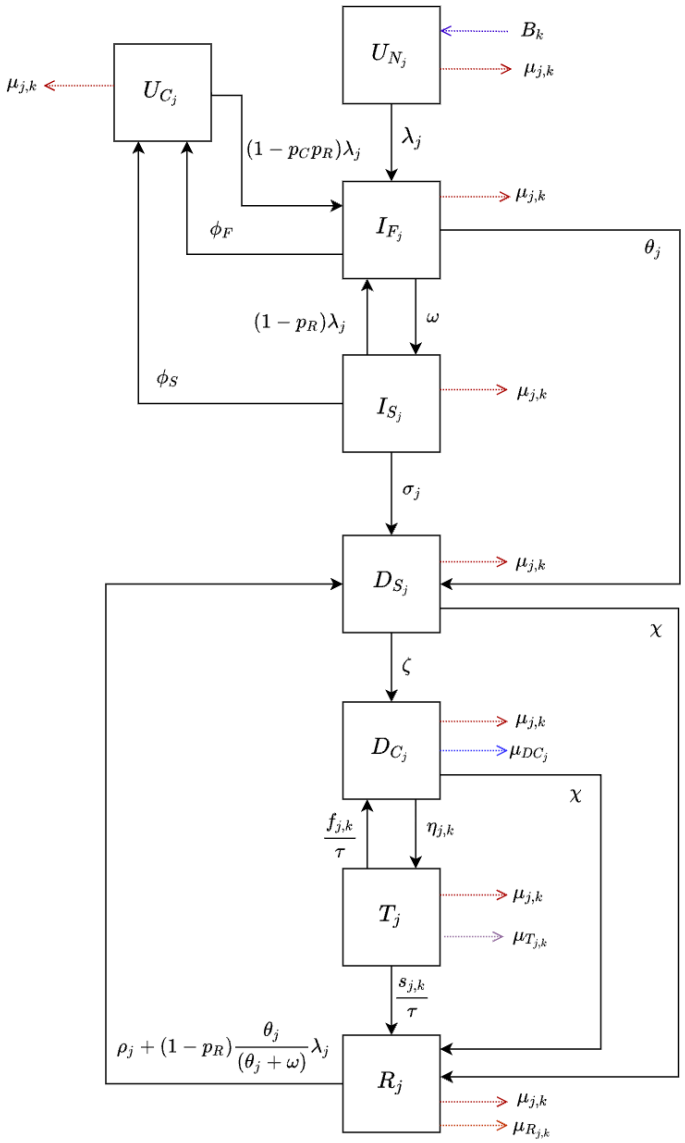
28 Harris RC, Sumner T, Knight GM, *et al.* Age-targeted tuberculosis vaccination in China and implications for vaccine development: a modelling study. *Lancet Glob Health* 2019; **7**: e209–18.

29 Weerasuriya CK, Harris RC, McQuaid CF, *et al.* The epidemiologic impact and cost-effectiveness of new tuberculosis vaccines on multidrug-resistant tuberculosis in India and China. *BMC Med* 2021; **19**: 60.

30 Hutubessy RCW, Lauer JA, Giersing B, *et al.* The Full Value of Vaccine Assessments (FVVA): A Framework to Assess and Communicate the Value of Vaccines for Investment and Introduction Decision Making. *SSRN Electron J* 2021. DOI:10.2139/ssrn.3841999.

Figures and Tables

Figure 1: Tuberculosis natural history model structure.



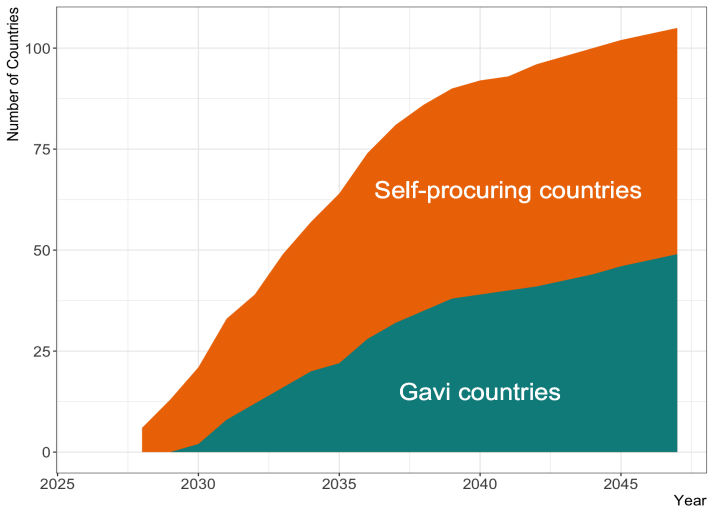
D_C = Clinical Disease, D_S = Subclinical Disease; I_F = Infection-Fast, I_S = Infection-Slow, R = Resolved, T = On-Treatment, U_C = Uninfected-Cleared, U_N = Uninfected-Naive.

See Supplementary Material section 1 for further details.

Table 1: Characteristics of modelled vaccine delivery scenarios

	Infant Vaccine Scenarios		**Adolescent/Adult Vaccine Scenarios**		
Characteristics	***Basecase***	***Accelerated Scale-up***	***Basecase***	***Accelerated Scale-up***	***Routine Only***
Ages targeted	*Neonatal:* Routine	*Neonatal:* Routine	*Age 9:* Routine *Ages ≥10:* One-time vaccination campaign over 5 years	*Age 9:* Routine *Ages ≥10:* One-time vaccination campaign in 2025	*Age 9:* Routine
Introduction year	Country-specific	2025	Country-specific	2025	Country-specific
Vaccine rollout trend	5-year linear scale-up to coverage	Instant scale-up to coverage	5-year linear scale-up to coverage	Instant scale-up to coverage	5-year linear scale-up to coverage
Coverage target *(Low/Med/High)*	75% / 85% / 95%		*Age 9:* 70% / 80% / 90% *Ages ≥10:* 50% / 70% / 90%		

Figure 2: Assumed cumulative number of countries introducing the novel vaccine by year for the *Basecase* and *Routine Only* scenarios.



The earliest vaccine introduction occurs in 2028 and the latest in 2047. See Supplementary Material section 7 for full details.

Table 2: Estimated health impact in 2050 by WHO region, income level, and tuberculosis burden level for select vaccine scenarios (all 10-years duration of protection and medium coverage targets). Value in cell is the median estimate and 95% uncertainty range.

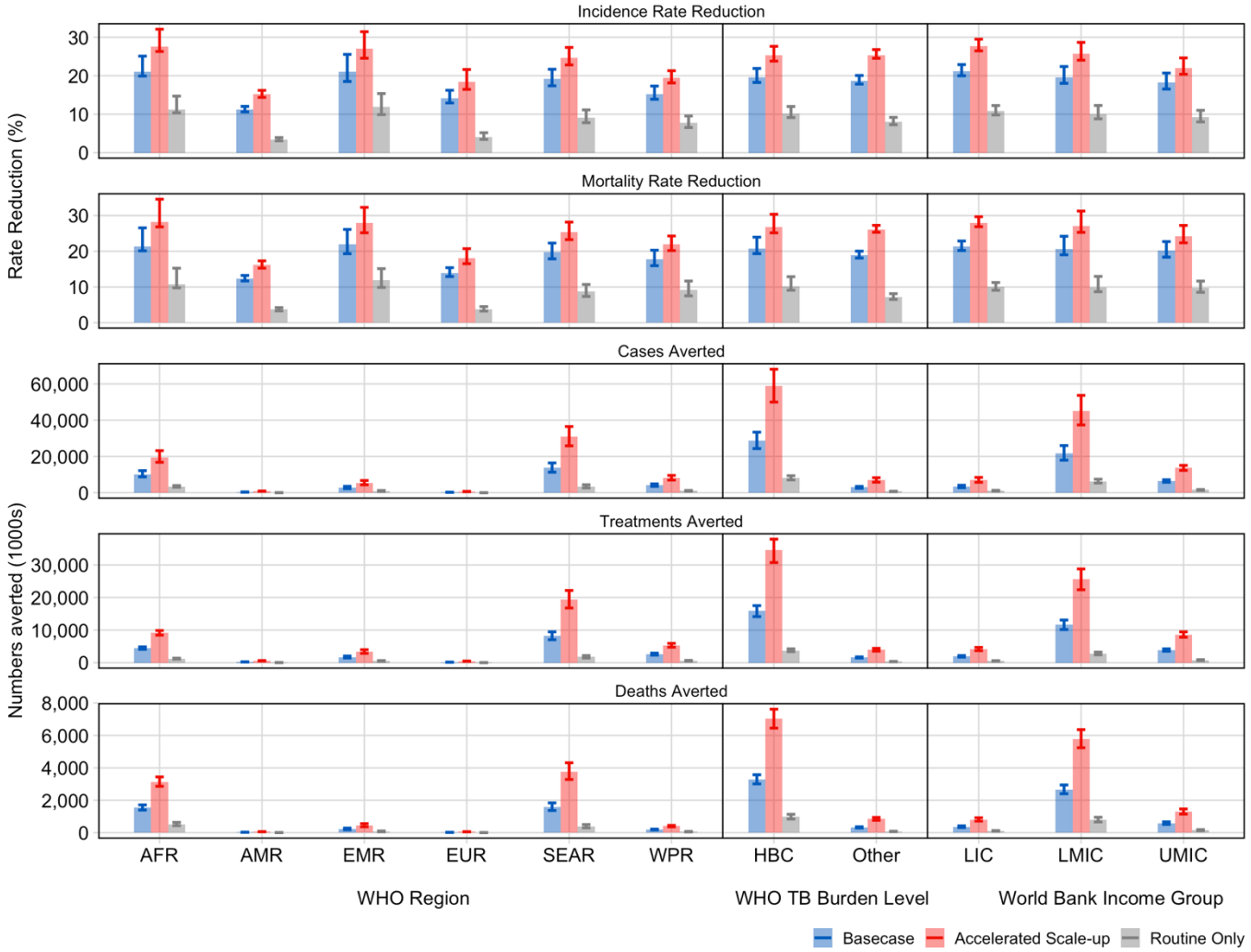
	Health Impact Measure	All modelled countries	WHO Region						World Bank Income Group			TB Burden Level	
Vaccine Scenario			**AFR**	**AMR**	**EMR**	**EUR**	**SEAR**	**WPR**	**LIC**	**LMIC**	**UMIC**	**HBC**	**All other countries**
Adolescent/*adult vaccine*													
Basecase	IRR in 2050 (%)	19·5% (18·3–21·6)	21·1% (19·9–25·1)	11·2% (10·6–12·0)	21·1% (18·5–25·5)	14·2% (12·9–16·2)	19·2% (17·4–21·7)	15·2% (13·9–17·3)	21·2% (20·0–22·9)	19·6% (18·0–22·4)	18·3% (16·5–20·7)	19·6% (18·3–21·9)	18·7% (17·8–20·1)
	MRR in 2050 (%)	20·6% (19·2–23·4)	21·3% (20·1–26·5)	12·4% (11·7–13·2)	21·9% (19·3–26·1)	13·9% (12·9–15·4)	19·8% (17·9–22·3)	17·7% (15·9–20·3)	21·4% (20·2–22·9)	20·6% (19·0–24·2)	20·2% (18·3–22·7)	20·8% (19·3–23·9)	18·9% (18·1–20·0)
	Averted cases before 2050	31·5m (26·9–36·9)	10·2m (8·7–12·1)	0·4m (0·3–0·4)	2·8m (2·2–3·5)	0·2m (0·2–0·3)	13·8m (11·3–16·4)	4·1m (3·5–4·8)	3·4m (2·8–4·1)	21·8m (18·0–26·0)	6·4m (5·8–7·1)	28·6m (24·4–33·4)	2·9m (2·4–3·5)
	Averted deaths before 2050	3·6m (3·3–3·9)	1·5m (1·4–1·7)	0·02m (0·02–0·03)	0·2m (0·2–0·3)	0·02m (0·02–0·02)	1·6m (1·4–1·8)	0·2m (0·2–0·2)	0·4m (0·3–0·4)	2·7m (2·4–2·9)	0·6m (0·5–0·7)	3·3m (3·0–3·6)	0·3m (0·3–0·4)
	Averted tx before 2050	17·5m (15·6–19·2)	4·5m (4·1–4·8)	0·2m (0·2–0·3)	1·7m (1·4–2·0)	0·2m (0·1–0·2)	8·2m (7·1–9·5)	2·6m (2·3–2·9)	1·9m (1·7–2·2)	11·7m (10·2–13·1)	3·9m (3·5–4·2)	15·9m (14·1–17·5)	1·6m (1·4–1·8)
Accelerated Scale-up	IRR in 2050 (%)	25·2% (23·9–27·5)	27·6% (26·3–32·1)	15·2% (14·4–16·2)	27·1% (24·5–31·4)	18·4% (16·5–21·6)	24·7% (22·8–27·4)	19·4% (18·1–21·3)	27·7% (26·5–29·5)	25·7% (24·0–28·6)	22·0% (20·4–24·6)	25·3% (23·8–27·6)	25·4% (24·5–26·8)
	MRR in 2050 (%)	26·7% (25·2–29·9)	28·2% (26·8–34·6)	16·2% (15·3–17·3)	27·9% (25·2–32·3)	18·1% (16·5–20·7)	25·3% (23·2–28·2)	21·8% (20·2–24·3)	28·0% (26·9–29·7)	27·0% (25·3–31·2)	24·3% (22·3–27·2)	26·8% (25·1–30·4)	26·1% (25·3–27·2)
	Averted cases before 2050	65·7m (55·8–76·2)	19·5m (16·8–23·2)	0·8m (0·7–1·0)	5·4m (4·4–6·7)	0·6m (0·5–0·7)	31·1m (25·9–36·5)	8·1m (7·0–9·5)	7·0m (5·7–8·4)	45·2m (37·4–53·7)	13·7m (12·3–15·1)	58·8m (50·0–68·1)	7·0m (5·8–8·3)
	Averted deaths before 2050	7·9m (7·3–8·5)	3·1m (2·9–3·4)	0·1m (0·1–0·1)	0·4m (0·4–0·6)	0·1m (0·1–0·1)	3·8m (3·3–4·3)	0·4m (0·4–0·4)	0·8m (0·7–0·9)	5·8m (5·2–6·4)	1·3m (1·1–1·5)	7·0m (6·4–7·6)	0·8m (0·8–0·9)
	Averted tx before 2050	38·6m (34·4–42·3)	9·2m (8·5–9·9)	0·6m (0·5–0·7)	3·4m (2·9–4·0)	0·4m (0·4–0·5)	19·4m (16·8–22·2)	5·3m (4·8–5·9)	4·2m (3·7–4·7)	25·7m (22·4–28·8)	8·6m (7·8–9·5)	34·5m (30·7–37·9)	4·0m (3·5–4·4)

Routine Only	IRR in 2050 (%)	9·9% (9·0–11·6)	11·2% (10·4–14·7)	3·5% (3·1–3·9)	11·9% (9·9–15·4)	4·1% (3·4–5·2)	9·1% (7·8–11·1)	7·7% (6·5–9·5)	10·8% (9·8–12·3)	10·0% (8·8–12·3)	9·2% (8·0–11·0)	10·2% (9·1–12·0)	8·0% (7·3–9·2)
	MRR in 2050 (%)	9·9% (8·9–12·3)	10·7% (9·7–15·2)	3·7% (3·3–4·2)	11·9% (9·9–15·1)	3·7% (3·2–4·5)	8·7% (7·3–10·7)	9·2% (7·5–11·7)	10·0% (9·1–11·2)	9·9% (8·7–13·0)	9·8% (8·5–11·6)	10·2% (9·1–12·9)	7·2% (6·5–8·1)
	Averted cases before 2050	8·8m (7·7–10·1)	3·5m (3·0–3·9)	0·04m (0·03–0·05)	0·9m (0·7–1·2)	0·02m (0·02–0·03)	3·4m (2·6–4·4)	1·0m (0·8–1·2)	1·0m (0·8–1·3)	6·3m (5·3–7·4)	1·5m (1·3–1·7)	8·1m (7·0–9·4)	0·7m (0·6–0·8)
	Averted deaths before 2050	1·1m (0·9–1·2)	0·5m (0·4–0·6)	0·003m (0·003–0·004)	0·1m (0·1–0·1)	0·002m (0·002–0·003)	0·4m (0·3–0·5)	0·1m (0·0–0·1)	0·1m (0·1–0·1)	0·8m (0·7–0·9)	0·2m (0·1–0·2)	1·0m (0·8–1·1)	0·1m (0·1–0·1)
	Averted tx before 2050	4·1m (3·7–4·6)	1·2m (1·1–1·4)	0·02m (0·02–0·03)	0·5m (0·4–0·6)	0·01m (0·01–0·02)	1·8m (1·4–2·2)	0·6m (0·5–0·7)	0·5m (0·5–0·6)	2·8m (2·4–3·2)	0·8m (0·7–0·9)	3·8m (3·4–4·2)	0·3m (0·3–0·4)
Infant vaccine													
Basecase	IRR in 2050 (%)	8·8% (7·9–10·4)	11·0% (10·0–14·6)	2·7% (2·4–3·1)	12·0% (9·7–15·6)	2·9% (2·5–3·4)	6·9% (5·8–8·6)	7·2% (5·9–9·2)	10·1% (9·1–11·5)	9·1% (7·9–11·2)	7·0% (6·2–8·1)	9·0% (8·1–10·7)	7·1% (6·4–8·2)
	MRR in 2050 (%)	9·8% (8·7–12·0)	11·3% (10·1–15·7)	3·7% (3·2–4·3)	13·4% (10·5–18·1)	3·3% (2·9–3·9)	7·2% (5·9–9·6)	11·2% (8·5–15·4)	10·4% (9·4–11·9)	9·9% (8·5–12·7)	8·4% (7·2–10·0)	10·1% (8·9–12·5)	7·1% (6·4–8·0)
	Averted cases before 2050	6·7m (5·8–7·7)	2·9m (2·5–3·4)	0·03m (0·02–0·03)	0·8m (0·6–1·1)	0·02m (0·01–0·02)	2·2m (1·6–2·8)	0·8m (0·6–1·0)	0·8m (0·7–1·1)	4·9m (4·2–5·7)	1·0m (0·8–1·1)	6·2m (5·3–7·1)	0·5m (0·4–0·6)
	Averted deaths before 2050	0·9m (0·8–1·0)	0·5m (0·4–0·6)	0·003m (0·002–0·003)	0·1m (0·1–0·1)	0·002m (0·002–0·002)	0·3m (0·2–0·4)	0·1m (0·0–0·1)	0·1m (0·1–0·1)	0·7m (0·6–0·8)	0·1m (0·1–0·1)	0·8m (0·7–1·0)	0·1m (0·1–0·1)
	Averted tx before 2050	2·7m (2·4–2·9)	0·9m (0·8–0·9)	0·02m (0·01–0·02)	0·4m (0·3–0·5)	0·01m (0·01–0·01)	1·0m (0·8–1·2)	0·4m (0·3–0·5)	0·4m (0·3–0·4)	1·8m (1·6–2·1)	0·4m (0·4–0·5)	2·4m (2·2–2·7)	0·2m (0·2–0·3)
Accelerated Scale-up	IRR in 2050 (%)	14·3% (13·0–16·7)	16·7% (15·5–21·6)	4·6% (4·2–5·2)	17·6% (14·5–22·3)	7·5% (6·2–9·9)	12·9% (11·0–15·8)	10·3% (8·7–12·6)	16·6% (15·3–18·6)	14·5% (12·8–17·7)	12·1% (10·7–14·4)	14·4% (13·0–17·1)	13·4% (12·4–14·9)
	MRR in 2050 (%)	15·9% (14·3–19·3)	17·5% (15·9–24·1)	5·8% (5·2–6·6)	19·2% (15·5–24·7)	7·7% (6·5–9·5)	13·4% (11·2–17·0)	15·0% (12·1–19·3)	17·5% (16·1–19·5)	15·9% (13·9–20·2)	14·4% (12·6–17·0)	16·1% (14·3–19·9)	14·1% (13·1–15·3)
	Averted cases before 2050	16·3m (14·1–18·8)	6·3m (5·4–7·2)	0·1m (0·1–0·1)	1·7m (1·3–2·2)	0·1m (0·1–0·1)	6·6m (5·1–8·6)	1·5m (1·2–1·9)	2·1m (1·7–2·6)	11·5m (9·6–13·7)	2·7m (2·4–3·1)	14·7m (12·6–17·1)	1·6m (1·3–1·9)
	Averted deaths before 2050	2·3m (2·0–2·6)	1·1m (0·9–1·2)	0·01m (0·01–0·01)	0·2m (0·1–0·2)	0·01m (0·01–0·01)	0·9m (0·7–1·2)	0·1m (0·1–0·2)	0·3m (0·2–0·3)	1·7m (1·4–2·0)	0·3m (0·3–0·4)	2·0m (1·8–2·3)	0·2m (0·2–0·3)

	Averted tx before 2050	7·7m (6·9–8·6)	2·2m (2·0–2·4)	0·04m (0·04–0·05)	0·9m (0·8–1·2)	0·04m (0·04–0·05)	3·6m (2·9–4·3)	0·9m (0·7–1·0)	1·1m (0·9–1·2)	5·1m (4·5–6·0)	1·4m (1·3–1·7)	6·9m (6·2–7·8)	0·7m (0·7–0·8)

Abbreviations: AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, HBC = high burden countries, IRR = incidence rate reduction, LIC = low-income countries, LMIC = lower-middle income countries, MRR = mortality rate reduction, SEAR = WHO South-East Asian Region, tx = treatments, UMIC = upper-middle income countries, WPR = WHO Western Pacific Region. See Supplementary Material section 10 for all scenarios.

Figure 3: Incidence and mortality rate reductions in 2050, and cumulative cases, treatments, and deaths averted between vaccine introduction and 2050 for the adolescent/adult vaccine with varying delivery scenarios (50% efficacy vaccine, medium coverage, 10-years duration of protection), by WHO region, WHO TB burden level, and World Bank income group.



Abbreviations: AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, HBC = high-burden countries, LIC = low-income countries, LMIC = lower-middle income countries, SEAR = WHO South-East Asian Region, UMIC = upper-middle income countries, WPR = WHO Western Pacific Region

Supplementary Material for *The impact of alternative delivery strategies for novel tuberculosis vaccines in low- and middle-income countries: a modelling study*

Rebecca A. Clark et al.

Table of Contents

SUPPLEMENTAL METHODS: 3
1. Model structure and equations 3
1.1 Tuberculosis natural history dimension 3
1.1.1 Tuberculosis natural history structure 3
1.1.2 Tuberculosis natural history equations 5
1.1.3 Force of infection equation 6
1.2 HIV and ART structure 7
1.2.1 HIV and ART description 7
1.2.2 HIV and ART diagram 7
1.2.3 HIV and ART equations 8
1.2.4 Natural history equations incorporating HIV and ART 8
1.3 Access to Care Dimension 9
1.3.1 Access to care description 9
2. Model Parameters and Data Sources 10
2.1 Model Parameters and Data Sources 10
2.2 Operationalizing Age Varying Parameters 13
3. Tuberculosis treatment 14
3.1 Tuberculosis treatment initiation 14
3.2 Tuberculosis treatment outcomes 14
4. Calibration methodology 16
5. Low- and middle-income countries 17
5.1 Eligible countries 17
5.2 Countries excluded from attempting calibration 18
5.3 Countries incorporating the HIV structure 19
6. No-New-Vaccine baselines 20
6.1 *Status Quo No-New-Vaccine* baseline 20
6.2 *2025 End TB No-New-Vaccine* baseline 20
7. Vaccination 21
7.1 Vaccine profile 21
7.2 Vaccine delivery scenarios 21
7.2.1 Country-specific introduction years 21
7.2.2 Vaccine coverage targets 24
7.3 Vaccine implementation 26

7.3.1 Vaccine structure 26
7.3.1 Vaccine implementation in the tuberculosis natural history model 28
8. Model outcomes 29
8.1 Epidemiological impact measures 29
8.2 Groupings for reporting model outcomes 29
8.2 Calculating uncertainty 34
SUPPLEMENTAL RESULTS: 35
9. Model Calibration 35
9.1 LMIC countries calibration 35
9.2 WHO Region and World Bank Income Group for Calibrated LMICs 35
9.3 *Status Quo No-New-Vaccine* baseline calibration target values 36
9.4 Calibrated *Status-Quo No-New-Vaccine* baseline trends 45
10. Vaccine Health Impact Results 49
10.1 Incidence and mortality rate reductions and cumulative cases, treatments, and deaths averted 49
References 60

SUPPLEMENTAL METHODS:

1. Model structure and equations

We created a compartmental tuberculosis vaccine model, which includes separate structures to account for key modelling components required. The structures, or "dimensions" we incorporated into the low- and middle-income country (LMIC) modelling are age, tuberculosis natural history, HIV and ART, and access to care.

1.1 Tuberculosis natural history dimension

1.1.1 Tuberculosis natural history structure

The core natural history model is specified in Figure S1.1. Model parameters used in the tuberculosis natural history dimension and their definitions are provided in Table S3.1.

Those with no previous exposure or infection with *Mtb* [Uninfected-Naive (U_N)] could become infected at rate λ_j and progress to an Infection-Fast (I_F) class following initial infection. From Infection-Fast, three possible pathways were possible: (i) Fast progression to Subclinical Disease (D_S), where individuals are infectious with a reduced infectiousness compared to clinical tuberculosis, but display no symptoms of tuberculosis disease;[1] (ii) self-clearance to Uninfected-Cleared (U_C), where individuals are no longer infected with *Mtb* and therefore are not at risk of progression to tuberculosis disease without reinfection;[2] or (iii) continue to remain latently infected with a risk of reactivation and progression to disease, albeit at a lower rate than Infection-Fast, by transitioning to the Infection-Slow (I_S) class. Those in the Infection-Slow class could self-clear to the Uninfected-Cleared class, be reinfected and return to the Infection-Fast class, or reactivate their infection and progress to Subclinical Disease.

Once in the Subclinical Disease class, individuals could naturally cure (*without* treatment) to the Resolved (R) class, or progress to Clinical Disease (D_C), where individuals are infectious and display symptoms of tuberculosis disease. Treatment initiation from Clinical Disease to On-Treatment (T) began in 1960 and increased following a sigmoid curve to 2019, with average treatment duration assumed to be 6 months.[3,4] Treatment completions transitioned to the Resolved class and treatment non-completions returned to Clinical Disease. Deaths occurring on-treatment and in clinical disease counted toward the total number of tuberculosis deaths during the year. Those with clinical disease could also naturally cure to the resolved class. Individuals in the Resolved class could be reinfected or relapse to Subclinical Disease but could *not* enter Infection-Fast or Infection-Slow directly. We assumed that the infection and resolved classes are partially protected against reinfection.[5,6] In those who have self-cleared, we assumed the level of protection against reinfection is half of the protection against reinfection for the infection and resolved classes.

Age was modelled in single years from ages 0 to 79 and aggregated into two categories for ages 80 to 89, and ages 90 to 99. Births and ageing occurred at the beginning of each year.

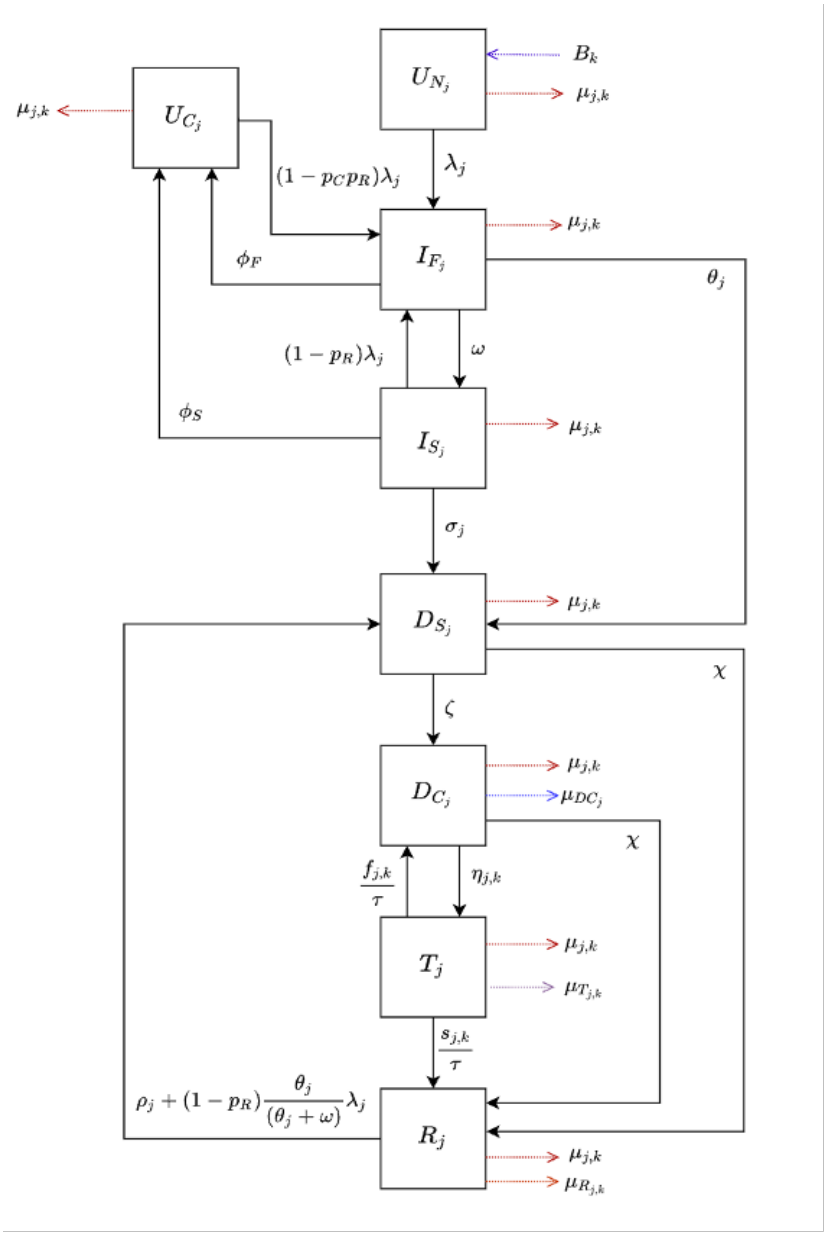


Figure S1.1 Tuberculosis natural history model

Abbreviations: D_C = Clinical Disease; D_S = Subclinical Disease; I_F = Infection-Fast; I_S = Infection-Slow; R = Resolved; T = On-Treatment; U_C = Uninfected-Cleared; U_N = Uninfected-Naive.

1.1.2 Tuberculosis natural history equations

$Age\ j = 0$

$$\frac{dU_{N_j}}{dt} = B_k - (\lambda_j + \mu_{j,k})U_{N_j}$$

$Age\ j \neq 0$

$$\frac{dU_{N_j}}{dt} = -(\lambda_j + \mu_{j,k})U_{N_j}$$

$$\frac{dU_{C_j}}{dt} = \phi_F I_{F_j} + \phi_S I_{S_j} - [(1 - p_C p_R)\lambda_j + \mu_{j,k}]U_{C_j}$$

$$\frac{dI_{F_j}}{dt} = \lambda_j U_{N_j} + (1 - p_C p_R)\lambda_j U_{C_j} + [(1 - p_R)\lambda_j]I_{S_j} - (\phi_F + \omega + \theta_j + \mu_{j,k})I_{F_j}$$

$$\frac{dI_{S_j}}{dt} = \omega I_{F_j} - (\phi_S + \sigma_j + (1 - p_R)\lambda_j + \mu_{j,k})I_{S_j}$$

$$\frac{dD_{S_j}}{dt} = \theta_j I_{F_j} + \sigma_j I_{S_j} + [\rho_j + (1 - p_R)\frac{\theta_j}{\theta_j + \omega}\lambda_j]R_j - (\chi + \zeta + \mu_{j,k})D_{S_j}$$

$$\frac{dD_{C_j}}{dt} = \zeta D_{S_j} + \frac{f_{j,k}}{\tau}T_j - (\chi + \eta_{j,k} + \mu_{DC_j} + \mu_{j,k})D_{C_j}$$

$$\frac{dT_j}{dt} = \eta_{j,k} D_{C_j} - \left(\frac{s_{j,k} + f_{j,k}}{\tau} + \mu_{T_{j,k}} + \mu_{j,k}\right)T_j$$

$$\frac{dR_j}{dt} = \frac{s_{j,k}}{\tau}T_j + (D_{S_j} + D_{C_j})\chi - [\rho_j + (1 - p_R)\frac{\theta_j}{\theta_j + \omega}\lambda_j + \mu_{R_j} + \mu_{j,k}]R_j$$

1.1.3 Force of infection equation

The equation for the age-specific force of infection (λ_j), or the rate at which Uninfected-Naïve individuals acquire *Mtb* infection in the population, is given below. Clinically, infection with *Mtb* can present as pulmonary tuberculosis which impacts the lungs, and extrapulmonary tuberculosis (EPTB) which occurs in sites other than the lungs.[7,8] EPTB is not infectious, and as we are modelling *Mtb* transmission we would want to exclude it. However, the WHO tuberculosis estimates which we calibrated to include both EPTB and pulmonary tuberculosis. Therefore, instead of excluding EPTB from the model, we discounted the force of infection by the proportion of incident cases that are EPTB to account for the fact that they are not infectious and calibrated to the targets that include both EPTB and pulmonary tuberculosis. We also discounted the force of infection to account for the relative reduced infectiousness of subclinical disease compared to clinical disease.

$$\lambda_j = p_T \times \sum_{y=1}^{n_{ygroups}} C[m,y] \times \left(\frac{(1-ep)(TD_{C_y} + rTD_{S_y})}{N_y} \right)$$

where:

$$N_y = \sum_{j=j_{min}}^{j_{max}} U_{N_j} + U_{C_j} + I_{F_j} + I_{S_j} + D_{S_j} + D_{C_j} + T_j + R_j$$

$$TD_{C_y} = \sum_{j=j_{min}}^{j_{max}} D_{C_j} \qquad TD_{S_y} = \sum_{j=j_{min}}^{j_{max}} D_{S_j}$$

Parameter	Definition
j	Age of individual (in years)
y	Age group of contact
$n_{ygroups}$	Number of contact age groups
p_T	Accounting for the probability of transmission per infectious contact
m	Age group of individual
$C[m,y]$	Contact rate between individual of age group m and contact of age group y from Prem et al.[9]
ep	Average proportion of tuberculosis cases that are extrapulmonary
r	Proportional reduction in infectiousness from subclinical disease
TD_{C_y}	Total population in a clinical disease class in age group y
TD_{S_y}	Total population in a subclinical disease class in age group y
N_y	Total population alive in age group y
j_{min}	Minimum age j within age group y
j_{max}	Maximum age j within age group y

1.2 HIV and ART structure

1.2.1 HIV and ART description

In order to account for the influences of human immunodeficiency virus (HIV) and antiretroviral therapy (ART) on the risk of infection with *Mtb* and progression to tuberculosis disease,[10,11] we have implemented an HIV structure composed of 3 compartments: HIV uninfected [HIV_0], people living with HIV (PLHIV) not on ART [HIV_1], and PLHIV on ART [ART]. HIV uninfected individuals were diagnosed with HIV and moved from the HIV_0 compartment to the HIV_1 compartment with rate λ_H. Within the HIV_1 compartment, there is a higher risk of tuberculosis progression and an increased tuberculosis mortality rate compared to the HIV_0 compartment. PLHIV are initiated on treatment with ART from HIV_1 following a sigmoid trend. The increases in tuberculosis mortality rate and tuberculosis progression are reduced while in ART compared to HIV_1, but still higher than in HIV_0. ART also reduces the HIV mortality rate. Model parameters used in the HIV and ART structure and their definitions are provided in Table S3.1.

1.2.2 HIV and ART diagram

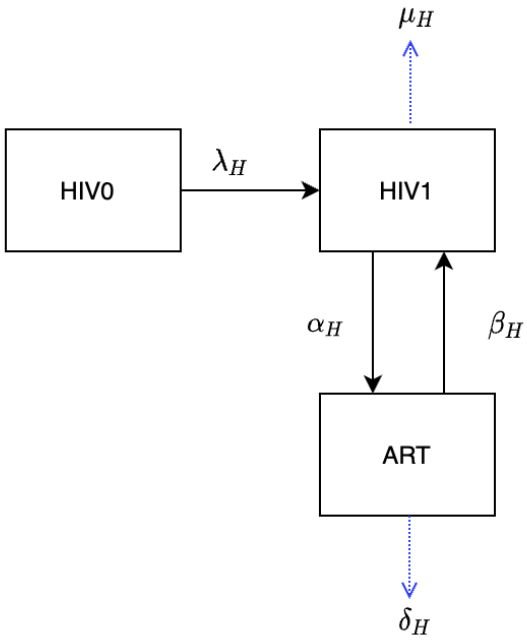


Figure S1.2 HIV and ART structure

1.2.3 HIV and ART equations

$$\frac{d\ \mathrm{HIV}_0}{dt} = -\lambda_H \mathrm{HIV}_0$$

$$\frac{d\ \mathrm{HIV}_1}{dt} = \lambda_H \mathrm{HIV}_0 + \beta_H \mathrm{ART} - (\alpha_H + \mu_H)\mathrm{HIV}_1$$

$$\frac{d\ \mathrm{ART}}{dt} = \alpha_H \mathrm{HIV}_1 - (\beta_H + \delta_H)\mathrm{ART}$$

1.2.4 Natural history equations incorporating HIV and ART

Let $p_{adj} = (1 + th1(\theta_{mul} - 1))$

$Age\ j = 0$	$Age\ j \neq 0$
$\frac{dU_{N_j}}{dt} = B_k - (\lambda_j + \mu_{j,k})U_{N_j}$	$\frac{dU_{N_j}}{dt} = -(\lambda_j + \mu_{j,k})U_{N_j}$

$$\frac{dU_{C_j}}{dt} = \phi_F I_{F_j} + \phi_S I_{S_j} - [(1 - p_C p_R)\lambda_j + \mu_{j,k}]U_{C_j}$$

$$\frac{dI_{F_j}}{dt} = \lambda_j U_{N_j} + (1 - p_C p_R)\lambda_j U_{C_j} + [(1 - p_R)\lambda_j]I_{S_j} - (\phi_F + \omega + p_{adj}\theta_j + \mu_{j,k})I_{F_j}$$

$$\frac{dI_{S_j}}{dt} = \omega I_{F_j} - (\phi_S + p_{adj}\sigma_j + (1 - p_R)\lambda_j + \mu_{j,k})I_{S_j}$$

$$\frac{dD_{S_j}}{dt} = p_{adj}\theta_j I_{F_j} + p_{adj}\sigma_j I_{S_j} + [p_{adj}\rho_j + (1 - p_R)\frac{p_{adj}\theta_j}{p_{adj}\theta_j + \omega}\lambda_j]R_j - (\chi + \zeta + \mu_{j,k})D_{S_j}$$

$$\frac{dD_{C_j}}{dt} = \zeta D_{S_j} + \frac{f_{j,k}}{\tau}T_j - (\chi + \eta_{j,k} + m_{adj}\mu_{DC_j} + \mu_{j,k})D_{C_j}$$

$$\frac{dT_j}{dt} = \eta_{j,k} D_{C_j} - \left(\frac{s_{j,k} + f_{j,k}}{\tau} + m_{adj}\mu_{T_{j,k}} + \mu_{j,k}\right)T_j$$

$$\frac{dR_j}{dt} = \frac{s_{j,k}}{\tau}T_j + (D_{S_j} + D_{C_j})\chi - [p_{adj}\rho_j + (1 - p_R)\frac{p_{adj}\theta_j}{p_{adj}\theta_j + \omega}\lambda_j + m_{adj}\mu_{R_j} + \mu_{j,k}]R_j$$

1.3 Access to Care Dimension

1.3.1 Access to care description

The access to care dimension is incorporated to allow for the negative correlation between tuberculosis burden and health care access to prevent the overestimation of vaccine impact, as well as to facilitate future analyses of equity implications of vaccine introduction. The access to care dimension contains 2 classes: high-access-to-care, representing the top 3 quintiles (60% of the population) and low-access-to-care, representing the bottom 2 quintiles (40% of the population). We assumed that there was no transition between the high- and low-access-to-care classes, as well as assuming random mixing between the high-access-to-care and low-access-to-care classes.

To constrain relative burden between access-to-care classes, we calibrated the relative tuberculosis prevalence in the high-access-to-care class to the low-access-to-care class in 2019. The calibration target, 0·674, was calculated as a weighted average from ten studies, with lower and upper bounds (0·575–0·801) representing the 25th and 75th percentiles of the datasets.[12–21]

To incorporate access to care into our model, we assume that the differences in tuberculosis burden between classes are due to differences in the force of infection, the rate of care-seeking (i.e., tuberculosis treatment initiation), and the rate of tuberculosis progression. We assume relative to the low-access-to-care strata, the high-access-to-care strata has a reduced force of infection per contact, an increased rate of treatment initiation, and a reduced rate of tuberculosis progression. Differential burden was implemented by introducing a new parameter p_E, such that $p_E \in [0, 1]$ for the high-access-to-care and $p_E = 0$ and included within the model natural history structure as described in Table S1.1. This new parameter was fitted during calibration.

Table S1.1 Implementing the access-to-care parameter

	Access-to-Care
Force of infection	$p_T \times \sum_{y=1}^{n_{ygroups}} (1 - p_E) \times C[m, y] \times \left(\frac{(1-ep)(TD_{C_y} + rTD_{S_y})}{N_y}\right)$
Treatment Initiation Rate	$\frac{\eta_{j,k}}{(1-p_E)}$
Rate of Tuberculosis Progression	$(1 - p_E) \times \theta_j$ $(1 - p_E) \times \sigma_j$ $(1 - p_E) \times \rho_j$

2. Model Parameters and Data Sources

2.1 Model Parameters and Data Sources

Parameters used in the natural history model structure and the HIV and ART model structure are provided in Table S2.1 below, along with their definitions, sources, and information on whether the parameter is fixed or varied (as well as whether they are varied by age or time) during calibration. Further details about how the age varying parameters are implemented are provided in section 2.2.

Table S2.1 Demographic and tuberculosis natural history parameters and definitions

Description	Units	Symbol	Prior	Fixed or Varying During Calibration	Age Varying	Time Varying	Source
Births and deaths (excluding on-treatment mortality)							
Birth rate	Per year	B_k	United Nations World Population Prospects population estimates and projections	Fixed	No	Yes	[22]
Background mortality rate	Per year	$\mu_{j,k}$	Calculated in the model from United Nations population estimates and projections	Fixed	Yes, age specific mortality rates from demographic dataset	Yes	[22]
Mortality rate for clinical tuberculosis disease	Per person per year	μ_{DC_j}	(0–0·178)	Varying	Yes, value for children is greater than value for adults	No	[23]
Mortality rate post-tuberculosis disease	Per person per year	μ_{R_j}	$0.22\mu_{j,k}$	Fixed relationship	Yes, because $\mu_{j,k}$ varies	Yes, because $\mu_{j,k}$ varies	[24]
Natural history							
Force of infection	Per year	λ_j	Fitted	Fixed equation	Yes, age specific contact rates[9]	No	*Calculated*
Probability of transmission per infectious contact	-	p_T	(0–0·0068)	Varying	No	No	*Assumed*

Fraction of total tuberculosis disease that is extrapulmonary	-	ep	Country-specific average of previous 3 years	Fixed	No	No	[25,26]
Infectiousness of subclinical relative to clinical tuberculosis	-	r	0·80	Fixed	No	No	[27]
Rate of self-clearance from I_F to U_C	Per person per year	ϕ_F	0·00000140	Fixed	No	No	[2]
Rate of self-clearance from I_S to U_C	Per person per year	ϕ_S	(0·0254–0·0467)	Varying	No	No	[2]
Rate of fast progression to disease, by age	Per person per year	θ_j	(0·0696–0·111)	Varying	Yes, value for children is less than value for adults	No	[2]
Rate from I_F to I_S	Per person per year	ω	0·5	Fixed	No	No	*Defined*
Rate of reactivation from I_S, by age	Per person per year	σ_j	(0·000135–0·00113)	Varying	Yes, value for children is less than value for adults	No	[2]
Rate of progression from D_S to D_C	Per person per year	ζ	(0–1)	Varying	No	No	*Assumed*
Rate of natural cure from D_C and D_S	Per person per year	χ	(0·1–0·25)	Varying	No	No	[28,29]
Rate of relapse from R, by age	Per person per year	ρ_j	(0·0001–0·07)	Varying	Yes, value for children is less than value for adults	No	[30–32]
Treatment outcome parameters							
Treatment duration	Number of years	τ	0·5	Fixed	No	No	[3,4]
Rate of on-treatment mortality	Per person per year	$\mu_{T_j} = \frac{\kappa_j}{\tau}$	Country-specific	Varying	Yes, value for children greater than value for adults	Yes	[33]
Rate of treatment completion	Per person per year	$\frac{s_j}{\tau}$	Country-specific	Fixed equation	Yes, indirectly scaled by s_{Age}	Yes	[33]

Rate of treatment non-completion	Per person per year	$\frac{f_j}{\tau}$	Country-specific	Fixed equation	Yes, indirectly scaled by s_{Age}	Yes	[33]
Protection parameters							
Protection from reinfection I_S, I_F, R	-	p_R	(0·6–0·85)	Varying	No	No	[5,6,28,29,34]
Relative protection from reinfection for self-clearance compared to p_R	-	p_C	0·50	Fixed	No	No	*Assumed*
SES parameter	-	p_E	(0–1)	Varying	No	No	*Assumed*
HIV parameters							
HIV incidence rate	Per year	λ_H	(0–1)	Varying	No	No	*Assumed*
Rate of ART initiation	Per year	α_H	(0–10)	Varying	No	No	*Assumed*
Rate of ART discontinuation	Per year	β_H	0·074	Fixed	No	No	[35,36]
Mortality rate from HIV not on ART	Per year	μ_H	0·10	Fixed	No	No	[37]
Mortality rate from HIV on ART	Per year	δ_H	0·026	Fixed	No	No	[38]
Relative increase in progression rate for HIV_1	-	θ_{mul}	(3·94–14·45)	Varying	No	No	[39]
Relative reduction in θ_{mul} for HIV and ART compartments	-	$th1$	HIV_0 = 0 HIV_1 = 1·00 ART = 0·35	Fixed	No	No	[11]
Relative mortality rate adjustment for HIV and ART compartments	-	m_{adj}	HIV_0 = 1·00 HIV_1 = 1·50 ART = 1·15	Fixed	No	No	[11,23,40,41]

2·2 Operationalizing Age Varying Parameters

We assume that aspects of tuberculosis natural history and mortality vary by age. This is implemented by stratifying certain natural history parameters by age and applying age-specific prior ranges and relative constraints during calibration.[42] The following table describes the method used to operationalise the age varying differences in parameters between adults, defined as all ages greater than and equal to 15, and children, defined as all ages less than 15. Age varying for the treatment initiation rate is described in the section 3.

Table S2.2 How age varying parameters are operationalised

Parameter	Parameter prior range	Age-specific constraints during calibration	Sample the corresponding age scaling parameter	Adults (θ_{A15})	Children (θ_{A0})
θ_j Rate per year of fast progression	Sample from $(0.0696, 0.111)$	Retain if value for children is less than value for adults (but still within the prior range)	Sample j_1 from $(0, 1)$	Sample θ_{A15} from $(0.0696, 0.111)$	$\max(0.0696, \theta_{A15} \times j_1)$
σ_j Rate per year of reactivation	Sample from $(0.000135, 0.00113)$	Retain if value for children is less than value for adults (but still within the prior range)	Sample j_2 from $(0, 1)$	Sample σ_{A15} from $(0.000135, 0.00113)$	$\max(0.000135, \sigma_{A15} \times j_2)$
ρ_j Rate per year of relapse	Sample from $(0.0001, 0.07)$	Retain if value for children is less than value for adults (but still within the prior range)	Sample j_3 from $(0, 1)$	Sample ρ_{A15} from $(0.0001, 0.07)$	$\max(0.0001, \rho_{A15} \times j_3)$
μ_{DC_j} Clinical tuberculosis mortality rate per year	Sample from $(0, 0.178)$	Retain if value for children is greater than value for adults	Sample S_{Age} from $(0, 1)$	$\mu_{DC_{A0}} \times S_{Age}$	Sample $\mu_{DC_{A0}}$ from $(0, 0.178)$
$\mu_{T_j} = \frac{\kappa_j}{\tau}$ On-treatment mortality rate per year	Sample from $(0, \frac{\kappa_{max}}{\tau})$	Retain if value for children is greater than value for adults	Sample S_{Age} from $(0, 1)$	$\frac{\kappa_{A0}}{\tau} \times S_{Age}$	Sample κ_{A0} from $(0, \kappa_{max})$

3. Tuberculosis treatment

3.1 Tuberculosis treatment initiation

Tuberculosis treatment was assumed to start in 1960, aligned roughly with the discovery and widespread use of rifampicin, and increase following a sigmoid curve (Figure S3.1) to 2019. The treatment initiation rate parameter, η_j, represents the age specific rate of treatment initiation from the clinical disease compartment to the on-treatment compartment. During calibration, a country-specific value for η_j was sampled between 0 and 1. η_j was multiplied by an age scaling parameter for children, j_4, also sampled between 0 and 1, to ensure that the treatment initiation rate in children was less than in adults. This was then multiplied by the value of the sigmoid curve at each year. The treatment initiation rate was calibrated to the country-specific notification rate in 2019 overall and by age reported by the WHO.[25] Due to inconsistencies in the availability of private sector treatment notification data, the contribution of the private sector was not explicitly represented in our model aside from where it had already been incorporated in WHO estimates.

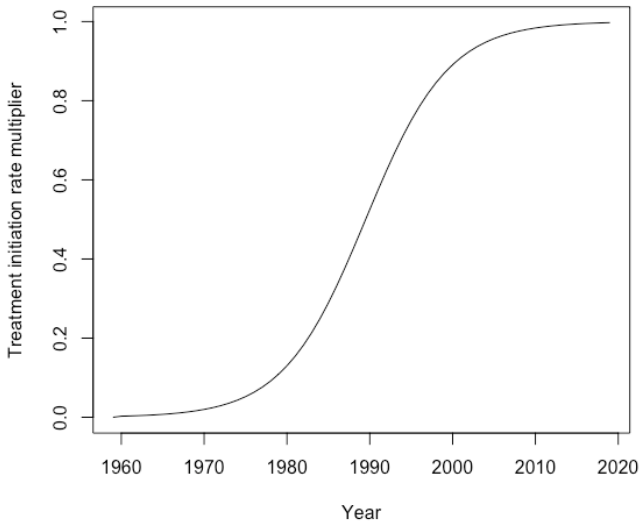


Figure S3.1 Sigmoid curve representing the scale-up in tuberculosis treatment from 1960-2019

3.2 Tuberculosis treatment outcomes

There are three possible exits from the on-treatment compartment: treatment completion, which progresses to the resolved compartment, treatment non-completion, which returns to the clinical disease compartment, and on-treatment mortality, which counts toward tuberculosis mortality. To account for the variability in tuberculosis treatment outcomes and possible underreporting of on-treatment mortality, we used the following country-specific process:

1. For each country separately, the proportion of treatment completions out of the sum of the number of treatment completions and non-completions (previously called "treatment failures") was calculated and averaged over the years of available data from WHO.

Let s_R = Reported number of treatment completions, f_R = Reported number of treatment non-completions

Note: reported number of treatment non-completions included 0·5 × (reported number lost to follow up)

$$\mathrm{SFR} = \frac{s_R}{s_R + f_R}$$

Ex. In India, averaged over 2012–2018, SFR = 0·96. This can be interpreted as of the sum of treatment completions and non-completions, on average, 96% are completions and 4% non-completions.

2. A value for child treatment mortality (κ_{A0}) was sampled between 0 and $(2 \times \text{Average Reported Treatment Mortality})$. The average reported treatment mortality is multiplied by 2 to give an upper bound in the case of unreported data.

   Ex. For India, $\kappa_{A0} \in (0, 0.135)$

3. The age multiplier, S_{Age}, was sampled from $(0, 1)$, and multiplied by κ_{A0} to calculate the adult treatment mortality

$$\kappa_{A15} = \kappa_{A0} \times S_{Age}$$

4. The success and failure rates per year were calculated as in Table S3.1

Table S3.1 Calculating treatment outcome parameter values for adults and children

Parameter	Adults	Children
κ_j On-treatment mortality fraction	$\kappa_{A0} \times S_{Age}$	Sample κ_{A0} from 0 to 2 x Average mortality on-treatment
s_j On-treatment completion fraction	$(1 - \kappa_{A15})\mathrm{SFR}$	$(1 - \kappa_{A0})\mathrm{SFR}$
f_j On-treatment non-completion fraction	$(1 - \kappa_{A15})(1 - \mathrm{SFR})$	$(1 - \kappa_{A0})(1 - \mathrm{SFR})$

5. Each of the parameters in Table S3.1 were divided by τ to obtain the on-treatment mortality rate per year, on-treatment completion rate per year, and on-treatment non-completion rate per year.

4. Calibration methodology

The model was fitted to calibration targets using history matching with emulation, a relatively new calibration method that allows us to explore high-dimensional parameter spaces efficiently and robustly.[43–46] History matching progresses as a series of iterations, called waves, where implausible areas of the parameter space, i.e., areas that are unable to give a match between the model output and the empirical data, are found and discarded. In order to identify implausible parameter sets, emulators are used. Emulators are statistical approximations of model outputs that are built using a modest number of model runs. Emulators provide an estimate of the value of the model at any parameter set of interest, with the advantage that they are orders of magnitude faster than the model.

History matching with emulation, implemented through the *hmer* package in R,[47] considerably reduced the size of the parameter space to investigate. Rejection sampling was then performed on the reduced space to identify at least 1000 parameter sets that matched all targets for each country.

If countries were unable to find at least 1000 fully fitted parameter sets using history matching with emulation, they were subsequently assessed using an Approximate Bayesian Computation using Markov Chain Monte Carlo method (ABC-MCMC). ABC-MCMC was conducted using the *easyABC* package in R, modified by the Sebastian Funk, Gwenan Knight, and the Tuberculosis Modelling group at LSTHM for adaptive sampling and to accept seeded parameter values.[48,49] We used parameter sets with the maximum number of targets fitted using history matching with emulation as a starting seed, with the ABC-MCMC algorithm continuously adapting using the last 1000 points and the noise factor set to 0·0001.

5. Low- and middle-income countries

5.1 Eligible countries

There were 135 low and middle income countries (LMICs) based on the 2019 World Bank Income Level classifications.[50] The 135 countries were broken down into 29 low-income countries (LICs), 50 lower middle-income countries (LMICs), and 56 upper middle-income countries (UMICs). Distribution by World Bank Income and WHO region are shown below in Table S5.1.

Table S5.1 LMICs by WHO Region and World Bank Income Level 2019

WHO Region	World Bank Income Level 2019			*Total*
	LIC	LMIC	UMIC	
AFR	21	19	5	45
AMR	1	4	20	25
EMR	5	6	5	16
EUR	1	4	15	20
SEAR	1	7	3	11
WPR	0	10	8	18
Total	29	50	56	135

Abbreviations: AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, LIC = low-income countries, LMIC = lower-middle income countries, SEAR = WHO South-East Asian Region, UMIC = upper-middle income countries, WPR = WHO Western Pacific Region

5.2 Countries excluded from attempting calibration

Of the 135 LMIC countries, 20 countries were excluded from attempting calibration due to the following reasons:

Table S5.2 Countries excluded from attempting calibration and reasons for exclusion

Country	Reason for Exclusion
American Samoa	Missing critical epidemiological data for calibration, no contact matrices available
Belize	No case notification or incidence data for children
Comoros	No case notification data
Democratic Republic of the Congo	No case notification data by age
Republic of the Congo	No population estimates
Democratic People's Republic of Korea	Missing critical epidemiological data for calibration
Djibouti	No case notification data by age
Dominica	Missing critical epidemiological data for calibration, no contact matrices available
Federated States of Micronesia	Missing critical epidemiological data for calibration, no contact matrices available
Grenada	Missing critical epidemiological data for calibration, no contact matrices available
Haiti	Missing 2020 contact matrix
Kiribati	Missing 2020 contact matrix
Kosovo	Missing critical epidemiological data for calibration
Lebanon	Missing 2020 contact matrix
Marshall Islands	Missing critical epidemiological data for calibration, no contact matrices available
Samoa	No case notification or incidence data for children
Somalia	No contact matrices available
St. Lucia	No case notification or incidence data for children
Tuvalu	No contact matrices available
West Bank and Gaza	Missing critical epidemiological data for calibration

5.3 Countries incorporating the HIV structure

A separate stratum was included to dynamically model the tuberculosis-HIV co-epidemic if the proportion of tuberculosis cases among people living with HIV (PLHIV) was greater than or equal to 15%, and if the HIV prevalence in the country was greater than 1%, resulting in 23 of the 115 worth running countries incorporating the HIV structure (Table S5.3).

Table S5.3 Countries incorporating the HIV structure with their corresponding HIV prevalence and proportion of tuberculosis cases among PLHIV.

Country	HIV Prevalence (%)	Proportion of tuberculosis cases among PLHIV (%)
Botswana	16·5	48·6
Central African Republic	2·1	25·4
Côte d'Ivoire	1·7	17·5
Cameroon	2·0	26·8
Gabon	2·3	32·8
Ghana	1·1	20·8
The Gambia	1·2	17·7
Guinea-Bissau	2·1	31·3
Equatorial Guinea	4·8	26·5
Guyana	1·1	19·0
Kenya	2·9	26·2
Lesotho	16·0	61·6
Mozambique	7·2	33·8
Malawi	5·9	46·6
Namibia	8·4	32·5
Rwanda	1·8	21·1
Eswatini	17·4	60·1
Togo	1·5	16·2
Tanzania	2·9	23·6
Uganda	3·4	39·0
South Africa	12·8	58·0
Zambia	6·7	46·2
Zimbabwe	9·6	59·8

6. No-New-Vaccine baselines

6.1 *Status Quo No-New-Vaccine* baseline

The primary no-new-vaccine simulated was the "*Status Quo No-New-Vaccine*" baseline, which assumed non-vaccine tuberculosis interventions continue at current levels into the future. As reported country-level data includes the high coverage levels of neonatal BCG vaccination, this was not explicitly modelled. We assumed that BCG vaccination would not be discontinued over the model time horizon.

All countries were fitted to nine calibration targets in 2019:

- The tuberculosis incidence rate per 100,000 population (all ages, ages 0-14, and ages 15+)
- The tuberculosis case notification rate per 100,000 population (all ages, ages 0-14, and ages 15+)
- The tuberculosis mortality rate per 100,000 population (all ages)
- The ratio of the prevalence of subclinical tuberculosis with the prevalence of active tuberculosis (subclinical + clinical tuberculosis)
- The ratio of the prevalence of active tuberculosis in the low access-to-care class relative to the high access-to-care

In addition to the targets above, countries incorporating the HIV structure were fitted to four HIV specific calibration targets for all ages in 2019:

- HIV prevalence
- ART coverage
- Tuberculosis incidence rate in PLHIV per 100,000 population
- Tuberculosis mortality rate in PLHIV per 100,000 population

6.2 *2025 End TB No-New-Vaccine* baseline

To provide conservative estimates on absolute vaccine impact, we simulated an alternative *No-New-Vaccine* baseline assuming scale-up between 2019 and 2025 in order to meet the End TB incidence target in 2025 of a reduction in 50% of the tuberculosis incidence rate in 2015 by 2025 for all ages.[51] To implement this, an additional parameter, p_F (equal to 1 up to and including 2019 and sampled between 0 and 1 afterwards), was included in the model as a contact rate multiplier within the force of infection equation, and as a multiplier on the progression to disease flows. Using the fully fitted parameter sets for each country from the *Status Quo No-New-Vaccine baseline*, we then varied p_F during calibration to hit the country-specific target of a reduction in 50% of the tuberculosis incidence rate in 2015 in 2025.

7. Vaccination

7.1 Vaccine profile

The vaccine profile for an adult/adolescent vaccine and infant vaccine were based on the WHO Preferred Product Characteristics for New Tuberculosis vaccines,[52] and are outlined in Table S7.1 below.

Table S7.1 WHO Preferred Product Characteristics for New Tuberculosis Vaccines

Vaccine	Host infection status at time of vaccination required for efficacy	Effect type	Vaccine efficacy	Duration of protection
Adolescent / Adult	Pre- and post-infection	Prevention of disease	50%	Lifelong
				10 years
Infant	Pre-infection	Prevention of disease	80%	Lifelong
				10 years

Vaccine efficacy was assumed to be the same in both PLHIV and HIV-naïve recipients in countries incorporating the HIV structure, and in both younger age groups and older adults. The vaccine was assumed to have the same impact on preventing drug-susceptible and drug-resistant tuberculosis as specified in the WHO PPCs,[52] and as we were modelling a prevention of disease vaccine, there was no direct impact on *Mtb* transmission or the force of infection.

7.2 Vaccine delivery scenarios

The infant vaccine was implemented in two scenarios, and, separately, the adolescent/adult vaccine was implemented in three scenarios. The *Basecase* and *Accelerated Scale-up* scenarios included routine neonatal vaccination for the infant vaccine (85% coverage), and routine vaccination of 9-year-olds (80% coverage) with a one-time vaccination campaign for ages ten and older (70% coverage) for the adolescent/adult vaccine. The *Routine Only* scenario (adolescent/adult vaccine only) was introduced through routine 9-year-old vaccination only (i.e., no campaign). Specifics of the infant and adolescent/adult vaccine scenarios are provided in Table S7.5.

7.2.1 Country-specific introduction years

In the *Basecase* and *Routine Only* scenarios, vaccines were introduced in country-specific introduction years between 2028 and 2047. To calculate the specific year of introduction, countries were divided into two general categories: those procuring with support from Gavi, the Vaccine Alliance, and those self-procuring. Determination of country status was based on eligibility information posted on Gavi's website.[53] Countries transitioning from Gavi support are able to benefit from Gavi pricing and incremental financing for a period of 5-10 years. For countries that have already initiated the period of transition by 2019, this window will have largely ended by the time of tuberculosis vaccine availability through Gavi. As such, these countries were categorised as self-procuring

countries. Countries that have not yet commenced transition, including India and Nigeria, were categorised as Gavi supported countries, given the long grace period post-commencement of transition. For more information, please see Gavi, https://www.gavi.org/types-support/sustainability/transition (retrieved December 1, 2020).

Through a consultative process with experts from WHO, Gavi, PATH, PDVAC, CHAI, and industry partners, factors influencing likelihood of being an early or late adopter were identified for both Gavi and self-procuring countries. Identified factors include disease burden, immunization capacity, and early adopter status. Country-specific registration timelines and commercial prioritization were also deemed important determinants of introduction timing for self-procuring countries.

Additional factors for Gavi countries: For countries procuring through Gavi, timelines for introduction are also influenced by Gavi processes. Prior to offering a new vaccine, Gavi requires that products be licensed, included in Gavi's Vaccine Investment Strategy, reviewed by SAGE, recommended in a WHO position paper, WHO prequalified, and approved for procurement by Gavi (Table S7.2). In addition, time for country application processing, contracting, and delivery must be factored. Through consultations, it was determined that a baseline time of roughly two years post licensure would be needed for Gavi processes prior to first country introduction, assuming several steps advance in parallel.

Table S7.2 Timelines for Gavi processes post licensure

	Cumulative additional time (years)		
Activities post licensure	**Low End**	**High End**	**Average**
WHO PQ	0·25	1·00	0·63
SAGE Policy Review & WHO Position Paper	0·25	0·50	0·38
Gavi Decision	0·25	0·50	0·38
National review & Country applications	0·25	0·75	0·50
Contracting & delivery	0·25	0·50	0·38
Years	**1·25**	**3·25**	**2·25**

Weight of criteria, indicators, and scoring: Differential weight was assigned to criteria based on their relative impact on the order of country adoption. This weight varied for self-procuring and Gavi countries (Table S7.3).

Table S7.3 Weight of criteria influencing order of country adoption

Criteria	**Self-procuring countries**	**Gavi countries**
Disease burden	30%	45%
Immunization capacity	15%	30%
Early adopter/leader	15%	25%
Lack of regulatory barriers	15%	NA
Commercial prioritization	25%	NA

The following indicators were used to measure each of the variables identified in Table S7.3.

Table S7.4 Indicators of criteria influencing order of country adoption

Criteria	Indicator
Disease burden	Tuberculosis incidence
Immunization capacity	% receiving 3 doses DPT3 among infants 1 years of age (The percent of infants receiving 3 doses DPT3 is commonly used as a proxy for assessing immunization infrastructure)
Lack of regulatory barriers	Signatories to WHO PQ or SRA collaborative registration scheme Lack of requirements for additional local clinical trial data
Early adopter/leader	Time to policy adoption of universal Xpert MTB/RIF screening for presumed tuberculosis cases Time to adoption of HPV
Commercial prioritization	
Ability to finance vaccines	GDP per capita
Political will to address tuberculosis	Spending per tuberculosis case
Market potential	Population

To standardise across these varied metrics, a point value ranging from 1–5 per criteria was assigned, with a score of 1 correlating with an earlier adopter and score of 5 correlating with a later adopter.

*Continuous variable*s such as disease burden or population were divided into quintiles. Those in the highest quintile were assigned a score of 1, those in the second highest quintile received a score of 2, and so forth. *Categorical variables* such as registration or early adopter status were scored based on whether countries met fixed criteria. For instance, countries that are signatories of WHO PQ or SRA collaborative registration schemes were assigned a score of 1. Those that are not signatories and have requirements for additional clinical trial data in local populations received a score of 5.

Scores were then weighted as reflected in Table S7.3 and aggregated into a composite score to determine countries' relative position in the queue of introductions. Composite scores for each of the 135 countries are provided in the SupplementaryMaterial_CountryTimelines.xls.

Assumptions for the pace of introduction—i.e., how many countries per year would introduce the product and what the scale up curve might look like— was informed with data from pneumococcal vaccine (PCV) scale-up.[54] The percent of countries adopting each year (year 1 to year 12) for PCV was calculated. These annual percentages were then applied to tuberculosis vaccine scale up (based on a total n=135 countries: 78 self-procuring countries and 57 Gavi countries). The first year of tuberculosis vaccine scale up was estimated to be 2028, with Gavi countries following a similar scale up trajectory but delayed by two years due to required Gavi lead time for processing new vaccines (Table S7.2). Because PCV data is only available for 12 years, data was extrapolated for years 13 to 20 of tuberculosis vaccine roll out at a steady state. Country introduction timelines were adjusted— where applicable—to group countries with the same composite score in the same year of adoption. The cumulative number of countries introducing the vaccine by year is shown in Figure S7.1, and the country-specific introduction year for each country is in Table S8.1.

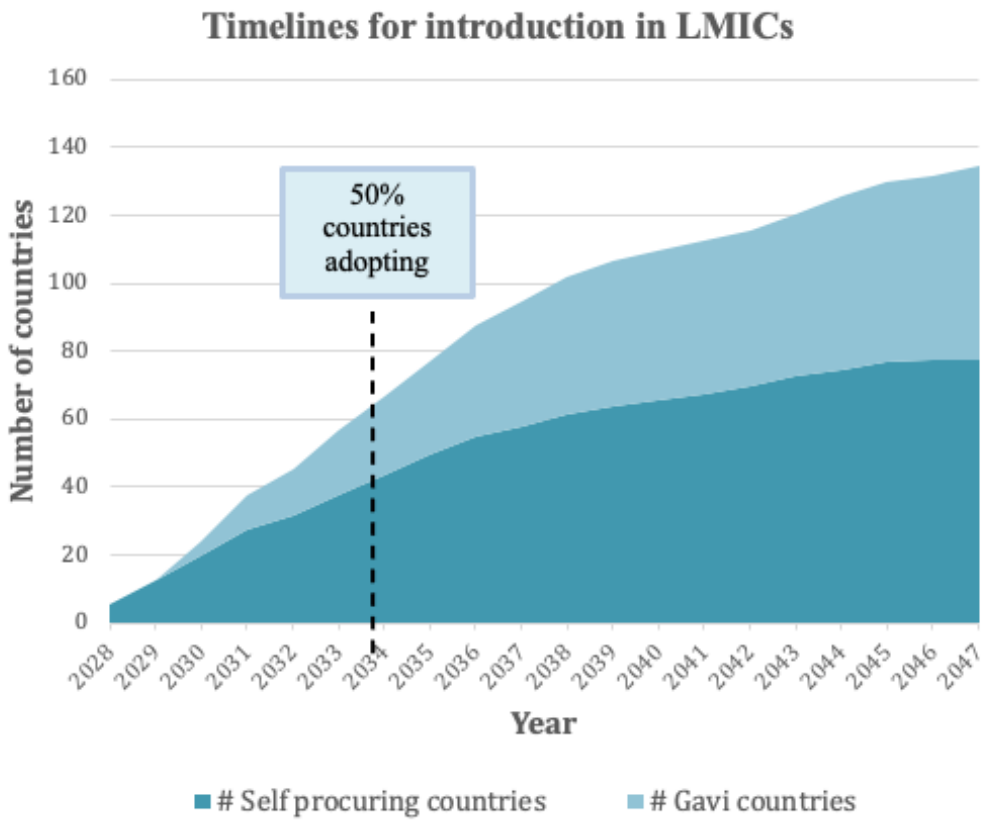


Figure S7.1 Assumed cumulative number of countries introducing a novel vaccine per year

7.2.2 Vaccine coverage targets

For each vaccine implementation scenario, low, medium, and high coverage targets for 5 years post-introduction were evaluated. The medium coverage target for the routine infant vaccination was 85%, based on the 2019 DTP3 (diphtheria, tetanus toxoid, and pertussis) average coverage level according to the WHO and UNICEF estimates of national immunisation coverage, with 10% uncertainty (low coverage = 75%, high coverage = 95%).[54] Routine adolescent vaccination assumed a medium coverage target of 80% aligning with HPV coverage in South Africa combined with aggregated secondary school enrolment in China and India as assumed in Harris 2020,[55] also with 10% uncertainty targets (low coverage = 70%, high coverage = 90%). The medium coverage target for the adolescent/adult campaign was 70% aligning with the lower bound of the MenAfriVac campaigns in sub-Saharan Africa as assumed in Harris 2020,[55] with a wider uncertainty of 20% (low coverage = 50%, high coverage = 90%). In the *Accelerated Scale-up* implementation, the 5-year coverage targets are achieved instantly in year 1, while in the *Basecase* and *Routine Only* implementations, the scale-up to coverage occurs linearly over 5 years.

Table S7.5 Vaccine scenarios for the infant and adolescent/adult vaccines

Characteristics	Infant Vaccine Scenarios		Adolescent/Adult Vaccine Scenarios		
	Basecase	***Accelerated Scale-up***	***Basecase***	***Accelerated Scale-up***	***Routine Only***
Ages Targeted	*Neonatal:* Routine	*Neonatal:* Routine	*Age 9:* Routine *Ages 10+:* One-time vaccination campaign over 5 years	*Age 9:* Routine *Ages 10+:* One-time vaccination campaign in 2025	*Age 9:* Routine
Introduction Year	Country-specific	2025	Country-specific	2025	Country-specific
Vaccine Rollout Trend	5-year linear scale-up to coverage	Instant scale-up to coverage	5-year linear scale-up to coverage	Instant scale-up to coverage	5-year linear scale-up to coverage
Target Coverage *(Low/Med/High)*	75% / 85% / 95%		Age 9: 70% / 80% / 90% Ages 10+: 50% / 70% / 90%		

7.3 Vaccine implementation

7.3.1 Vaccine structure

To simplify accounting for the number of vaccinees and vaccinations in the model, we included vaccines through an additional "vaccine structure" with three compartments (Figure S7.2) with the influences of vaccines on tuberculosis natural history parameters occurring separately in the natural history structure (Figure S7.3).

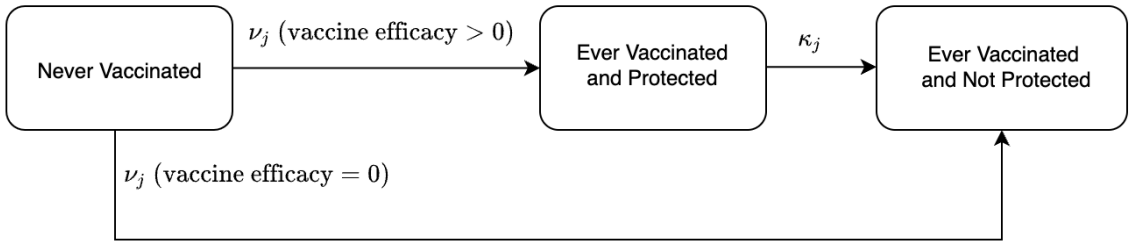


Figure S7.2 Vaccine structure

Before vaccination, all individuals in the model begin in the *Never Vaccinated* compartment, with no vaccine protection. Upon vaccination, individuals either transition to the *Ever Vaccinated and Protected* compartment (with vaccine protection) or *Ever Vaccinated and Not Protected* compartment (with no vaccine protection), depending on vaccine specific host infection status at time of vaccination required for vaccine take and their infection status at the time of vaccination, summarised in Table S7.6.

In this work, we modelled the infant vaccine as a pre-infection (PRI) vaccine, meaning the individual must be uninfected at the time of vaccination for the vaccine to be efficacious ("take"). We modelled the adolescent/adult vaccine as a pre- and post-infection (PPI) vaccine, which means that it will be efficacious in any infection status at time of vaccination aside from active disease. We assumed that the effect of disease on the immune response is likely to be substantially larger than any additional benefit from the vaccine, and therefore would not be efficacious in those compartments. For example, the Phase 2b M72/AS01$_E$ trial saw a small number of cases in each arm within the first 6 months after ruling out those who were XPERT positive on the day they were tested. Assuming those cases were individuals who were subclinical but not XPERT positive on the day they were tested, the vaccine had no impact on their disease progression.[56]

The arrow directly from *Never Vaccinated* to *Ever Vaccinated and Not Protected* was included to account for individuals who may be accidentally administered a vaccine which would not be efficacious (i.e., would not "take" and therefore vaccine efficacy is zero) given their infection status at the time of vaccination. As individuals with subclinical disease present with no symptoms, it is possible that they may be accidentally vaccinated, as seen in the Phase 2b M72/AS01E trial. Similarly, with a PRI vaccine, if no pre-vaccination testing is available, it is possible that individuals who are not uninfected may be vaccinated. By including the flow directly to *Ever Vaccinated and Not Protected*, we could easily identify and track these individuals, and ensure they received no protection from the vaccine in the model.

Table S7.6 Transitions within the vaccine structure following vaccination based on natural history state and host infection status at time of vaccination required for vaccine take

	Host infection status at the time of vaccination required for vaccine to take	
Natural History State (Infection Status) at time of vaccination	**Pre-infection vaccine** (i.e., the infant vaccine)	**Pre- and post-infection vaccine** (i.e., the adolescent/adult vaccine)
Uninfected – Naïve	*Ever Vaccinated and Protected*	*Ever Vaccinated and Protected*
Uninfected – Cleared	*Ever Vaccinated and Not Protected*	*Ever Vaccinated and Protected*
Infection – Fast	*Ever Vaccinated and Not Protected*	*Ever Vaccinated and Protected*
Infection – Slow	*Ever Vaccinated and Not Protected*	*Ever Vaccinated and Protected*
Subclinical Disease	*Ever Vaccinated and Not Protected*	*Ever Vaccinated and Not Protected*
Clinical Disease	*NA*	*NA*
On-treatment	*NA*	*NA*
Resolved	*Ever Vaccinated and Not Protected*	*Ever Vaccinated and Protected*

Waning, or loss of vaccine protection, moved individuals from the *Ever Vaccinated and Protected* compartment to the *Ever Vaccinated and Not Protected* compartment. We assumed duration of protection was 10 years on average, in addition to a sensitivity analysis with lifelong duration of protection. The shape of waning immunity was modelled as an exponential distribution, based on similar shapes for waning vaccine immunity of BCG[57] and other vaccines.[58,59]

7.3.1 Vaccine implementation in the tuberculosis natural history model

Vaccines are incorporated in the tuberculosis natural history structure as indicated with the orange boxes in Figure S7.3 by reducing the rate of progression to disease parameters into the subclinical disease compartment from the infection-fast, infection-slow, and resolved compartments by (1-pv), where pv is the vaccine efficacy. Vaccine efficacy was modelled as "degree", also known as "leaky". Degree vaccines assume that everyone who has been vaccinated receives some protection from the vaccine equivalent to the value of the vaccine efficacy.

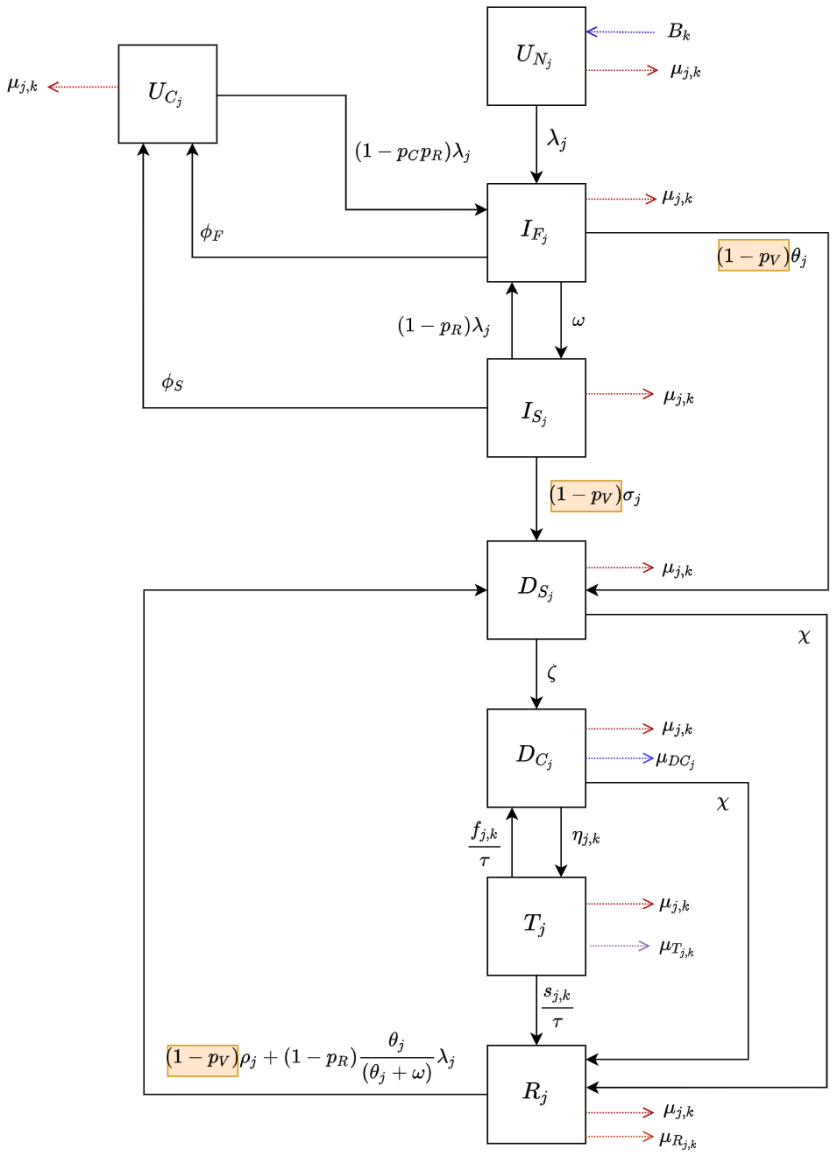


Figure S7.3 Tuberculosis natural history model incorporating vaccination

Abbreviations: D_C = Clinical Disease; D_S = Subclinical Disease; I_F = Infection-Fast; I_S = Infection-Slow; R = Resolved; T = On-Treatment; U_C = Uninfected-Cleared; U_N = Uninfected-Naive.

8. Model outcomes

8.1 Epidemiological impact measures

The following measures were calculated for each vaccine scenario as the median and 95% uncertainty range

- Percent incidence rate reduction in 2050 for each vaccine scenario compared to the *No-New-Vaccine* baseline
- Incidence rate per 100,000 population in 2035 for each vaccine scenario
- Percent mortality rate reduction in 2050 for each vaccine scenario compared to the *No-New-Vaccine* baseline
- Cumulative cases averted for each vaccine scenario between vaccine introduction (either 2025 or country-specific years) and 2050 compared to the *No-New-Vaccine* baseline
- Cumulative deaths averted for each vaccine scenario between vaccine introduction (either 2025 or country-specific years) and 2050 compared to the *No-New-Vaccine* baseline
- Cumulative treatments averted for each vaccine scenario between vaccine introduction (either 2025 or country-specific years) and 2050 compared to the *No-New-Vaccine* baseline

8.2 Groupings for reporting model outcomes

The epidemiological impact measures were calculated and reported by WHO region, World Bank Income Group, for tuberculosis burden, and overall. Countries are divided into the six WHO regions, [African region (AFR), region of the Americas (AMR), Eastern-Mediterranean region (EMR), South-East Asian region (SEAR), and Western-Pacific region (WPR)], three income groups based on the World Bank Income Groups for low- and middle-income countries [low-income countries (LIC), lower-middle-income countries (LMIC) or upper-middle-income countries (UMIC)], and by whether they were or were not included on the WHO high TB burden list (*High TB Burden* vs *Other* respectively). Groups for each of the LMICs are in Table S8.1.

Table S8.1 Country-specific introduction year, WHO region, World Bank income group, and WHO TB burden level for LMICs

Country	Gavi/Self Procuring	Introduction Year	WHO Region	World Bank Income Group	WHO High TB Burden
Afghanistan	Gavi	2031	EMR	LIC	Other
Albania	Self-Procuring	2035	EUR	UMIC	Other
Algeria	Self-Procuring	2032	AFR	LMIC	Other
American Samoa	Self-Procuring	2044	WPR	UMIC	Other
Angola	Self-Procuring	2032	AFR	LMIC	High TB Burden
Argentina	Self-Procuring	2031	AMR	UMIC	Other
Armenia	Self-Procuring	2033	EUR	UMIC	Other
Azerbaijan	Self-Procuring	2028	EUR	UMIC	Other
Bangladesh	Gavi	2035	SEAR	LMIC	High TB Burden
Belarus	Self-Procuring	2028	EUR	UMIC	Other
Belize	Self-Procuring	2034	AMR	UMIC	Other
Benin	Gavi	2037	AFR	LMIC	Other
Bhutan	Self-Procuring	2034	SEAR	LMIC	Other
Bolivia	Self-Procuring	2037	AMR	LMIC	Other
Bosnia and Herzegovina	Self-Procuring	2039	EUR	UMIC	Other
Botswana	Self-Procuring	2028	AFR	UMIC	Other
Brazil	Self-Procuring	2030	AMR	UMIC	High TB Burden
Bulgaria	Self-Procuring	2029	EUR	UMIC	Other
Burkina Faso	Gavi	2039	AFR	LIC	Other
Burundi	Gavi	2044	AFR	LIC	Other
Cabo Verde	Self-Procuring	2043	AFR	LMIC	Other
Cambodia	Gavi	2036	WPR	LMIC	Other
Cameroon	Gavi	2031	AFR	LMIC	Other
Central African Republic	Gavi	2033	AFR	LIC	High TB Burden
Chad	Gavi	2033	AFR	LIC	Other
China	Self-Procuring	2029	WPR	UMIC	High TB Burden
Colombia	Self-Procuring	2030	AMR	UMIC	Other
Comoros	Gavi	2046	AFR	LMIC	Other
Congo	Gavi	2035	AFR	LMIC	High TB Burden
Costa Rica	Self-Procuring	2033	AMR	UMIC	Other
Côte d'Ivoire	Gavi	2034	AFR	LMIC	Other
Cuba	Self-Procuring	2035	AMR	UMIC	Other
Democratic People's Republic of Korea	Gavi	2035	SEAR	LIC	High TB Burden

Democratic Republic of the Congo	Gavi	2030	AFR	LIC	High TB Burden
Djibouti	Gavi	2043	EMR	LMIC	Other
Dominica	Self-Procuring	2031	AMR	UMIC	Other
Dominican Republic	Self-Procuring	2031	AMR	UMIC	Other
Ecuador	Self-Procuring	2033	AMR	UMIC	Other
Egypt	Self-Procuring	2033	EMR	LMIC	Other
El Salvador	Self-Procuring	2039	AMR	LMIC	Other
Equatorial Guinea	Self-Procuring	2042	AFR	UMIC	Other
Eritrea	Gavi	2047	AFR	LIC	Other
Ethiopia	Gavi	2030	AFR	LIC	High TB Burden
Fiji	Self-Procuring	2031	WPR	UMIC	Other
Gabon	Self-Procuring	2038	AFR	UMIC	High TB Burden
Gambia	Gavi	2039	AFR	LIC	Other
Georgia	Self-Procuring	2029	EUR	UMIC	Other
Ghana	Gavi	2040	AFR	LMIC	Other
Grenada	Self-Procuring	2035	AMR	UMIC	Other
Guatemala	Self-Procuring	2036	AMR	UMIC	Other
Guinea	Gavi	2033	AFR	LIC	Other
Guinea-Bissau	Gavi	2043	AFR	LIC	Other
Guyana	Self-Procuring	2030	AMR	UMIC	Other
Haiti	Gavi	2033	AMR	LIC	Other
Honduras	Self-Procuring	2037	AMR	LMIC	Other
India	Gavi	2033	SEAR	LMIC	High TB Burden
Indonesia	Self-Procuring	2034	SEAR	UMIC	High TB Burden
Iran	Self-Procuring	2031	EMR	UMIC	Other
Iraq	Self-Procuring	2033	EMR	UMIC	Other
Jamaica	Self-Procuring	2036	AMR	UMIC	Other
Jordan	Self-Procuring	2037	EMR	UMIC	Other
Kazakhstan	Self-Procuring	2028	EUR	UMIC	Other
Kenya	Gavi	2032	AFR	LMIC	High TB Burden
Kiribati	Self-Procuring	2041	WPR	LMIC	Other
Kosovo	Self-Procuring	2045	EUR	UMIC	Other
Kyrgyz Republic	Gavi	2044	EUR	LMIC	Other
Lao People's Democratic Republic	Gavi	2035	WPR	LMIC	Other
Lebanon	Self-Procuring	2038	EMR	UMIC	Other
Lesotho	Gavi	2039	AFR	LMIC	High TB Burden
Liberia	Gavi	2037	AFR	LIC	High TB Burden
Libya	Self-Procuring	2035	EMR	UMIC	Other

Madagascar	Gavi	2031	AFR	LIC	Other
Malawi	Gavi	2038	AFR	LIC	Other
Malaysia	Self-Procuring	2028	WPR	UMIC	Other
Maldives	Self-Procuring	2034	SEAR	UMIC	Other
Mali	Gavi	2037	AFR	LIC	Other
Marshall Islands	Self-Procuring	2041	WPR	UMIC	Other
Mauritania	Gavi	2042	AFR	LMIC	Other
Mexico	Self-Procuring	2029	AMR	UMIC	Other
Micronesia	Self-Procuring	2045	WPR	LMIC	Other
Mongolia	Self-Procuring	2032	WPR	LMIC	High TB Burden
Montenegro	Self-Procuring	2044	EUR	UMIC	Other
Morocco	Self-Procuring	2029	EMR	LMIC	Other
Mozambique	Gavi	2032	AFR	LIC	High TB Burden
Myanmar	Gavi	2031	SEAR	LMIC	High TB Burden
Namibia	Self-Procuring	2030	AFR	UMIC	High TB Burden
Nepal	Gavi	2036	SEAR	LMIC	Other
Nicaragua	Gavi	2047	AMR	LMIC	Other
Niger	Gavi	2036	AFR	LIC	Other
Nigeria	Gavi	2030	AFR	LMIC	High TB Burden
North Macedonia	Self-Procuring	2038	EUR	UMIC	Other
Pakistan	Gavi	2031	EMR	LMIC	High TB Burden
Papua New Guinea	Gavi	2032	WPR	LMIC	High TB Burden
Paraguay	Self-Procuring	2035	AMR	UMIC	Other
Peru	Self-Procuring	2029	AMR	UMIC	Other
Philippines	Self-Procuring	2030	WPR	LMIC	High TB Burden
Republic of Moldova	Self-Procuring	2034	EUR	LMIC	Other
Russian Federation	Self-Procuring	2030	EUR	UMIC	Other
Rwanda	Gavi	2045	AFR	LIC	Other
Samoa	Self-Procuring	2046	WPR	UMIC	Other
Sao Tome and Principe	Gavi	2044	AFR	LMIC	Other
Senegal	Gavi	2038	AFR	LMIC	Other
Serbia	Self-Procuring	2036	EUR	UMIC	Other
Sierra Leone	Gavi	2037	AFR	LIC	High TB Burden
Solomon Islands	Gavi	2047	WPR	LMIC	Other
Somalia	Gavi	2030	EMR	LIC	Other
South Africa	Self-Procuring	2029	AFR	UMIC	High TB Burden
South Sudan	Gavi	2034	AFR	LIC	Other
Sri Lanka	Self-Procuring	2028	SEAR	LMIC	Other

St. Lucia	Self-Procuring	2031	AMR	UMIC	Other
St. Vincent and the Grenadines	Self-Procuring	2032	AMR	UMIC	Other
Sudan	Gavi	2036	EMR	LIC	Other
Suriname	Self-Procuring	2040	AMR	UMIC	Other
Swaziland	Self-Procuring	2036	AFR	LMIC	Other
Syrian Arab Republic	Gavi	2036	EMR	LIC	Other
Tajikistan	Gavi	2045	EUR	LIC	Other
Thailand	Self-Procuring	2031	SEAR	UMIC	High TB Burden
Timor-Leste	Self-Procuring	2031	SEAR	LMIC	Other
Togo	Gavi	2041	AFR	LIC	Other
Tonga	Self-Procuring	2040	WPR	UMIC	Other
Tunisia	Self-Procuring	2036	EMR	LMIC	Other
Turkey	Self-Procuring	2030	EUR	UMIC	Other
Turkmenistan	Self-Procuring	2034	EUR	UMIC	Other
Tuvalu	Self-Procuring	2043	WPR	UMIC	Other
Uganda	Gavi	2034	AFR	LIC	High TB Burden
Ukraine	Self-Procuring	2033	EUR	LMIC	Other
United Republic of Tanzania	Gavi	2031	AFR	LMIC	High TB Burden
Uzbekistan	Gavi	2038	EUR	LMIC	Other
Vanuatu	Self-Procuring	2042	WPR	LMIC	Other
Venezuela	Self-Procuring	2035	AMR	UMIC	Other
Vietnam	Self-Procuring	2038	WPR	LMIC	High TB Burden
West Bank and Gaza	Self-Procuring	2043	EMR	LMIC	Other
Yemen	Gavi	2036	EMR	LIC	Other
Zambia	Gavi	2034	AFR	LMIC	High TB Burden
Zimbabwe	Gavi	2032	AFR	LMIC	Other

Abbreviations: AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, LIC = low-income countries, LMIC = lower-middle income countries, SEAR = WHO South-East Asian Region, UMIC = upper-middle income countries, WPR = WHO Western Pacific Region

8.2 Calculating uncertainty

To appropriately represent the global uncertainty and remove inter-country variability in parameters that are likely to be the same across countries when generating impact estimates (e.g., those governing the underlying biology of *Mtb*), we used the following process:

1. We obtained 1000 fitted parameter sets for each country by thinning the total number of fitted parameter sets per country to 1000.

2. Within each country, the 1000 parameter sets were ordered and ranked from smallest to largest by 2019 tuberculosis incidence rate.

3. The parameter sets for all countries were then pairwise grouped on their rank value. For example, the rank 1 parameter sets were grouped together for all countries, the rank 2 parameter sets were grouped together for all countries, etc.

4. Within each pairwise rank group, we calculated the measure of interest by combining all information. For example, to calculate the incidence rate, we summed the number of cases from all countries with rank 1 and divided by the sum of the population for all countries with rank 1. This was continued for all ranks until there were 1000 estimates of the measure of interest.

5. We combined the 1000 estimates for the measure of interest, generated the distribution and calculated all country and group-level estimates.

SUPPLEMENTAL RESULTS:

9. Model Calibration

9.1 LMIC countries calibration

Of the 135 LMICs, there were 20 countries which were excluded from calibration due to missing crucial data for calibration (as described in Table S5.3). The 10 countries that did not calibrate out of the 115 worth running were: Algeria, Bosnia and Herzegovina, Cabo Verde, Guinea-Bissau, Guyana, Jamaica, North Macedonia, St. Vincent and the Grenadines, Tonga, and Turkmenistan.

9.2 WHO Region and World Bank Income Group for Calibrated LMICs

Table S9.1 WHO regions and World bank income groups for calibrated LMICs

WHO Region	**World Bank Income Level 2019**			***Total***
	LIC	LMIC	UMIC	
AFR	19	15	5	39
AMR	0	4	13	17
EMR	4	5	3	12
EUR	0	4	12	16
SEAR	0	8	2	10
WPR	0	8	3	11
Total	23	44	38	105

Abbreviations: AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, LIC = low-income countries, LMIC = lower-middle income countries, SEAR = WHO South-East Asian Region, UMIC = upper-middle income countries, WPR = WHO Western Pacific Region

9.3 *Status Quo No-New-Vaccine* baseline calibration target values

Table S9.2 presents the common country-specific calibration targets for the 105 calibrated countries, and Table S9.3 highlights the HIV specific calibration targets for the 21 countries incorporating the HIV structure. Two additional calibration targets were assumed consistent across countries: the fraction of subclinical tuberculosis among active tuberculosis in 2019 [50·4% (36·1%–79·7%)],[1] and the risk ratio of active tuberculosis in the low-access-to-care group relative to high-access-to-care in 2019 [67·4 (57·5, 80·1)].[12–21]

Table S9.2 Values for the seven country specific calibration targets for all calibrated countries in 2019. Point values represent the mean with 95% confidence intervals in brackets.

Country	Tuberculosis Incidence Rate (per 100,000 population per year)			Tuberculosis Notification Rate (per 100,000 population per year)			Tuberculosis Mortality Rate (per 100,000 population per year)
	Ages 0–14	Ages 15+	Ages 0–99	Ages 0–14	Ages 15+	Ages 0–99	Ages 0–99
Afghanistan	92·8 (48·9–136·2)	260·5 (137·1–383·8)	189·3 (115·7–262·9)	71·0 (56·8–85·2)	187·2 (149·7–224·6)	137·8 (110·3–165·4)	26 (16–39)
Albania	2·6 (2·2–3·0)	19·3 (16·4–22·3)	16·3 (13·9–18·7)	2·2 (1·8–2·6)	16·9 (13·5–20·2)	14·3 (11·4–17·2)	0·3 (0·2–0·5)
Angola	107·8 (58·6–155)	565·1 (312·0–818·2)	351·9 (213·7–487·0)	59·4 (47·5–71·3)	384·3 (307·5–461·2)	232·8 (186·3–279·4)	62 (39–89)
Argentina	9·1 (7·9–10·9)	35·5 (29·6–41·5)	29·0 (24·6–33·5)	8·1 (6·5–9·8)	31·2 (24·9–37·4)	25·6 (20·4–30·7)	1·6 (1·4–1·8)
Armenia	7·7 (5·7–9·8)	31·1 (23·0–39·3)	26·4 (19·6–32·8)	6·2 (4·9–7·4)	24·9 (19·9–29·9)	21·0 (16·8–25·2)	0·6 (0·4–0·8)
Azerbaijan	19·5 (14–24·6)	72·8 (53·3–92·3)	59·7 (44·8–74·6)	7·6 (6·1–9·1)	44·6 (35·7–53·6)	48·0 (38·4–57·6)	6·1 (5·6–6·6)
Bangladesh	74·4 (49·6–96·9)	276·4 (187·9–364·9)	221·4 (156·4–285·8)	27·8 (22·2–33·3)	235·3 (188·3–282·4)	178·8 (143·1–214·6)	24 (15–35)
Belarus	4·3 (3·2–5·3)	34·4 (25·5–43·4)	29·6 (22·2–36·0)	0·5 (0·4–0·6)	28 (22·4–33·6)	23·3 (18·7–28·0)	3·3 (3·1–3·5)
Benin	11·4 (6·6–16·3)	86·5 (49·9–124·6)	55·1 (33·9–77·1)	4·6 (3·7–5·6)	59·2 (47·3–71·0)	36·1 (28·9–43·4)	11 (7·2–15)
Bhutan	32·1 (23·8–40·9)	210·6 (154·5–263·3)	170·4 (123·2–209·7)	14·5 (11·6–17·4)	171·5 (137·2–205·8)	131·7 (105·4–158·0)	18 (12–26)

Bolivia	25·8 (15·3–36·9)	137·7 (82·6–200·3)	104·2 (65·1–147·7)	6·9 (5·6–8·3)	90·3 (72·3–108·4)	64·8 (51·8–77·8)	11 (8·1–15)
Botswana	74·6 (55·3–93·9)	340·8 (249·0–432·5)	251·8 (191·0–312·5)	29·8 (23·9–35·8)	187·2 (149·8–224·7)	134·1 (107·3–160·9)	78 (61–96)
Brazil	7·0 (5·9–8·1)	55·8 (47·4–64·2)	45·5 (38·9–52·1)	6·0 (4·8–7·3)	48·5 (38·8–58·2)	39·6 (31·7–47·5)	3·2 (2·9–3·4)
Bulgaria	8·8 (6·4–10·7)	21·8 (16·6–28·5)	20·0 (15·7–25·7)	5·3 (4·2–6·3)	20·7 (16·5–24·8)	18·4 (14·7–22·1)	1·6 (1·6–1·7)
Burkina Faso	9·8 (5·6–14·3)	77·4 (44·5–106·7)	47·2 (28·5–64·0)	1·5 (1·2–1·8)	42·0 (33·6–50·4)	24·2 (19·4–29)	11 (7·2–16)
Burundi	24·8 (13·8–34·4)	174·7 (100·1–254·1)	104·1 (65·0–147·4)	6·2 (5·0–7·4)	102·1 (81·7–122·5)	58·6 (46·9–70·3)	24 (15–35)
Cambodia	68·3 (39·0–97·5)	387·3 (220·1–545·8)	285·1 (175·9–400·3)	36·1 (28·9–43·3)	247·0 (197·6–296·4)	181·4 (145·1–217·7)	20 (13–28)
Cameroon	43·8 (24·6–62·0)	274·9 (154·2–395·6)	177·8 (108·2–247·3)	11·4 (9·2–13·7)	154·6 (123·7–185·6)	94·0 (75·2–112·8)	48 (34–65)
Central African Republic	182·3 (100·8–263·9)	826·7 (450·9–1202·5)	547·9 (337·2–758·7)	79·1 (63·3–94·9)	391·2 (313·0–469·5)	253·9 (203·1–304·6)	158 (111–215)
Chad	36·2 (20·1–52·2)	235·8 (129·7–342)	144·2 (87·8–194·4)	14 (11·2–16·8)	148·5 (118·8–178·2)	85·5 (68·4–102·6)	31 (21–42)
China	14·9 (12·5–16·8)	67·5 (57·4–77·6)	58·1 (49·7–66·5)	2·6 (2·1–3·1)	61·2 (49·0–73·5)	50·8 (40·6–61)	2·3 (2·1–2·6)
Colombia	7·2 (5·4–8·8)	43·6 (33·4–53·9)	35·8 (25·8–43·7)	3·5 (2·8–4·2)	35·7 (28·5–42·8)	28·4 (22·7–34·1)	3·4 (3–3·9)
Costa Rica	1·7 (1·2–2·1)	12·3 (9–15·6)	10·1 (7·5–12·5)	1·3 (1·1–1·6)	9·8 (7·9–11·8)	8·0 (6·4–9·6)	0·8 (0·7–0·9)
Cote d'Ivoire	30·8 (17·7–43·8)	213·5 (120·1–306·9)	136·1 (81·7–190·5)	9·5 (7·6–11·4)	134·7 (107·8–161·6)	82·5 (66–99)	30 (20–41)
Cuba	0·4 (0·3–0·5)	7·6 (6·4–8·7)	6·4 (5·5–7·4)	0·3 (0·2–0·4)	6·6 (5·3–7·9)	5·6 (4·5–6·7)	0·4 (0·3–0·5)
Dominican Republic	6·7 (5·0–8·4)	55·4 (41·2–69·6)	41·9 (31·7–52·1)	2·7 (2·2–3·2)	45·2 (36·2–54·3)	33·4 (26·8–40·1)	4 (2·4–6)
Ecuador	8·7 (6·4–11·0)	59·7 (43·8–75·6)	45·5 (34·5–57·0)	3·9 (3·1–4·7)	49·1 (39·2–58·9)	36·5 (29·2–43·8)	4·6 (3·9–5·3)
Egypt	2·6 (2·3–2·9)	16·6 (14·2–18·1)	12·0 (10·0–12·9)	1·4 (1·1–1·7)	11·4 (9·1–13·7)	8 (6·4–9·6)	0·5 (0·4–0·5)

El Salvador	18·5 (13·3–23·7)	72 (53–93·2)	58·9 (43·4–72·8)	7·8 (6·2–9·3)	53·7 (43–64·5)	46·6 (37·3–56)	1·7 (1·4–2)
Equatorial Guinea	45·9 (39·9–53·9)	257·3 (222·3–292·4)	184·4 (154·9–206·5)	19·2 (15·3–23)	169·0 (135·2–202·8)	114·3 (91·4–137·2)	39 (31–48)
Eritrea	29·6 (7·6–51·6)	127·3 (32·8–220·3)	85·8 (31·5–143)	15·8 (12·7–19)	78·2 (62·6–93·9)	52·3 (41·8–62·7)	17 (8–29)
Ethiopia	37·6 (24·3–53·1)	207·9 (133·1–282·6)	140·1 (94·6–184·7)	24·4 (19·5–29·3)	149·6 (119·7–179·5)	99·1 (79·3–118·9)	22 (14–30)
Fiji	57·5 (38·4–76·7)	69·9 (47·7–92·2)	66·3 (49·4–83·2)	47·2 (37·7–56·6)	55·5 (44·4–66·6)	53 (42·4–63·6)	5·3 (4·9–5·7)
Gabon	160·9 (92·8–235·2)	732·7 (410·3–1025·8)	506·3 (317·6–736·5)	45·4 (36·3–54·5)	368·7 (295–442·4)	248·5 (198·8–298·2)	110 (66–165)
Gambia	37·6 (26·1–50·2)	251·6 (175·3–327·8)	157·6 (115·0–200·2)	12·5 (10–15·1)	189·8 (151·8–227·7)	111·6 (89·2–133·9)	27 (20–35)
Georgia	20 (16·2–23·7)	87·6 (72–103·2)	75·1 (62·6–87·6)	9 (7·2–10·8)	65·6 (52·5–78·7)	54·3 (43·4–65·1)	4·2 (3·8–4·6)
Ghana	55·4 (16·7–96·8)	194·2 (57·7–335·9)	144·7 (55·9–230·1)	7·2 (5·8–8·7)	72·8 (58·2–87·3)	48·3 (38·6–58)	50 (29–77)
Guatemala	10·9 (7·9–14·1)	34·4 (24·1–43·9)	26·2 (19·9–33)	7·4 (5·9–8·9)	28 (22·4–33·6)	21·1 (16·9–25·4)	2·4 (2·1–2·6)
Guinea	37·8 (21·6–54·1)	276·9 (166·2–401·5)	172·3 (109·6–242·7)	20·9 (16·7–25)	210·9 (168·7–253·1)	128·3 (102·7–154)	29 (20–39)
Honduras	4·3 (3·2–5·3)	43·2 (31·3–55·1)	30·8 (23·6–39)	1·6 (1·3–1·9)	35·4 (28·3–42·5)	24·9 (19·9–29·8)	5 (4·2–5·8)
India	91·6 (55·8–127·6)	229·4 (139·6–320·1)	193·2 (125·9–259·8)	40 (32–48)	201·1 (160·9–241·4)	158·2 (126·6–189·9)	33 (30–35)
Indonesia	200·2 (179–221·3)	352·1 (314·5–389·6)	312·2 (284·2–340·3)	98·8 (79–118·6)	245·5 (196·4–294·6)	207·7 (166·1–249·2)	36 (33–38)
Iran	3·0 (2·3–3·9)	16 (11·8–20·8)	13·3 (9·6–15·7)	1·6 (1·2–1·9)	13·1 (10·5–15·8)	10·3 (8·2–12·3)	1·2 (1·1–1·2)
Iraq	12·7 (10·7–14·7)	57·5 (49·3–65·7)	40·7 (35·6–45·8)	3·8 (3–4·6)	24·8 (19·9–29·8)	16·8 (13·5–20·2)	2·1 (1·9–2·3)
Jordan	1·1 (0·8–1·4)	7·7 (5·7–9·8)	5·5 (4·2–6·9)	0·9 (0·7–1)	6·2 (5–7·5)	4·4 (3·5–5·3)	0·1 (0·1–0·2)
Kazakhstan	6·7 (3·9–9·3)	91 (56·1–128·9)	70·1 (41·5–97)	6·6 (5·2–7·9)	92·1 (73·7–110·5)	67·4 (53·9–80·9)	1·9 (1·4–2·4)

Kenya	87·4 (43·2–126·2)	384·8 (193·9–572·4)	266·3 (150·3–382·3)	40·3 (32·2–48·3)	237·9 (190·3–285·5)	160·4 (128·3–192·5)	62 (42–85)
Kyrgyz Republic	16·8 (14·4–19·7)	154·7 (131·6–180·1)	110·7 (93·5–126·2)	14·6 (11·7–17·6)	134·7 (107·8–161·6)	95·7 (76·5–114·8)	5·9 (5·4–6·3)
Lao PDR	47·5 (25·9–64·8)	206 (119·5–288·5)	153·4 (94·8–209·2)	4·1 (3·3–4·9)	138·5 (110·8–166·2)	95·1 (76·1–114·1)	30 (19–44)
Lesotho	137·7 (75·4–202·9)	905·8 (494·7–1323·8)	658·7 (376·4–941·1)	41·2 (32·9–49·4)	472 (377·6–566·4)	332·1 (265·7–398·6)	224 (153–309)
Liberia	129·2 (69·6–188·9)	444·4 (232·5–615·3)	303·8 (188·4–425·3)	70·2 (56·2–84·3)	234·8 (187·8–281·7)	167·9 (134·3–201·4)	74 (49–103)
Libya	15·8 (8·4–23·1)	75·9 (41–110·8)	59 (33·9–84·1)	5·4 (4·3–6·5)	43·2 (34·6–51·8)	32·7 (26·1–39·2)	12 (7·1–19)
Madagascar	69·8 (38·6–101)	342 (192·8–497·4)	233·6 (140·9–322·6)	28 (22·4–33·6)	212·4 (169·9–254·9)	138 (110·4–165·6)	46 (27–68)
Malawi	48·2 (18·5–77·8)	218·4 (85·5–360·8)	144·9 (69·8–225·5)	18·9 (15·1–22·6)	146 (116·8–175·2)	90·7 (72·6–108·9)	37 (24–53)
Malaysia	12·9 (11–14·5)	114·9 (98·4–135·4)	90·8 (78·2–106·4)	11·2 (9–13·5)	101·4 (81·1–121·7)	80 (64–96)	4·8 (4·3–5·3)
Maldives	3·8 (2·8–4·7)	44·7 (32·9–56·4)	35·8 (26·4–45·2)	2·8 (2·3–3·4)	35·5 (28·4–42·6)	29 (23·2–34·8)	2·1 (1·9–2·3)
Mali	9·8 (5·7–14)	90·7 (53·1–125·5)	50·9 (32·6–71·2)	3·7 (3–4·4)	63·4 (50·7–76·1)	35·2 (28·1–42·2)	9·1 (6–13)
Mauritania	22·2 (12·7–31·6)	132·3 (77·2–191·1)	88·4 (55·2–123·7)	8·6 (6·9–10·4)	85·4 (68·3–102·5)	55·1 (44·1–66·1)	17 (10–25)
Mexico	3·9 (3–5·1)	29·7 (22·3–38·2)	23·5 (17·2–29)	2·0 (1·6–2·4)	24·5 (19·6–29·4)	18·6 (14·9–22·3)	2 (1·9–2·2)
Mongolia	201·3 (70·5–332·2)	537·7 (183·7–851·3)	434·1 (186–682·1)	40·9 (32·7–49)	173·4 (138·8–208·1)	132·6 (106·1–159·1)	10 (9·2–12)
Montenegro	0·9 (0·7–1·1)	17·7 (15–19·5)	14·6 (12·4–17·5)	0·9 (0·7–1·1)	15·4 (12·3–18·4)	12·7 (10·2–15·3)	0·2 (0·2–0·2)
Morocco	24·4 (20·3–28·5)	123·9 (105·1–142·7)	96 (82·3–112·4)	21·2 (17–25·5)	107·6 (86·1–129·2)	84·3 (67·5–101·2)	8·1 (5–12)
Mozambique	259·8 (111·3–400·8)	444 (189·4–692·6)	362·2 (207·5–517)	95·4 (76·3–114·5)	492·3 (393·9–590·8)	316·2 (253–379·5)	37 (25–52)
Myanmar	271·3 (142·8–392·7)	339·7 (182·3–497·0)	322 (199·8–442·2)	169·2 (135·4–203·1)	276·7 (221·3–332)	248·9 (199·1–298·6)	41 (27–59)

Namibia	152·1 (99·9–206·4)	698·9 (444·8–889·5)	481·1 (336·7–641·4)	79·6 (63·7–95·5)	449·1 (359·3–538·9)	312·7 (250·2–375·3)	107 (80–137)
Nepal	60·3 (30·7–89·9)	312·6 (158·8–466·4)	237·7 (129·3–346)	20·4 (16·3–24·5)	147·2 (117·8–176·7)	110·1 (88·1–132·1)	59 (32–92)
Nicaragua	13·8 (10·2–17·9)	54·5 (39·2–69·7)	42·8 (32·1–53·5)	8·9 (7·1–10·6)	45·2 (36·2–54·2)	34·3 (27·5–41·2)	2·3 (1·9–2·6)
Niger	17·2 (9·5–24·1)	153·9 (85·5–213·8)	85·8 (51·5–115·8)	4·6 (3·6–5·5)	93·9 (75·1–112·7)	49·3 (39·4–59·1)	17 (10–25)
Nigeria	94·5 (51·3–137·8)	316·3 (170·5–461·3)	218·9 (134·9–303)	10·8 (8·6–12·9)	95·2 (76·1–114·2)	58·4 (46·7–70·1)	77 (49–110)
Pakistan	100·1 (64·5–137)	351·2 (224·7–477·8)	263·2 (180·1–346·3)	59·9 (47·9–71·8)	200·9 (160·7–241)	151·6 (121·3–181·9)	20 (16–25)
Papua New Guinea	353·2 (256·9–417·4)	476·9 (353·2–600·5)	433·0 (353·2–512·8)	220·2 (176·2–264·3)	402·2 (321·8–482·7)	342·6 (274·1–411·1)	50 (34–70)
Paraguay	11·2 (9·2–12·6)	60·1 (50·1–70·2)	46·8 (39·7–52·5)	9·6 (7·7–11·5)	52·9 (42·3–63·4)	40·2 (32·2–48·3)	4·5 (3·8–5·2)
Peru	26·8 (19·5–34·1)	148·1 (111·1–189·3)	120·0 (89·2–147·6)	16·6 (13·3–19·9)	123·4 (98·7–148·0)	97·7 (78·2–117·2)	8·8 (7·2–11)
Philippines	209·4 (91·0–324·7)	705·1 (310·0–1101·5)	554·0 (276·6–831·5)	129·5 (103·6–155·4)	487·5 (390·0–585·1)	378·4 (302·8–454·1)	26 (22–29)
Republic of Moldova	18·7 (15·3–20·2)	91·2 (76·5–105·9)	79·1 (66·8–91·5)	15·7 (12·6–18·9)	79·6 (63·7–95·6)	69·5 (55·6–83·4)	6·2 (5·4–7·1)
Russian Federation	7·6 (4·5–10·6)	59·5 (35·2–82·9)	50·0 (30·2–69·2)	7·7 (6·1–9·2)	59·2 (47·4–71·1)	50·3 (40·2–60·3)	6·7 (6–7·4)
Rwanda	12·3 (9·0–15·7)	86·8 (63·1–110·4)	57·0 (42·8–71·3)	8·6 (6·9–10·4)	72·0 (57·6–86·4)	45·7 (36·5–54·8)	7·5 (5·5–9·7)
Sao Tome and Principe	21·0 (4·4–38·6)	184·9 (36·2–329·5)	116·3 (29·8–200·0)	12·1 (9·7–14·6)	103·7 (82·9–124·4)	65·1 (52·1–78·1)	26 (13–44)
Senegal	21·5 (14·3–30·1)	182·5 (128·8–246·9)	116·6 (79·8–153·4)	8·5 (6·8–10·2)	137·0 (109·6–164·4)	82·0 (65·6–98·4)	18 (12–25)
Serbia	1·3 (1·1–1·5)	17·5 (14·8–18·9)	14·8 (12·5–17·1)	1·1 (0·9–1·3)	14·4 (11·5–17·2)	12·6 (10·1–15·1)	0·5 (0·5–0·6)
Sierra Leone	100·6 (56·6–147·7)	431·8 (237·5–626·2)	294·4 (179·2–409·6)	73·9 (59·1–88·6)	333·4 (266·7–400·0)	227·7 (182·2–273·3)	40 (26–56)
Solomon Islands	24·6 (17·5–31·6)	94·8 (67·3–122·2)	65·7 (49·3–82·1)	19·7 (15·8–23·7)	75·1 (60·0–90·1)	52·8 (42·3–63·4)	7·3 (4·7–10)

South Africa	224·0 (141·5–306·5)	774·1 (488·0–1060·2)	614·8 (409·8–818)	97·0 (77·6–116·4)	464·2 (371·4–557·0)	357·8 (286·3–429·4)	99 (59–150)
South Sudan	106·6 (56·5–158·8)	309·4 (170·2–464·1)	226·0 (135·6–316·4)	72·8 (58·2–87·3)	200·8 (160·6–240·9)	147·6 (118·0–177·1)	42 (28–60)
Sri Lanka	15·5 (10·8–19·6)	80·2 (54·9–104·8)	65·7 (45·5–79·7)	4·6 (3·7–5·6)	49·1 (39·3–59·0)	38·5 (30·8–46·2)	3·6 (2·9–4·4)
Sudan	19·8 (12·2–27·3)	97·6 (58·5–136·6)	67·7 (44·4–88·8)	11·3 (9·1–13·6)	68·3 (54·6–81·9)	46·2 (37·0–55·5)	10 (6·6–15)
Suriname	4·5 (3·8–5·8)	37·7 (28·2–47·1)	29·2 (20·6–36·1)	3·8 (3·1–4·6)	29·9 (23·9–35·9)	22·9 (18·3–27·5)	4·5 (3·7–5·4)
Swaziland	80·6 (43·7–117·4)	532·4 (294·2–770·6)	365·8 (209·0–513·9)	40·5 (32·4–48·6)	378·3 (302·6–453·9)	250·5 (200·4–300·6)	84 (55–118)
Syrian Arab Republic	6·6 (4·7–8·3)	24·6 (17·8–31·4)	18·7 (14·1–23·4)	4·2 (3·4–5·1)	20·1 (16·1–24·1)	15·2 (12·1–18·2)	0·1 (0·1–0·1)
Tajikistan	18·2 (13·3–22·9)	121·0 (88·7–153·4)	82·6 (62·2–103·0)	11·7 (9·4–14·0)	91·2 (73–109·5)	61·7 (49·4–74·1)	8·5 (7·6–9·4)
Thailand	28·2 (20·5–35·9)	174·4 (127·8–221·0)	150·8 (112·0–188·1)	7·5 (6·0–9·0)	147·5 (118·0–177·0)	126·1 (100·9–151·3)	16 (13–21)
Timor-Leste	157·6 (89·2–228·1)	702·9 (394·6–1011·2)	494·9 (301·6–696·0)	75·5 (60·4–90·6)	454·6 (363·6–545·5)	313·2 (250·6–375·8)	90 (54–134)
Togo	5·7 (4·5–6·6)	58·7 (46·1–71·3)	37·1 (29·7–44·5)	2·6 (2·1–3·1)	52·2 (41·8–62·7)	31·9 (25·5–38·2)	3·6 (2·5–5)
Tunisia	11·3 (8·1–14·1)	42·9 (31·6–54·2)	35·1 (26·5–44·5)	7·5 (6·0–9·0)	34·8 (27·8–41·8)	28·2 (22·6–33·8)	1·3 (0·9–1·6)
Turkey	2·8 (2·4–3·3)	19·0 (15·8–22·2)	15·6 (13·2–18·0)	2·4 (2·0–2·9)	17·0 (13·6–20·4)	13·5 (10·8–16·2)	0·4 (0·3–0·4)
Uganda	77·7 (35·0–121·4)	304 (135·1–472·9)	198·8 (106·2–293·7)	39·9 (31·9–47·9)	238·1 (190·5–285·7)	148·9 (119·1–178·6)	35 (24–48)
Ukraine	18·5 (10·7–25·7)	89·2 (51·4–124·4)	77·3 (47·7–106·8)	8·3 (6·7–10·0)	67·0 (53·6–80·5)	57·7 (46·2–69·2)	12 (9·9–13)
United Republic of Tanzania	82·6 (22·8–145·5)	356·1 (98·2–617·1)	236·2 (89·6–384·4)	48·1 (38·5–57·8)	211·7 (169·4–254·1)	140·0 (112·0–168·0)	55 (32–84)
Uzbekistan	33·7 (21·1–46·3)	80·9 (51·1–110·7)	66·7 (45·5–91)	23·1 (18·4–27·7)	60·0 (48·0–72·0)	49·3 (39·5–59·2)	5·4 (5·0–5·8)
Vanuatu	16·4 (11·2–20·7)	59·8 (40·3–76·2)	40·0 (30·7–53·4)	12·1 (9·6–14·5)	43·0 (34·4–51·6)	31·0 (24·8–37·2)	5·4 (3·5–7·7)

Venezuela	11·5 (8·4–14·1)	58·0 (42·5–72·5)	45·6 (34·0–56·1)	7·2 (5·8–8·7)	47·0 (37·6–56·4)	36·1 (28·9–43·3)	3·4 (2·7–4·2)
Vietnam	35·7 (20·5–49·1)	218·7 (126·9–311·9)	176·2 (105·7–247·8)	7·6 (6·1–9·1)	136·0 (108·8–163·2)	106·3 (85·0–127·5)	12 (8·0–16)
Yemen	15·7 (14·0–18·4)	67·7 (56·4–79·0)	48·0 (41·1–54·9)	10·8 (8·7–13)	50·7 (40·5–60·8)	35·1 (28·0–42·1)	6·6 (4·7–8·9)
Zambia	80·6 (45·3–114·6)	534·3 (302·4–766·2)	330·3 (201·6–459·1)	31·1 (24·9–37·4)	339·5 (271·6–407·4)	202·4 (161·9–242·9)	86 (62–114)
Zimbabwe	43·7 (30·8–56·7)	306·9 (212·5–413·2)	198·0 (143·4–252·6)	19·0 (15·2–22·8)	234·2 (187·3–281)	143·4 (114·8–172·1)	43 (33–54)

Table S9.3 HIV specific calibration targets for countries including the HIV structure for 2019 and for ages 0–99. Point values represent the mean with 95% confidence intervals in brackets.

Country	HIV Prevalence (%)	ART Coverage (%)	Tuberculosis Incidence Rate in PLHIV (per 100,000 population per year)	Tuberculosis Mortality Rate in PLHIV (per 100,000 population per year)
Botswana	16·5 (14·8–17·8)	82 (74–89)	123 (95–155)	49 (23–81)
Central African Republic	2·1 (1·8–2·7)	46 (37–59)	137 (88–195)	61 (17–115)
Côte d'Ivoire	1·7 (1·4–1·9)	63 (54–74)	24 (16–35)	8·5 (2·3–15·5)
Cameroon	2 (1·7–2·2)	62 (54–68)	48 (31–69)	19 (5–37)
Gabon	2·3 (1·7–3)	51 (38–66)	171 (65–327)	26 (0–194)
Ghana	1·1 (0·8–1·5)	45 (32–61)	30 (15–52)	16 (0–40)
Gambia	1·2 (0·9–1·5)	29 (23–37)	28 (21–37)	7·9 (3·3–12·1)
Equatorial Guinea	4·8 (3·5–6·5)	35 (27–48)	48 (41–55)	16 (8–24)
Kenya	2·9 (2·5–3·2)	74 (65–86)	70 (43–104)	24 (6–48)
Lesotho	16 (15·1–16·9)	65 (61–70)	403 (250–591)	168 (38–328)
Mozambique	7·2 (5·9–9·2)	60 (48–74)	122 (75–180)	18 (4–38)
Malawi	5·9 (5·2–5·9)	79 (71–84)	68 (36–109)	23 (1–49)
Namibia	8·4 (7·6–8·8)	85 (79–91)	158 (113–210)	50 (20–88)
Rwanda	1·8 (1·6–2)	87 (77–95)	12 (9·2–15)	2·5 (1·1–4·3)
Swaziland	17·4 (16·5–19·2)	96 (88–100)	218 (129–329)	61 (11–125)

Togo	1·5 (1·2–1·7)	64 (54–79)	6 (4·8–7·4)	1 (0·3–1·8)
United Republic of Tanzania	2·9 (2·6–3·1)	75 (67–81)	56 (27–97)	20 (0–48)
Uganda	3·4 (3·2–3·6)	84 (78–92)	78 (46–119)	19 (3–39)
South Africa	12·8 (11·8–13·7)	70 (64–74)	357 (248–486)	62 (0–168)
Zambia	6·7 (5·4–7·3)	85 (80–92)	154 (100–220)	53 (15–99)
Zimbabwe	9·6 (8·2–10·9)	85 (74–97)	119 (88–154)	31 (13–53)

9.4 Calibrated *Status-Quo No-New-Vaccine* baseline trends

Each country was calibrated individually to either the nine or fourteen calibration targets as in section 9.3. Here we show the tuberculosis incidence and mortality rate targets for the selected grouping for reporting model outcomes. In Figure S9.1, looking by WHO region, we see the incidence rates are highest in AFR and SEAR, and lowest in AMR and EUR. In Figure S9.2, we see that correspondingly, the mortality rates are highest in AFR and SEAR, and lowest in AMR, EUR, and WPR. The estimated model medians for all WHO regions demonstrate decreasing trends from 2019 to 2050. In Figure S9.3 and Figure S9.4, we show the incidence and mortality rate trends by income group. Both incidence and mortality rates follow a trend with the highest estimated medians in lower-middle-income countries, followed by low-income countries and high-income countries, which aligns with the expectation of burden within each region. In Figure S9.5 and S9.6, we compare incidence and mortality rates between countries included on the WHO high TB burden list and all other countries modelled, and as expected, higher values are predicted for countries on the high TB burden list.

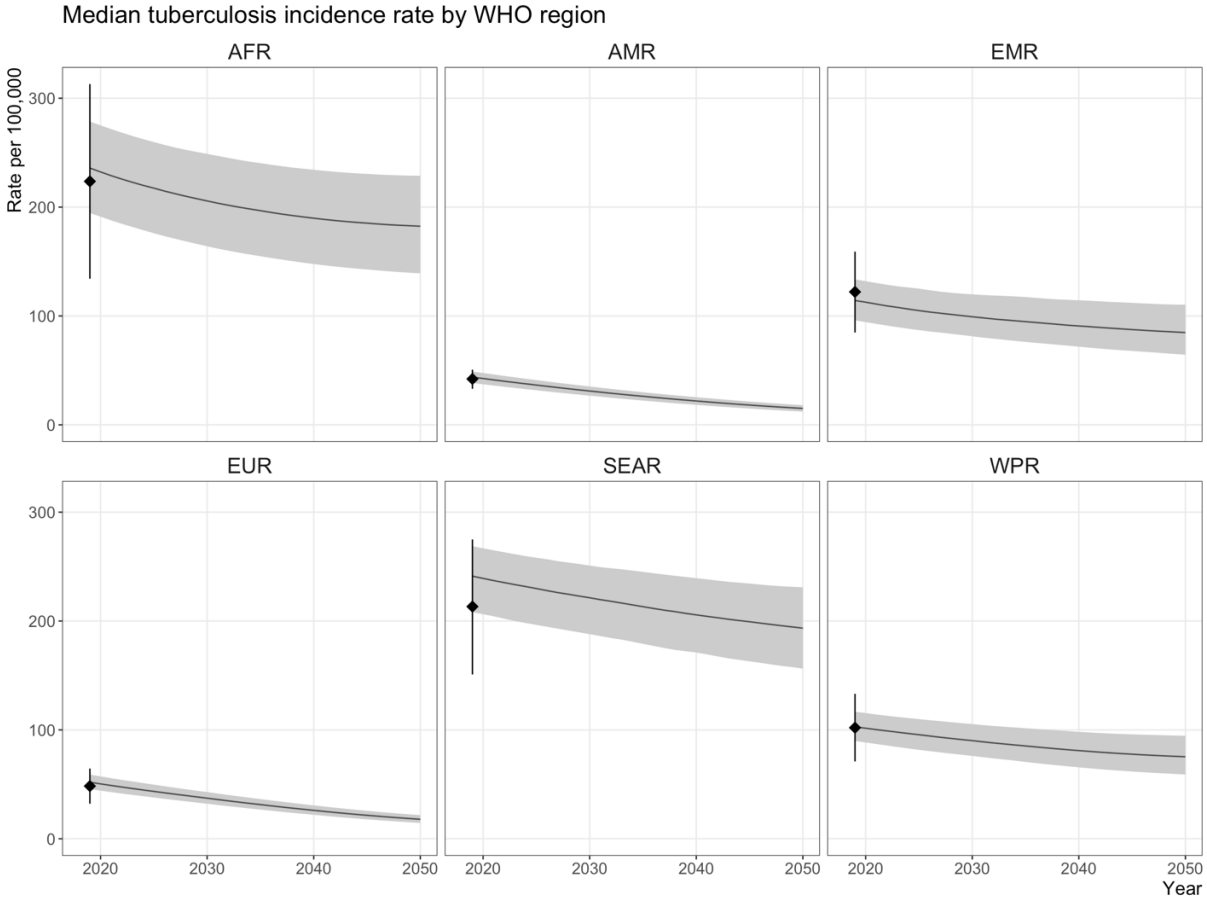


Figure S9.1 Tuberculosis incidence rates for the *Status Quo No-New-Vaccine* baseline by WHO region. The black diamond is the WHO median estimate of the incidence in 2019 for the 105 modelled LMICs by WHO region with 95% uncertainty range. The black line is the model estimated median incidence rate, with shaded 95% uncertainty ranges.

AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, SEAR = WHO South-East Asian Region, WPR = WHO Western Pacific Region

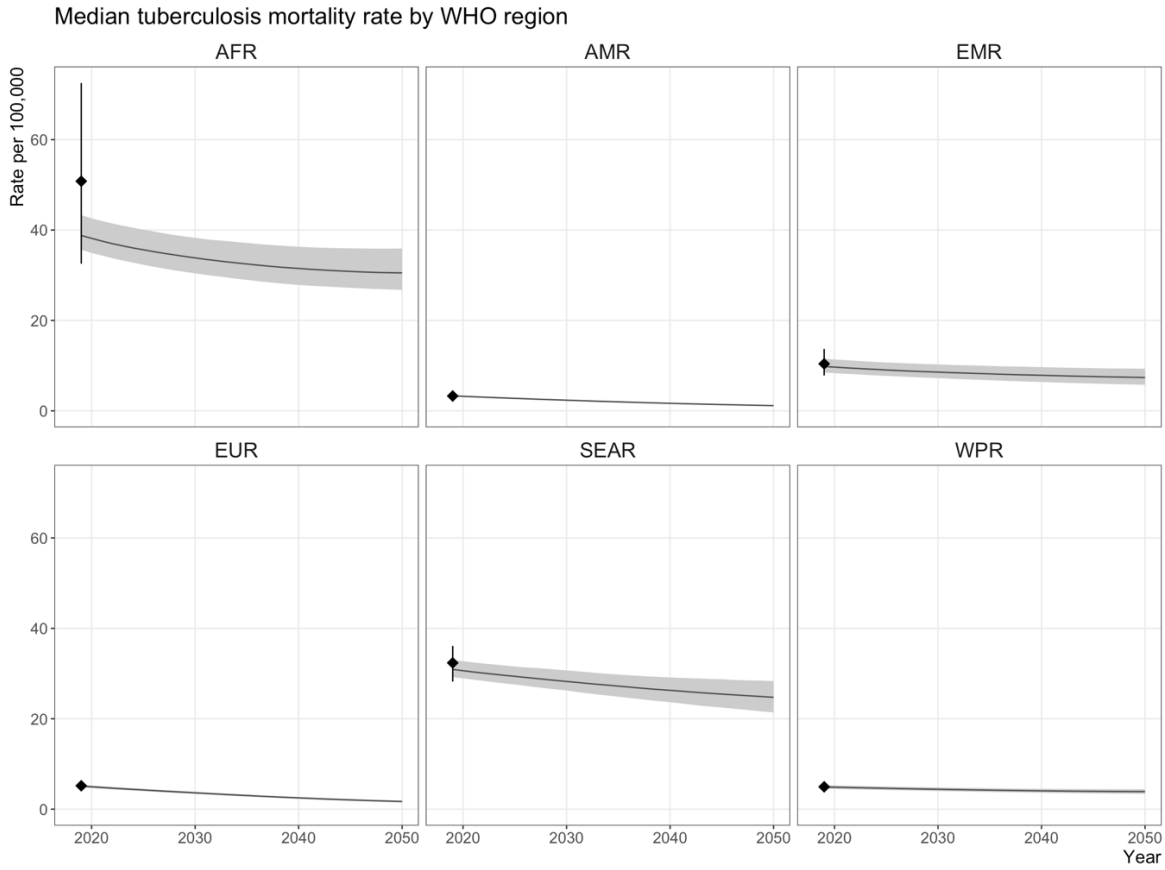


Figure S9.2 Tuberculosis mortality rates for the *Status Quo No-New-Vaccine* baseline by WHO region. The black diamond is the WHO median estimate of the mortality rate in 2019 for the 105 modelled LMICs by WHO region with 95% uncertainty range. The black line is the model estimated median mortality rate, with shaded 95% uncertainty ranges.

AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, SEAR = WHO South-East Asian Region, WPR = WHO Western Pacific Region

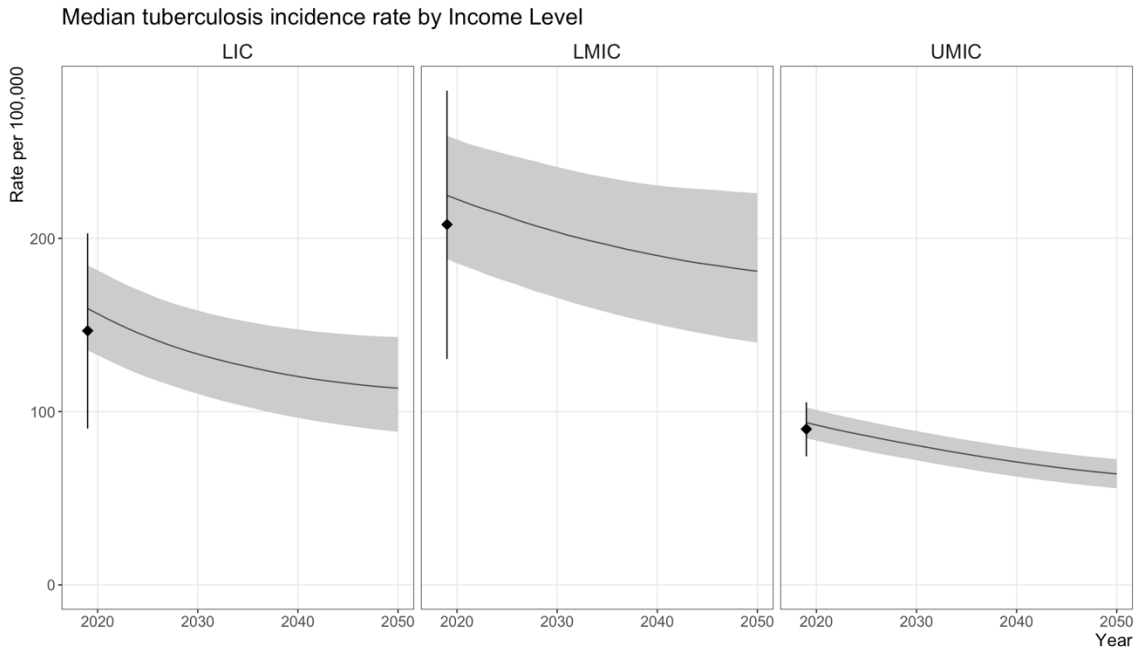


Figure S9.3 Tuberculosis incidence rates for the *Status Quo No-New-Vaccine* baseline by income group. The black diamond is the WHO median estimate of the incidence rate in 2019 for the 105 modelled LMICs by income group with 95% uncertainty range. The black line is the model estimated median incidence rate, with shaded 95% uncertainty ranges.

LIC = low-income countries, LMIC = lower-middle income countries, UMIC = upper-middle income countries

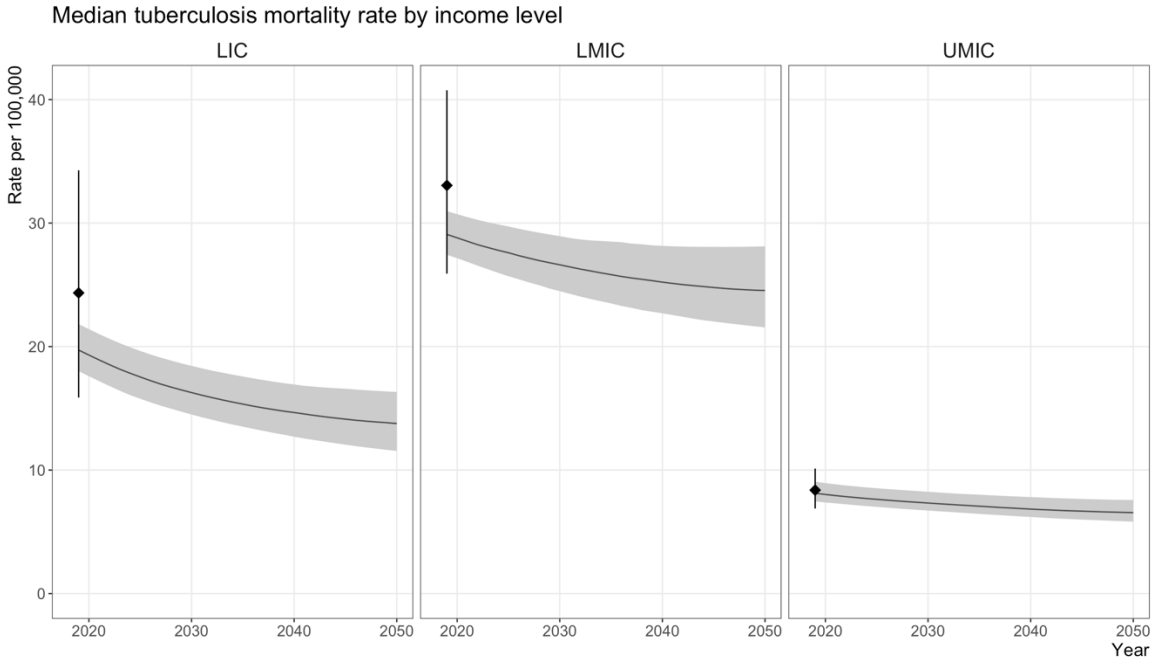


Figure S9.4 Tuberculosis mortality rates for the *Status Quo No-New-Vaccine* baseline by income group. The black diamond is the WHO median estimate of the mortality rate in 2019 for the 105 modelled LMICs by income group with 95% uncertainty range. The black line is the model estimated median mortality rate, with shaded 95% uncertainty ranges.

LIC = low-income countries, LMIC = lower-middle income countries, UMIC = upper-middle income countries

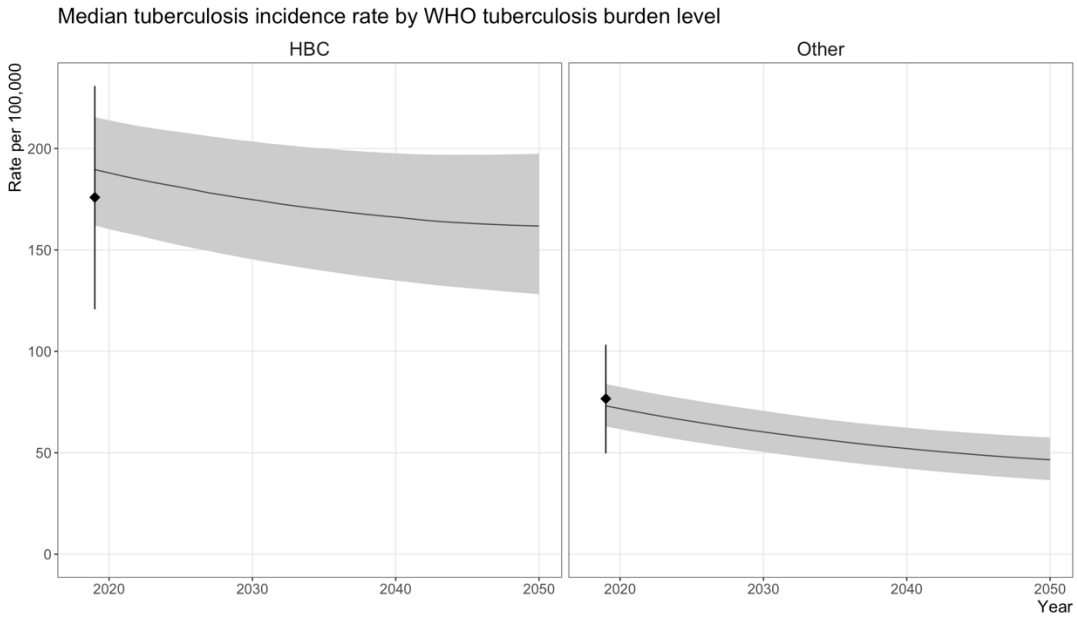


Figure S9.5 Tuberculosis incidence rates for the *Status Quo No-New-Vaccine* baseline for the countries included on the WHO high-TB-burden list and for all other countries modelled. The black diamond is the WHO median estimate of the incidence rate in 2019 for the 105 modelled LMICs by burden level with 95% uncertainty range. The black line is the model estimated median incidence rate, with shaded 95% uncertainty ranges.

HBC = high burden countries

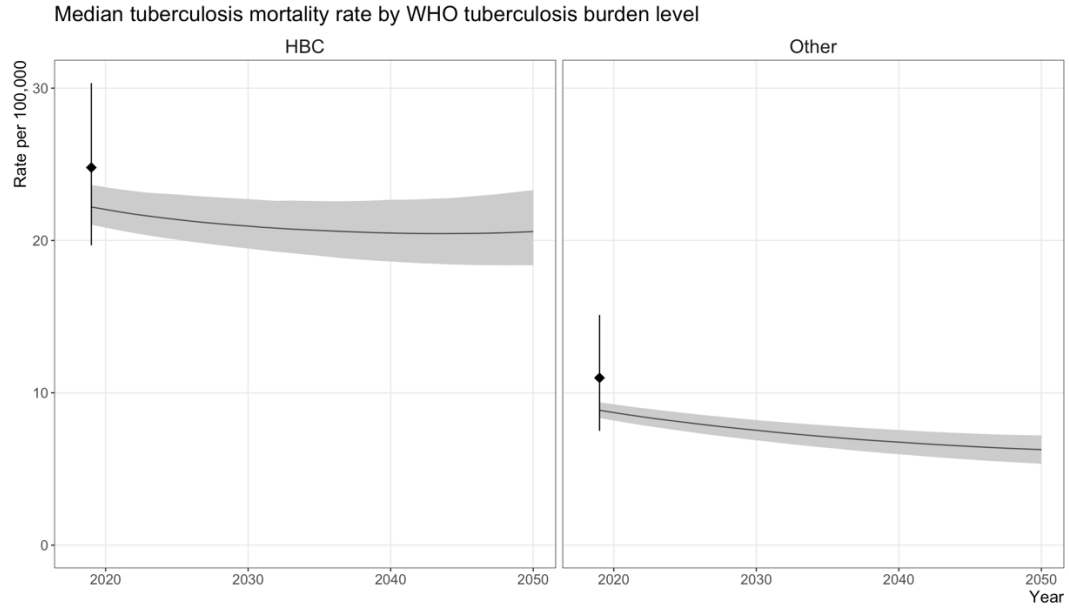


Figure S9.6 Tuberculosis mortality rates for the *Status Quo No-New-Vaccine* baseline for the countries included on the WHO high-TB-burden list and for all other countries modelled. The black diamond is the WHO median estimate of the mortality rate in 2019 for the 105 modelled LMICs by burden level with 95% uncertainty range. The black line is the model estimated median mortality rate, with shaded 95% uncertainty ranges.

HBC = high burden countries

10. Vaccine Health Impact Results

10.1 Incidence and mortality rate reductions and cumulative cases, treatments, and deaths averted

As stated in the main text, delivery of a 50% efficacy vaccine with an average of 10-years protection and medium coverage will have a substantial impact, which varies based on delivery and vaccine characteristics. For the adolescent/adult vaccine, compared to the *Basecase* implementation, the *Accelerated Scale-up* scenario averted approximately double the number of cases, treatments, and deaths by 2050, and almost eight times as many as the *Routine Only* scenario, demonstrating the benefits of instantly introducing and scaling-up to coverage, as well as including a campaign for ages ten and over. We performed scenario analyses by varying certain vaccine and delivery characteristics, the results of which are presented in Table S10.1 (adolescent/adult vaccine) and Table S10.2 (infant vaccine) below, as the median estimate and 95% uncertainty range. Decreasing the target vaccine coverage correspondingly decreased the health impact estimates, and increasing the target vaccine coverage, increasing the duration of protection to lifelong, or increasing the vaccine efficacy increases the health impact estimates.

The order of vaccine scenario health impact results within each table is as follows:

Primary scenarios (as in main text)

- *Basecase*, medium coverage, 50% efficacy, 10-years protection
- *Accelerated Scale-up*, medium coverage, 50% efficacy, 10-years protection
- *Routine Only*, medium coverage, 50% efficacy, 10-years protection (adolescent/adult vaccine only)

Low and high coverage targets

- *Basecase*, low coverage, 50% efficacy, 10-years protection
- *Basecase*, high coverage, 50% efficacy, 10-years protection
- *Accelerated Scale-up*, low coverage, 50% efficacy, 10-years protection
- *Accelerated Scale-up*, high coverage, 50% efficacy, 10-years protection
- *Routine Only*, low coverage, 50% efficacy, 10-years protection (adolescent/adult vaccine only)
- *Routine Only*, high coverage, 50% efficacy, 10-years protection (adolescent/adult vaccine only)

Lifelong duration of protection

- *Basecase*, medium coverage, 50% efficacy, lifelong protection
- *Accelerated Scale-up*, medium coverage, 50% efficacy, lifelong protection
- *Routine Only*, medium coverage, 50% efficacy, lifelong protection (adolescent/adult vaccine only)

75% efficacy (adolescent/adult vaccine only)

- *Basecase*, medium coverage, 75% efficacy, 10-years protection
- *Accelerated Scale-up*, medium coverage, 75% efficacy, 10-years protection

Table S10.1 Estimated health impact in 2050 by WHO region, income level, and tuberculosis burden level for the adolescent/adult vaccine scenarios

Vaccine Scenario	Health Impact Measure	All modelled countries	WHO Region						World Bank Income Group			TB Burden Level	
			AFR	AMR	EMR	EUR	SEAR	WPR	LIC	LMIC	UMIC	HBC	All other countries
Primary scenarios													
Basecase Medium coverage, 50% efficacy, 10 years protection	IRR in 2050 (%)	19·5% (18·3–21·6)	21·1% (19·9–25·1)	11·2% (10·6–12·0)	21·1% (18·5–25·5)	14·2% (12·9–16·2)	19·2% (17·4–21·7)	15·2% (13·9–17·3)	21·2% (20·0–22·9)	19·6% (18·0–22·4)	18·3% (16·5–20·7)	19·6% (18·3–21·9)	18·7% (17·8–20·1)
	MRR in 2050 (%)	20·6% (19·2–23·4)	21·3% (20·1–26·5)	12·4% (11·7–13·2)	21·9% (19·3–26·1)	13·9% (12·9–15·4)	19·8% (17·9–22·3)	17·7% (15·9–20·3)	21·4% (20·2–22·9)	20·6% (19·0–24·2)	20·2% (18·3–22·7)	20·8% (19·3–23·9)	18·9% (18·1–20·0)
	Averted cases before 2050	31·5m (26·9–36·9)	10·2m (8·7–12·1)	0·4m (0·3–0·4)	2·8m (2·2–3·5)	0·2m (0·2–0·3)	13·8m (11·3–16·4)	4·1m (3·5–4·8)	3·4m (2·8–4·1)	21·8m (18·0–26·0)	6·4m (5·8–7·1)	28·6m (24·4–33·4)	2·9m (2·4–3·5)
	Averted deaths before 2050	3·6m (3·3–3·9)	1·5m (1·4–1·7)	0·02m (0·02–0·03)	0·2m (0·2–0·3)	0·02m (0·02–0·02)	1·6m (1·4–1·8)	0·2m (0·2–0·2)	0·4m (0·3–0·4)	2·7m (2·4–2·9)	0·6m (0·5–0·7)	3·3m (3·0–3·6)	0·3m (0·3–0·4)
	Averted tx before 2050	17·5m (15·6–19·2)	4·5m (4·1–4·8)	0·2m (0·2–0·3)	1·7m (1·4–2·0)	0·2m (0·1–0·2)	8·2m (7·1–9·5)	2·6m (2·3–2·9)	1·9m (1·7–2·2)	11·7m (10·2–13·1)	3·9m (3·5–4·2)	15·9m (14·1–17·5)	1·6m (1·4–1·8)
Accelerated Scale-up Medium coverage, 50% efficacy, 10 years protection	IRR in 2050 (%)	25·2% (23·9–27·5)	27·6% (26·3–32·1)	15·2% (14·4–16·2)	27·1% (24·5–31·4)	18·4% (16·5–21·6)	24·7% (22·8–27·4)	19·4% (18·1–21·3)	27·7% (26·5–29·5)	25·7% (24·0–28·6)	22·0% (20·4–24·6)	25·3% (23·8–27·6)	25·4% (24·5–26·8)
	MRR in 2050 (%)	26·7% (25·2–29·9)	28·2% (26·8–34·6)	16·2% (15·3–17·3)	27·9% (25·2–32·3)	18·1% (16·5–20·7)	25·3% (23·2–28·2)	21·8% (20·2–24·3)	28·0% (26·9–29·7)	27·0% (25·3–31·2)	24·3% (22·3–27·2)	26·8% (25·1–30·4)	26·1% (25·3–27·2)
	Averted cases before 2050	65·7m (55·8–76·2)	19·5m (16·8–23·2)	0·8m (0·7–1·0)	5·4m (4·4–6·7)	0·6m (0·5–0·7)	31·1m (25·9–36·5)	8·1m (7·0–9·5)	7·0m (5·7–8·4)	45·2m (37·4–53·7)	13·7m (12·3–15·1)	58·8m (50·0–68·1)	7·0m (5·8–8·3)
	Averted deaths before 2050	7·9m (7·3–8·5)	3·1m (2·9–3·4)	0·1m (0·1–0·1)	0·4m (0·4–0·6)	0·1m (0·1–0·1)	3·8m (3·3–4·3)	0·4m (0·4–0·4)	0·8m (0·7–0·9)	5·8m (5·2–6·4)	1·3m (1·1–1·5)	7·0m (6·4–7·6)	0·8m (0·8–0·9)
	Averted tx before 2050	38·6m (34·4–42·3)	9·2m (8·5–9·9)	0·6m (0·5–0·7)	3·4m (2·9–4·0)	0·4m (0·4–0·5)	19·4m (16·8–22·2)	5·3m (4·8–5·9)	4·2m (3·7–4·7)	25·7m (22·4–28·8)	8·6m (7·8–9·5)	34·5m (30·7–37·9)	4·0m (3·5–4·4)
Routine Only Medium coverage, 50% efficacy, 10 years protection	IRR in 2050 (%)	9·9% (9·0–11·6)	11·2% (10·4–14·7)	3·5% (3·1–3·9)	11·9% (9·9–15·4)	4·1% (3·4–5·2)	9·1% (7·8–11·1)	7·7% (6·5–9·5)	10·8% (9·8–12·3)	10·0% (8·8–12·3)	9·2% (8·0–11·0)	10·2% (9·1–12·0)	8·0% (7·3–9·2)
	MRR in 2050 (%)	9·9% (8·9–12·3)	10·7% (9·7–15·2)	3·7% (3·3–4·2)	11·9% (9·9–15·1)	3·7% (3·2–4·5)	8·7% (7·3–10·7)	9·2% (7·5–11·7)	10·0% (9·1–11·2)	9·9% (8·7–13·0)	9·8% (8·5–11·6)	10·2% (9·1–12·9)	7·2% (6·5–8·1)
	Averted cases before 2050	8·8m (7·7–10·1)	3·5m (3·0–3·9)	0·04m (0·03–0·05)	0·9m (0·7–1·2)	0·02m (0·02–0·03)	3·4m (2·6–4·4)	1·0m (0·8–1·2)	1·0m (0·8–1·3)	6·3m (5·3–7·4)	1·5m (1·3–1·7)	8·1m (7·0–9·4)	0·7m (0·6–0·8)

	Averted deaths before 2050	1·1m (0·9–1·2)	0·5m (0·4–0·6)	0·003m (0·003–0·004)	0·1m (0·1–0·1)	0·002m (0·002–0·003)	0·4m (0·3–0·5)	0·1m (0·0–0·1)	0·1m (0·1–0·1)	0·8m (0·7–0·9)	0·2m (0·1–0·2)	1·0m (0·8–1·1)	0·1m (0·1–0·1)
	Averted tx before 2050	4·1m (3·7–4·6)	1·2m (1·1–1·4)	0·02m (0·02–0·03)	0·5m (0·4–0·6)	0·01m (0·01–0·02)	1·8m (1·4–2·2)	0·6m (0·5–0·7)	0·5m (0·5–0·6)	2·8m (2·4–3·2)	0·8m (0·7–0·9)	3·8m (3·4–4·2)	0·3m (0·3–0·4)
Low and high coverage													
Basecase Low coverage, 50% efficacy, 10 years protection	IRR in 2050 (%)	16·8% (15·7–18·7)	18·1% (17·1–21·8)	9·5% (8·9–10·2)	18·2% (15·9–22·2)	12·0% (10·9–13·8)	16·5% (14·9–18·7)	13·0% (11·8–14·9)	18·3% (17·2–19·8)	16·9% (15·5–19·3)	15·7% (14·2–17·9)	16·9% (15·7–18·9)	15·9% (15·2–17·2)
	MRR in 2050 (%)	17·6% (16·5–20·2)	18·3% (17·2–23·0)	10·4% (9·8–11·2)	18·9% (16·6–22·6)	11·7% (10·8–12·9)	16·9% (15·3–19·1)	15·2% (13·6–17·5)	18·3% (17·3–19·6)	17·7% (16·2–20·9)	17·3% (15·7–19·5)	17·9% (16·5–20·7)	16·1% (15·3–17·1)
	Averted cases before 2050	26·3m (22·5–30·7)	8·5m (7·4–10·1)	0·3m (0·2–0·3)	2·4m (1·9–2·9)	0·2m (0·2–0·2)	11·5m (9·4–13·7)	3·4m (2·9–4·0)	2·8m (2·3–3·4)	18·1m (15·0–21·6)	5·3m (4·8–5·9)	23·9m (20·3–27·8)	2·4m (2·0–2·9)
	Averted deaths before 2050	3·0m (2·8–3·3)	1·3m (1·2–1·4)	0·02m (0·02–0·02)	0·2m (0·1–0·2)	0·02m (0·01–0·02)	1·3m (1·1–1·5)	0·2m (0·1–0·2)	0·3m (0·3–0·4)	2·2m (2·0–2·5)	0·5m (0·4–0·6)	2·7m (2·5–3·0)	0·3m (0·2–0·3)
	Averted tx before 2050	14·5m (12·9–15·9)	3·7m (3·4–4·0)	0·2m (0·2–0·2)	1·4m (1·2–1·7)	0·1m (0·1–0·1)	6·8m (5·8–7·8)	2·2m (1·9–2·4)	1·6m (1·4–1·8)	9·7m (8·4–10·9)	3·2m (2·9–3·5)	13·2m (11·7–14·5)	1·3m (1·2–1·5)
Basecase High coverage, 50% efficacy, 10 years protection	IRR in 2050 (%)	21·8% (20·4–24·0)	23·5% (22·2–27·8)	12·6% (11·9–13·5)	23·5% (20·6–28·3)	15·9% (14·5–18·1)	21·4% (19·4–24·1)	17·0% (15·6–19·3)	23·6% (22·3–25·5)	21·9% (20·2–24·9)	20·3% (18·5–23·0)	21·9% (20·4–24·3)	20·9% (20·0–22·4)
	MRR in 2050 (%)	23·0% (21·5–26·1)	23·8% (22·5–29·5)	13·9% (13·1–14·8)	24·4% (21·5–28·9)	15·7% (14·6–17·3)	22·0% (20·0–24·8)	19·8% (17·9–22·6)	23·8% (22·6–25·5)	23·0% (21·2–26·9)	22·5% (20·5–25·3)	23·2% (21·6–26·6)	21·2% (20·3–22·4)
	Averted cases before 2050	35·8m (30·5–41·8)	11·5m (9·8–13·7)	0·4m (0·4–0·5)	3·2m (2·5–4·0)	0·3m (0·2–0·3)	15·7m (12·8–18·6)	4·7m (4·0–5·5)	3·8m (3·1–4·7)	24·6m (20·3–29·5)	7·3m (6·5–8·1)	32·4m (27·6–37·9)	3·3m (2·8–3·9)
	Averted deaths before 2050	4·1m (3·8–4·4)	1·7m (1·6–1·9)	0·03m (0·03–0·03)	0·3m (0·2–0·3)	0·02m (0·02–0·02)	1·8m (1·6–2·1)	0·2m (0·2–0·2)	0·4m (0·4–0·5)	3·0m (2·7–3·3)	0·7m (0·6–0·8)	3·7m (3·4–4·0)	0·4m (0·3–0·4)
	Averted tx before 2050	19·9m (17·7–21·8)	5·1m (4·7–5·5)	0·3m (0·2–0·3)	1·9m (1·6–2·3)	0·2m (0·2–0·2)	9·4m (8·0–10·8)	3·0m (2·6–3·3)	2·2m (1·9–2·5)	13·2m (11·6–14·9)	4·4m (4·0–4·8)	18·1m (16·1–19·9)	1·8m (1·6–2·0)
Accelerated Scale-up Low coverage, 50% efficacy, 10 years protection	IRR in 2050 (%)	20·8% (19·6–22·9)	22·7% (21·6–26·8)	12·0% (11·3–12·8)	22·5% (20·2–26·3)	14·9% (13·2–17·8)	20·3% (18·6–22·7)	15·7% (14·6–17·5)	22·9% (21·8–24·5)	21·2% (19·7–23·8)	18·1% (16·7–20·4)	20·8% (19·5–23·0)	20·8% (20·0–22·1)
	MRR in 2050 (%)	21·9% (20·6–24·8)	23·2% (21·9–28·9)	12·8% (12·0–13·7)	23·1% (20·7–27·0)	14·6% (13·2–16·9)	20·7% (18·9–23·4)	17·8% (16·4–20·0)	23·0% (22·0–24·6)	22·2% (20·6–26·0)	20·0% (18·3–22·6)	22·0% (20·6–25·2)	21·2% (20·5–22·3)
	Averted cases before 2050	51·0m (43·5–59·1)	15·3m (13·3–18·1)	0·6m (0·5–0·7)	4·3m (3·4–5·2)	0·5m (0·4–0·6)	24·0m (20·0–28·4)	6·2m (5·3–7·3)	5·5m (4·5–6·6)	35·1m (29·1–41·7)	10·5m (9·4–11·6)	45·6m (38·9–52·9)	5·4m (4·5–6·3)

	Averted deaths before 2050	6·1m (5·7–6·6)	2·5m (2·2–2·7)	0·04m (0·04–0·05)	0·4m (0·3–0·4)	0·04m (0·04–0·05)	2·9m (2·5–3·4)	0·3m (0·3–0·3)	0·6m (0·6–0·7)	4·5m (4·1–5·0)	1·0m (0·9–1·1)	5·5m (5·0–6·0)	0·7m (0·6–0·7)
	Averted tx before 2050	29·7m (26·6–32·6)	7·2m (6·6–7·7)	0·4m (0·4–0·5)	2·6m (2·2–3·1)	0·3m (0·3–0·4)	15·0m (13·0–17·2)	4·0m (3·6–4·5)	3·3m (2·9–3·6)	19·8m (17·3–22·3)	6·6m (6·0–7·3)	26·6m (23·8–29·3)	3·1m (2·7–3·4)
Accelerated Scale-up High coverage, 50% efficacy, 10 years protection	IRR in 2050 (%)	29·5% (28·0–31·9)	32·2% (30·7–37·0)	18·3% (17·2–19·4)	31·4% (28·6–36·2)	21·6% (19·5–25·1)	28·8% (26·7–31·7)	22·9% (21·5–25·0)	32·2% (30·9–34·2)	30·0% (28·2–33·1)	25·8% (24·0–28·7)	29·5% (27·9–32·0)	29·7% (28·8–31·2)
	MRR in 2050 (%)	31·2% (29·6–34·7)	33·0% (31·4–39·8)	19·4% (18·3–20·7)	32·4% (29·4–37·1)	21·4% (19·6–24·3)	29·6% (27·3–32·7)	25·7% (23·8–28·3)	32·6% (31·4–34·4)	31·5% (29·6–36·1)	28·3% (26·2–31·7)	31·3% (29·5–35·1)	30·6% (29·8–31·9)
	Averted cases before 2050	80·0m (67·9–93·0)	23·6m (20·1–28·1)	1·1m (0·9–1·2)	6·6m (5·3–8·1)	0·8m (0·7–0·9)	37·9m (31·6–44·3)	10·0m (8·6–11·8)	8·4m (6·9–10·1)	55·0m (45·5–65·4)	16·8m (15·1–18·4)	71·5m (60·7–83·1)	8·5m (7·1–10·1)
	Averted deaths before 2050	9·5m (8·8–10·3)	3·8m (3·5–4·2)	0·1m (0·1–0·1)	0·5m (0·4–0·7)	0·1m (0·1–0·1)	4·6m (4·0–5·2)	0·5m (0·4–0·5)	1·0m (0·9–1·1)	7·0m (6·4–7·7)	1·6m (1·4–1·8)	8·5m (7·8–9·2)	1·0m (0·9–1·1)
	Averted tx before 2050	47·0m (41·9–51·6)	11·2m (10·2–12·0)	0·7m (0·7–0·8)	4·1m (3·5–4·8)	0·6m (0·5–0·6)	23·7m (20·5–27·0)	6·6m (5·9–7·3)	5·1m (4·4–5·7)	31·3m (27·3–35·1)	10·6m (9·6–11·6)	42·2m (37·4–46·3)	4·9m (4·3–5·4)
Routine Only Low coverage, 50% efficacy, 10 years protection	IRR in 2050 (%)	8·8% (7·9–10·3)	9·9% (9·2–13·1)	3·1% (2·7–3·5)	10·6% (8·8–13·7)	3·6% (3·0–4·6)	8·1% (6·9–9·9)	6·8% (5·8–8·5)	9·5% (8·7–10·9)	8·9% (7·8–10·9)	8·2% (7·1–9·8)	9·0% (8·1–10·7)	7·1% (6·4–8·1)
	MRR in 2050 (%)	8·8% (7·8–10·9)	9·5% (8·6–13·5)	3·3% (2·9–3·7)	10·6% (8·7–13·4)	3·3% (2·9–4·0)	7·7% (6·5–9·5)	8·1% (6·6–10·3)	8·8% (8·0–10·0)	8·8% (7·7–11·5)	8·7% (7·5–10·3)	9·1% (8·0–11·4)	6·3% (5·7–7·2)
	Averted cases before 2050	7·8m (6·8–8·9)	3·1m (2·6–3·5)	0·04m (0·03–0·04)	0·8m (0·6–1·1)	0·02m (0·02–0·03)	3·0m (2·3–3·9)	0·9m (0·7–1·1)	0·9m (0·7–1·1)	5·5m (4·7–6·6)	1·3m (1·2–1·5)	7·2m (6·2–8·3)	0·6m (0·5–0·7)
	Averted deaths before 2050	0·9m (0·8–1·1)	0·5m (0·4–0·6)	0·003m (0·002–0·003)	0·1m (0·0–0·1)	0·002m (0·002–0·002)	0·3m (0·3–0·4)	0·1m (0·0–0·1)	0·1m (0·1–0·1)	0·7m (0·6–0·8)	0·1m (0·1–0·2)	0·9m (0·7–1·0)	0·1m (0·1–0·1)
	Averted tx before 2050	3·6m (3·3–4·0)	1·1m (1·0–1·2)	0·02m (0·02–0·02)	0·4m (0·4–0·6)	0·01m (0·01–0·01)	1·5m (1·3–1·9)	0·5m (0·4–0·6)	0·5m (0·4–0·5)	2·4m (2·1–2·9)	0·7m (0·6–0·8)	3·3m (3·0–3·7)	0·3m (0·3–0·3)
Routine Only High coverage, 50% efficacy, 10 years protection	IRR in 2050 (%)	11·1% (10·0–12·9)	12·5% (11·5–16·3)	3·9% (3·5–4·4)	13·3% (11·0–17·0)	4·6% (3·9–5·8)	10·1% (8·7–12·3)	8·6% (7·3–10·6)	12·0% (10·9–13·6)	11·1% (9·8–13·6)	10·2% (8·9–12·2)	11·3% (10·2–13·3)	8·9% (8·1–10·2)
	MRR in 2050 (%)	11·0% (9·9–13·7)	12·0% (10·9–16·9)	4·1% (3·7–4·7)	13·2% (11·0–16·8)	4·2% (3·6–5·0)	9·7% (8·2–11·9)	10·3% (8·4–13·0)	11·1% (10·1–12·5)	11·1% (9·7–14·4)	10·9% (9·5–12·9)	11·4% (10·1–14·3)	8·0% (7·3–9·0)
	Averted cases before 2050	9·9m (8·6–11·3)	3·9m (3·4–4·4)	0·04m (0·04–0·05)	1·0m (0·8–1·3)	0·03m (0·02–0·03)	3·8m (2·9–4·9)	1·1m (0·9–1·4)	1·2m (0·9–1·4)	7·0m (5·9–8·3)	1·7m (1·5–1·9)	9·1m (7·9–10·5)	0·8m (0·6–0·9)
	Averted deaths before 2050	1·2m (1·0–1·3)	0·6m (0·5–0·7)	0·004m (0·003–0·004)	0·1m (0·1–0·1)	0·002m (0·002–0·003)	0·4m (0·3–0·6)	0·1m (0·1–0·1)	0·1m (0·1–0·1)	0·9m (0·7–1·1)	0·2m (0·1–0·2)	1·1m (0·9–1·3)	0·1m (0·1–0·1)

	Averted tx before 2050	4·6m (4·1–5·1)	1·4m (1·2–1·5)	0·03m (0·02–0·03)	0·6m (0·4–0·7)	0·02m (0·01–0·02)	2·0m (1·6–2·4)	0·6m (0·5–0·8)	0·6m (0·5–0·7)	3·1m (2·7–3·6)	0·9m (0·8–1·0)	4·2m (3·8–4·7)	0·4m (0·3–0·4)
Lifelong protection													
Basecase Medium coverage, 50% efficacy, lifelong protection	IRR in 2050 (%)	38·7% (36·7–41·6)	40·4% (38·6–45·7)	28·6% (27·3–30·0)	41·7% (37·5–48·0)	30·2% (28·6–32·7)	38·1% (35·3–41·7)	33·6% (31·1–37·2)	40·2% (38·2–42·7)	38·8% (36·2–42·5)	37·8% (35·2–41·4)	39·1% (36·9–42·3)	35·7% (34·4–37·7)
	MRR in 2050 (%)	37·9% (35·9–41·7)	38·5% (36·6–45·1)	28·6% (27·4–30·0)	40·8% (36·9–46·7)	28·7% (27·3–30·5)	37·1% (34·3–40·6)	34·5% (31·7–38·2)	38·0% (36·1–40·3)	37·9% (35·5–42·6)	38·1% (35·4–41·7)	38·5% (36·3–42·5)	33·5% (32·0–35·2)
	Averted cases before 2050	50·8m (43·0–59·8)	16·4m (13·8–19·8)	0·6m (0·5–0·7)	4·6m (3·6–5·7)	0·4m (0·3–0·4)	21·9m (17·9–26·0)	7·0m (5·9–8·3)	5·4m (4·4–6·5)	35·0m (28·6–42·0)	10·6m (9·5–11·7)	46·2m (39·0–54·3)	4·7m (3·8–5·5)
	Averted deaths before 2050	5·5m (5·1–6·0)	2·4m (2·2–2·6)	0·04m (0·04–0·04)	0·4m (0·3–0·4)	0·03m (0·03–0·03)	2·4m (2·1–2·8)	0·3m (0·3–0·3)	0·5m (0·5–0·6)	4·1m (3·7–4·5)	0·9m (0·8–1·0)	5·0m (4·6–5·5)	0·5m (0·4–0·5)
	Averted tx before 2050	27·7m (24·5–30·5)	7·1m (6·5–7·7)	0·4m (0·4–0·5)	2·7m (2·3–3·2)	0·3m (0·2–0·3)	12·8m (10·9–14·7)	4·4m (3·9–4·9)	3·0m (2·6–3·4)	18·4m (16·0–20·7)	6·2m (5·7–6·8)	25·2m (22·3–27·8)	2·5m (2·2–2·8)
Accelerated Scale-up Medium coverage, 50% efficacy, lifelong protection	IRR in 2050 (%)	55·6% (53·5–58·7)	57·7% (55·8–63·0)	43·4% (41·9–45·1)	57·5% (52·8–64·1)	47·2% (44·7–50·7)	55·8% (52·5–59·7)	47·9% (45·1–51·9)	58·2% (56·2–60·7)	55·8% (52·9–59·6)	53·8% (50·8–57·8)	55·7% (53·4–59·1)	54·9% (53·6–56·8)
	MRR in 2050 (%)	55·7% (53·4–59·8)	56·5% (54·5–63·5)	43·7% (42·2–45·4)	57·1% (52·7–63·3)	46·1% (43·8–49·1)	55·2% (51·8–59·3)	49·4% (46·3–53·5)	57·1% (55·2–59·4)	55·8% (52·9–60·8)	55·1% (51·8–59·6)	55·9% (53·4–60·4)	54·4% (53·2–56·0)
	Averted cases before 2050	116·9m (98·5–136·6)	34·1m (28·4–41·2)	1·6m (1·3–1·8)	9·5m (7·6–11·7)	1·2m (1·0–1·3)	55·3m (45·7–64·8)	15·0m (12·8–17·7)	12·2m (9·9–14·8)	79·9m (65·6–95·6)	24·8m (22·3–27·2)	104·4m (88·1–122·1)	12·4m (10·3–14·7)
	Averted deaths before 2050	13·4m (12·4–14·5)	5·2m (4·8–5·8)	0·1m (0·1–0·1)	0·8m (0·6–0·9)	0·1m (0·1–0·1)	6·5m (5·7–7·4)	0·7m (0·6–0·8)	1·4m (1·2–1·6)	9·8m (9·0–10·8)	2·2m (2·0–2·5)	11·9m (11·0–13·0)	1·5m (1·3–1·6)
	Averted tx before 2050	67·9m (60·1–74·7)	16·1m (14·5–17·3)	1·1m (1·0–1·2)	5·9m (5·0–6·9)	0·8m (0·7–0·9)	34·2m (29·5–38·9)	9·7m (8·6–10·8)	7·3m (6·3–8·1)	45·1m (39·2–50·8)	15·4m (14·0–16·7)	60·9m (53·8–67·2)	7·0m (6·2–7·7)
Routine Only Medium coverage, 50% efficacy, lifelong protection	IRR in 2050 (%)	16·8% (15·4–19·2)	19·2% (18·0–24·1)	6·5% (5·8– 7·4)	20·5% (17·2–25·9)	6·8% (5·8– 8·3)	15·1% (13·1–18·0)	13·6% (11·6–16·5)	18·1% (16·6–20·2)	17·0% (15·1–20·2)	15·5% (13·6–18·2)	17·2% (15·6–19·8)	13·3% (12·2–15·1)
	MRR in 2050 (%)	15·8% (14·2–19·2)	17·3% (15·9–23·7)	6·3% (5·7–7·2)	19·3% (16·2–24·0)	5·9% (5·2–6·9)	13·7% (11·7–16·5)	14·4% (12·0–17·6)	15·8% (14·4–17·6)	15·9% (14·1–20·0)	15·5% (13·6–18·2)	16·3% (14·7–20·0)	11·3% (10·2–12·7)
	Averted cases before 2050	13·5m (11·7–15·6)	5·3m (4·6–6·1)	0·1m (0·1–0·1)	1·4m (1·1–1·8)	0·04m (0·03–0·05)	5·1m (4·0–6·5)	1·6m (1·2–1·9)	1·6m (1·3–2·0)	9·6m (8·1–11·4)	2·3m (2·0–2·7)	12·4m (10·7–14·4)	1·1m (0·9–1·2)
	Averted deaths before 2050	1·5m (1·3–1·7)	0·8m (0·6–0·9)	0·005m (0·004–0·006)	0·1m (0·1–0·1)	0·003m (0·003–0·004)	0·5m (0·4–0·7)	0·1m (0·1–0·1)	0·2m (0·1–0·2)	1·1m (1·0–1·4)	0·2m (0·2–0·3)	1·4m (1·2–1·6)	0·1m (0·1–0·1)

	Averted tx before 2050	6·2m (5·6–6·9)	1·9m (1·7–2·1)	0·04m (0·03–0·05)	0·8m (0·6–1·0)	0·02m (0·02–0·02)	2·6m (2·1–3·2)	0·9m (0·7–1·1)	0·8m (0·7–0·9)	4·2m (3·7–4·9)	1·2m (1·0–1·4)	5·7m (5·1–6·4)	0·5m (0·4–0·6)
75% efficacy vaccine													
Basecase Medium coverage, 75% efficacy, 10 years protection	IRR in 2050 (%)	28·3% (26·6–30·9)	30·6% (29·1–35·7)	16·7% (15·8–17·7)	30·2% (26·8–35·9)	20·7% (19·0–23·4)	27·7% (25·4–31·0)	22·3% (20·7–25·2)	30·7% (29·1–32·8)	28·5% (26·4–31·9)	26·4% (24·2–29·8)	28·4% (26·6–31·3)	27·2% (26·1–28·9)
	MRR in 2050 (%)	29·9% (28·1–33·5)	31·0% (29·5–37·8)	18·3% (17·4–19·5)	31·4% (28·0–36·8)	20·5% (19·2–22·5)	28·6% (26·1–31·8)	26·0% (23·7–29·3)	31·0% (29·5–32·9)	29·9% (27·8–34·4)	29·2% (26·8–32·6)	30·2% (28·2–34·1)	27·7% (26·7–29·1)
	Averted cases before 2050	46·5m (39·5–54·6)	15·0m (12·8–18·0)	0·5m (0·5–0·6)	4·1m (3·3–5·2)	0·3m (0·3–0·4)	20·4m (16·7–24·1)	6·1m (5·2–7·3)	5·0m (4·1–6·1)	32·0m (26·4–38·4)	9·6m (8·5–10·6)	42·2m (35·7–49·5)	4·3m (3·6–5·2)
	Averted deaths before 2050	5·3m (4·9–5·8)	2·3m (2·1–2·5)	0·04m (0·03–0·04)	0·3m (0·3–0·4)	0·03m (0·03–0·03)	2·3m (2·0–2·7)	0·3m (0·3–0·3)	0·5m (0·5–0·6)	3·9m (3·6–4·3)	0·9m (0·8–1·0)	4·8m (4·5–5·3)	0·5m (0·4–0·5)
	Averted tx before 2050	26·0m (23·0–28·5)	6·7m (6·1–7·2)	0·4m (0·3–0·4)	2·5m (2·1–3·0)	0·2m (0·2–0·3)	12·2m (10·4–14·0)	3·9m (3·5–4·4)	2·9m (2·5–3·2)	17·3m (15·0–19·4)	5·8m (5·2–6·3)	23·6m (20·9–26·0)	2·4m (2·1–2·7)
Accelerated Scale-up Medium coverage, 75% efficacy, 10 years protection	IRR in 2050 (%)	35·9% (34·2–38·5)	39·2% (37·7–44·6)	22·0% (20·8–23·2)	38·0% (34·7–43·6)	25·7% (23·3–29·6)	35·0% (32·6–38·2)	28·3% (26·6–30·7)	39·1% (37·6–41·2)	36·5% (34·4–39·9)	31·8% (29·6–35·2)	35·9% (34·1–38·7)	35·8% (34·8–37·5)
	MRR in 2050 (%)	37·8% (36·0–41·7)	40·1% (38·4–47·7)	23·4% (22·1–24·9)	39·1% (35·6–44·5)	25·6% (23·6–28·6)	35·8% (33·2–39·3)	31·6% (29·5–34·8)	39·5% (38·1–41·5)	38·2% (36·0–43·2)	34·9% (32·4–38·8)	37·9% (35·9–42·3)	36·9% (36·0–38·3)
	Averted cases before 2050	95·3m (80·8–111·2)	28·3m (24·0–34·0)	1·2m (1·1–1·4)	7·8m (6·2–9·6)	0·9m (0·8–1·1)	44·9m (37·2–52·7)	12·0m (10·2–14·2)	10·1m (8·2–12·1)	65·4m (54·1–78·0)	20·0m (17·9–22·0)	85·1m (72·0–99·2)	10·1m (8·4–12·0)
	Averted deaths before 2050	11·4m (10·5–12·3)	4·5m (4·1–5·0)	0·1m (0·1–0·1)	0·6m (0·5–0·8)	0·1m (0·1–0·1)	5·4m (4·8–6·2)	0·6m (0·5–0·7)	1·2m (1·0–1·3)	8·3m (7·6–9·2)	1·9m (1·7–2·1)	10·1m (9·3–11·0)	1·2m (1·1–1·4)
	Averted tx before 2050	56·0m (49·6–61·6)	13·4m (12·2–14·5)	0·9m (0·8–1·0)	4·9m (4·1–5·7)	0·7m (0·6–0·7)	28·2m (24·3–32·0)	7·9m (7·0–8·8)	6·1m (5·3–6·8)	37·2m (32·4–41·8)	12·6m (11·4–13·8)	50·2m (44·5–55·3)	5·8m (5·1–6·4)

Abbreviations: AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, HBC = high burden countries, IRR = incidence rate reduction, LIC = low-income countries, LMIC = lower-middle income countries, MRR = mortality rate reduction, SEAR = WHO South-East Asian Region, tx = treatments, UMIC = upper-middle income countries, WPR = WHO Western Pacific Region

Table S10.2 Estimated health impact in 2050 by WHO region, income level, and tuberculosis burden level for the infant vaccine scenarios

			WHO Region						World Bank Income Group			TB Burden Level	
Vaccine Scenario	**Health Impact Measure**	**All modelled countries**	**AFR**	**AMR**	**EMR**	**EUR**	**SEAR**	**WPR**	**LIC**	**LMIC**	**UMIC**	**HBC**	**All other countries**
Basecase Medium coverage, 80% efficacy, 10 years protection	IRR in 2050 (%)	8·8% (7·9–10·4)	11·0% (10·0–14·6)	2·7% (2·4–3·1)	12·0% (9·7–15·6)	2·9% (2·5–3·4)	6·9% (5·8–8·6)	7·2% (5·9–9·2)	10·1% (9·1–11·5)	9·1% (7·9–11·2)	7·0% (6·2–8·1)	9·0% (8·1–10·7)	7·1% (6·4–8·2)
	MRR in 2050 (%)	9·8% (8·7–12·0)	11·3% (10·1–15·7)	3·7% (3·2–4·3)	13·4% (10·5–18·1)	3·3% (2·9–3·9)	7·2% (5·9–9·6)	11·2% (8·5–15·4)	10·4% (9·4–11·9)	9·9% (8·5–12·7)	8·4% (7·2–10·0)	10·1% (8·9–12·5)	7·1% (6·4–8·0)
	Averted cases before 2050	6·7m (5·8–7·7)	2·9m (2·5–3·4)	0·03m (0·02–0·03)	0·8m (0·6–1·1)	0·02m (0·01–0·02)	2·2m (1·6–2·8)	0·8m (0·6–1·0)	0·8m (0·7–1·1)	4·9m (4·2–5·7)	1·0m (0·8–1·1)	6·2m (5·3–7·1)	0·5m (0·4–0·6)
	Averted deaths before 2050	0·9m (0·8–1·0)	0·5m (0·4–0·6)	0·003m (0·002–0·003)	0·1m (0·1–0·1)	0·002m (0·002–0·002)	0·3m (0·2–0·4)	0·1m (0·0–0·1)	0·1m (0·1–0·1)	0·7m (0·6–0·8)	0·1m (0·1–0·1)	0·8m (0·7–1·0)	0·1m (0·1–0·1)
	Averted tx before 2050	2·7m (2·4–2·9)	0·9m (0·8–0·9)	0·02m (0·01–0·02)	0·4m (0·3–0·5)	0·01m (0·01–0·01)	1·0m (0·8–1·2)	0·4m (0·3–0·5)	0·4m (0·3–0·4)	1·8m (1·6–2·1)	0·4m (0·4–0·5)	2·4m (2·2–2·7)	0·2m (0·2–0·3)
Accelerated Scale-up Medium coverage, 80% efficacy, 10 years protection	IRR in 2050 (%)	14·3% (13·0–16·7)	16·7% (15·5–21·6)	4·6% (4·2–5·2)	17·6% (14·5–22·3)	7·5% (6·2–9·9)	12·9% (11·0–15·8)	10·3% (8·7–12·6)	16·6% (15·3–18·6)	14·5% (12·8–17·7)	12·1% (10·7–14·4)	14·4% (13·0–17·1)	13·4% (12·4–14·9)
	MRR in 2050 (%)	15·9% (14·3–19·3)	17·5% (15·9–24·1)	5·8% (5·2–6·6)	19·2% (15·5–24·7)	7·7% (6·5–9·5)	13·4% (11·2–17·0)	15·0% (12·1–19·3)	17·5% (16·1–19·5)	15·9% (13·9–20·2)	14·4% (12·6–17·0)	16·1% (14·3–19·9)	14·1% (13·1–15·3)
	Averted cases before 2050	16·3m (14·1–18·8)	6·3m (5·4–7·2)	0·1m (0·1–0·1)	1·7m (1·3–2·2)	0·1m (0·1–0·1)	6·6m (5·1–8·6)	1·5m (1·2–1·9)	2·1m (1·7–2·6)	11·5m (9·6–13·7)	2·7m (2·4–3·1)	14·7m (12·6–17·1)	1·6m (1·3–1·9)
	Averted deaths before 2050	2·3m (2·0–2·6)	1·1m (0·9–1·2)	0·01m (0·01–0·01)	0·2m (0·1–0·2)	0·01m (0·01–0·01)	0·9m (0·7–1·2)	0·1m (0·1–0·2)	0·3m (0·2–0·3)	1·7m (1·4–2·0)	0·3m (0·3–0·4)	2·0m (1·8–2·3)	0·2m (0·2–0·3)
	Averted tx before 2050	7·7m (6·9–8·6)	2·2m (2·0–2·4)	0·04m (0·04–0·05)	0·9m (0·8–1·2)	0·04m (0·04–0·05)	3·6m (2·9–4·3)	0·9m (0·7–1·0)	1·1m (0·9–1·2)	5·1m (4·5–6·0)	1·4m (1·3–1·7)	6·9m (6·2–7·8)	0·7m (0·7–0·8)
Low and high coverage													
Basecase Low coverage, 80% efficacy,	IRR in 2050 (%)	7·9% (7·1–9·3)	9·8% (9·0–13·1)	2·4% (2·2–2·8)	10·8% (8·6–14·0)	2·5% (2·3–3·0)	6·2% (5·2–7·7)	6·5% (5·3–8·2)	9·0% (8·2–10·3)	8·1% (7·1–10·1)	6·3% (5·6–7·3)	8·1% (7·2–9·6)	6·3% (5·7–7·3)
	MRR in 2050 (%)	8·7% (7·8–10·7)	10·1% (9·0–14·1)	3·3% (2·9–3·9)	12·0% (9·4–16·2)	2·9% (2·5–3·4)	6·4% (5·2–8·6)	10·0% (7·6–13·8)	9·3% (8·4–10·7)	8·9% (7·6–11·4)	7·5% (6·4–8·9)	9·0% (8·0–11·2)	6·3% (5·7–7·2)

10 years protection	Averted cases before 2050	6·0m (5·2–6·8)	2·6m (2·2–3·0)	0·02m (0·02–0·03)	0·7m (0·5–1·0)	0·01m (0·01–0·02)	1·9m (1·5–2·5)	0·7m (0·5–0·9)	0·8m (0·6–0·9)	4·3m (3·7–5·1)	0·9m (0·7–1·0)	5·5m (4·8–6·3)	0·5m (0·4–0·6)
	Averted deaths before 2050	0·8m (0·7–0·9)	0·4m (0·4–0·5)	0·003m (0·002–0·003)	0·1m (0·0–0·1)	0·002m (0·001–0·002)	0·2m (0·2–0·3)	0·1m (0·0–0·1)	0·1m (0·1–0·1)	0·6m (0·5–0·7)	0·1m (0·1–0·1)	0·7m (0·6–0·8)	0·1m (0·1–0·1)
	Averted tx before 2050	2·4m (2·2–2·6)	0·8m (0·7–0·8)	0·01m (0·01–0·02)	0·4m (0·3–0·5)	0·01m (0·01–0·02)	0·9m (0·7–1·0)	0·3m (0·3–0·4)	0·3m (0·3–0·4)	1·6m (1·5–1·9)	0·4m (0·3–0·4)	2·2m (2·0–2·4)	0·2m (0·2–0·2)
Basecase High coverage, 80% efficacy, 10 years protection	IRR in 2050 (%)	9·7% (8·8–11·4)	12·1% (11·1–16·0)	3·0% (2·7–3·5)	13·3% (10·7–17·1)	3·2% (2·8–3·8)	7·7% (6·5–9·5)	8·0% (6·5–10·1)	11·2% (10·1–12·7)	10·0% (8·8–12·4)	7·7% (6·9–9·0)	9·9% (8·9–11·8)	7·8% (7·1–9·1)
	MRR in 2050 (%)	10·8% (9·6–13·2)	12·5% (11·2–17·3)	4·1% (3·6–4·8)	14·8% (11·6–19·9)	3·7% (3·2–4·3)	8·0% (6·5–10·6)	12·3% (9·4–16·9)	11·6% (10·4–13·2)	11·0% (9·4–14·0)	9·3% (8·0–11·1)	11·2% (9·9–13·8)	7·9% (7·2–8·9)
	Averted cases before 2050	7·5m (6·5–8·6)	3·3m (2·8–3·8)	0·03m (0·03–0·04)	0·9m (0·7–1·2)	0·02m (0·02–0·02)	2·4m (1·8–3·1)	0·9m (0·7–1·1)	0·9m (0·8–1·2)	5·4m (4·6–6·4)	1·1m (0·9–1·2)	6·9m (5·9–7·9)	0·6m (0·5–0·7)
	Averted deaths before 2050	1·0m (0·9–1·1)	0·5m (0·4–0·6)	0·003m (0·003–0·004)	0·1m (0·1–0·1)	0·002m (0·002–0·002)	0·3m (0·2–0·4)	0·1m (0·0–0·1)	0·1m (0·1–0·1)	0·8m (0·6–0·9)	0·1m (0·1–0·2)	0·9m (0·8–1·1)	0·1m (0·1–0·1)
	Averted tx before 2050	3·0m (2·7–3·3)	1·0m (0·9–1·0)	0·02m (0·02–0·02)	0·5m (0·4–0·6)	0·01m (0·01–0·01)	1·1m (0·9–1·3)	0·4m (0·4–0·5)	0·4m (0·4–0·5)	2·1m (1·8–2·3)	0·5m (0·4–0·6)	2·7m (2·5–3·0)	0·3m (0·2–0·3)
Accelerated Scale-up Low coverage, 80% efficacy, 10 years protection	IRR in 2050 (%)	12·9% (11·7–15·1)	15·0% (13·9–19·5)	4·1% (3·8–4·7)	15·8% (13·0–20·2)	6·8% (5·6–8·9)	11·6% (9·9–14·2)	9·2% (7·8–11·3)	15·0% (13·8–16·8)	13·1% (11·5–16·0)	10·9% (9·7–13·0)	13·0% (11·6–15·4)	12·0% (11·1–13·5)
	MRR in 2050 (%)	14·3% (12·8–17·4)	15·7% (14·2–21·8)	5·2% (4·6–5·9)	17·3% (13·9–22·3)	6·9% (5·8–8·5)	12·1% (10·1–15·4)	13·5% (10·8–17·4)	15·7% (14·5–17·6)	14·3% (12·4–18·3)	13·0% (11·3–15·3)	14·5% (12·8–18·0)	12·6% (11·7–13·8)
	Averted cases before 2050	14·6m (12·6–16·8)	5·6m (4·8–6·4)	0·1m (0·1–0·1)	1·5m (1·1–2·0)	0·1m (0·1–0·1)	5·9m (4·6–7·7)	1·4m (1·1–1·7)	1·9m (1·5–2·3)	10·3m (8·6–12·2)	2·4m (2·1–2·8)	13·2m (11·3–15·3)	1·4m (1·2–1·7)
	Averted deaths before 2050	2·0m (1·8–2·3)	1·0m (0·8–1·1)	0·01m (0·01–0·01)	0·1m (0·1–0·2)	0·01m (0·01–0·01)	0·8m (0·6–1·0)	0·1m (0·1–0·2)	0·2m (0·2–0·3)	1·5m (1·2–1·8)	0·3m (0·2–0·4)	1·8m (1·6–2·1)	0·2m (0·2–0·2)
	Averted tx before 2050	6·9m (6·2–7·7)	2·0m (1·8–2·2)	0·04m (0·03–0·04)	0·8m (0·7–1·1)	0·04m (0·03–0·05)	3·2m (2·6–3·9)	0·8m (0·6–0·9)	1·0m (0·8–1·1)	4·6m (4·0–5·4)	1·3m (1·1–1·5)	6·2m (5·5–7·0)	0·7m (0·6–0·7)
Accelerated Scale-up High coverage, 80% efficacy, 10 years protection	IRR in 2050 (%)	15·7% (14·3–18·3)	18·3% (17·0–23·5)	5·1% (4·7–5·7)	19·3% (15·9–24·3)	8·3% (6·9–10·8)	14·1% (12·1–17·3)	11·3% (9·6–13·8)	18·3% (16·8–20·4)	15·9% (14·1–19·3)	13·3% (11·8–15·7)	15·8% (14·2–18·6)	14·7% (13·7–16·4)
	MRR in 2050 (%)	17·4% (15·7–21·1)	19·2% (17·5–26·3)	6·4% (5·8–7·3)	21·0% (17·1–27·0)	8·5% (7·3–10·5)	14·7% (12·4–18·6)	16·5% (13·3–21·1)	19·2% (17·8–21·4)	17·5% (15·3–22·1)	15·8% (13·8–18·6)	17·7% (15·7–21·7)	15·5% (14·4–16·8)
	Averted cases before 2050	18·0m (15·5–20·8)	6·9m (5·9–7·9)	0·1m (0·1–0·1)	1·9m (1·4–2·4)	0·1m (0·1–0·1)	7·3m (5·7–9·4)	1·7m (1·3–2·1)	2·3m (1·9–2·9)	12·7m (10·6–15·1)	3·0m (2·6–3·4)	16·2m (13·9–18·9)	1·8m (1·5–2·1)

	Averted deaths before 2050	2·5m (2·2–2·8)	1·2m (1·0–1·4)	0·01m (0·01–0·01)	0·2m (0·1–0·2)	0·01m (0·01–0·01)	1·0m (0·7–1·3)	0·1m (0·1–0·2)	0·3m (0·2–0·4)	1·8m (1·5–2·2)	0·4m (0·3–0·4)	2·2m (1·9–2·6)	0·2m (0·2–0·3)
	Averted tx before 2050	8·5m (7·6–9·5)	2·5m (2·2–2·7)	0·05m (0·04–0·05)	1·0m (0·8–1·3)	0·05m (0·04–0·06)	3·9m (3·2–4·8)	0·9m (0·8–1·1)	1·2m (1·0–1·4)	5·7m (4·9–6·6)	1·6m (1·4–1·8)	7·7m (6·9–8·6)	0·8m (0·7–0·9)
Lifelong protection													
Basecase Medium coverage, 80% efficacy, lifelong protection	IRR in 2050 (%)	17·4% (15·9–20·1)	21·6% (20·0–27·6)	6·1% (5·5–7·0)	23·4% (19·2–29·6)	5·8% (5·2–6·6)	13·7% (11·7–16·7)	15·1% (12·5–18·8)	19·4% (17·7–22·0)	17·9% (15·9–21·7)	14·3% (12·8–16·4)	17·9% (16·2–20·9)	13·6% (12·3–15·6)
	MRR in 2050 (%)	18·1% (16·2–21·7)	20·9% (18·8–28·2)	7·5% (6·5–8·6)	24·6% (19·7–32·0)	6·3% (5·5–7·3)	13·5% (11·1–17·5)	20·8% (16·1–27·7)	18·9% (17·1–21·3)	18·4% (15·9–23·0)	15·9% (13·9–18·9)	18·7% (16·7–22·7)	12·8% (11·6–14·4)
	Averted cases before 2050	11·8m (10·2–13·7)	5·2m (4·4–6·0)	0·1m (0·0–0·1)	1·4m (1·1–1·8)	0·03m (0·03–0·03)	3·8m (2·9–4·9)	1·4m (1·1–1·8)	1·5m (1·2–1·8)	8·6m (7·3–10·1)	1·8m (1·5–2·0)	10·9m (9·4–12·6)	0·9m (0·8–1·1)
	Averted deaths before 2050	1·5m (1·3–1·7)	0·8m (0·7–0·9)	0·01m (0·00–0·01)	0·1m (0·1–0·2)	0·003m (0·003–0·004)	0·5m (0·3–0·6)	0·1m (0·1–0·2)	0·2m (0·1–0·2)	1·1m (1·0–1·3)	0·2m (0·2–0·2)	1·4m (1·2–1·6)	0·1m (0·1–0·1)
	Averted tx before 2050	4·6m (4·2–5·0)	1·5m (1·3–1·6)	0·03m (0·03–0·03)	0·7m (0·6–0·9)	0·02m (0·01–0·02)	1·7m (1·4–2·0)	0·7m (0·6–0·8)	0·7m (0·6–0·8)	3·2m (2·8–3·6)	0·8m (0·7–0·9)	4·2m (3·8–4·6)	0·4m (0·3–0·4)
Accelerated Scale-up Medium coverage, 80% efficacy, lifelong protection	IRR in 2050 (%)	31·8% (29·4–35·5)	36·2% (34·2–43·4)	11·8% (10·9–13·0)	37·1% (31·7–45·4)	17·2% (14·7–21·4)	29·6% (26·1–34·7)	23·7% (20·4–28·1)	36·1% (33·8–39·3)	32·1% (28·9–37·0)	28·4% (25·2–33·1)	32·1% (29·5–36·2)	29·5% (27·9–32·0)
	MRR in 2050 (%)	33·0% (30·2–38·3)	35·5% (33·0–45·5)	13·4% (12·2–14·9)	38·4% (32·2–47·3)	16·7% (14·6–19·9)	29·2% (25·3–35·1)	30·5% (25·3–37·4)	35·8% (33·5–38·8)	32·9% (29·4–39·8)	31·3% (27·8–36·2)	33·5% (30·3–39·3)	29·4% (27·7–31·4)
	Averted cases before 2050	32·2m (27·5–37·5)	12·0m (10·4–14·1)	0·1m (0·1–0·2)	3·2m (2·4–4·2)	0·1m (0·1–0·2)	13·5m (10·6–17·0)	3·1m (2·5–3·9)	4·1m (3·3–5·1)	22·6m (18·8–27·2)	5·5m (4·8–6·3)	29·1m (24·6–34·0)	3·2m (2·6–3·7)
	Averted deaths before 2050	4·2m (3·7–4·8)	2·0m (1·7–2·2)	0·01m (0·01–0·02)	0·3m (0·2–0·4)	0·01m (0·01–0·02)	1·7m (1·3–2·2)	0·2m (0·2–0·3)	0·5m (0·4–0·6)	3·1m (2·6–3·6)	0·6m (0·5–0·7)	3·8m (3·3–4·3)	0·4m (0·4–0·5)
	Averted tx before 2050	15·3m (13·7–17·1)	4·4m (4·0–4·7)	0·1m (0·1–0·1)	1·8m (1·4–2·2)	0·1m (0·1–0·1)	7·2m (6·0–8·7)	1·7m (1·4–2·0)	2·1m (1·8–2·4)	10·2m (8·9–11·9)	2·9m (2·5–3·4)	13·8m (12·3–15·5)	1·5m (1·3–1·6)

Abbreviations: AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, HBC = high burden countries, IRR = incidence rate reduction, LIC = low-income countries, LMIC = lower-middle income countries, MRR = mortality rate reduction, SEAR = WHO South-East Asian Region, tx = treatments, UMIC = upper-middle income countries, WPR = WHO Western Pacific Region

10.2 Comparing to the 2035 End TB incidence target

We calculated the incidence rate in 2035 for each *No-New-Vaccine* baseline and for each vaccine scenario to compare with the 2035 End TB incidence target of a 90% reduction in the tuberculosis incidence rate compared to the 2015 incidence rate. Results for all modelled countries, and for each of the select model groupings for outcome reporting are provided in Table S10.3, as the median estimate of the incidence rate per 100,000 population and 95% uncertainty range, with all vaccine scenarios assuming medium coverage and 10-years protection.

For all modelled countries, the estimated incidence rate in 2015 was approximately 164·2 per 100,000 population. A 90% reduction is equivalent to an incidence rate of 16·4 per 100,000 population. With the *Status Quo No-New-Vaccine* baseline, the closest vaccine scenario to reaching this target reduction is the *Accelerated Scale-up* scenario of an adolescent/adult vaccine with vaccine efficacy increased to 75%, which has an estimated incidence rate of 88·0 (70·8–104·6) per 100,000 population or meeting approximately 52% of the goal. With the *2025 End TB No-New-Vaccine* baseline, progress is increased, with the standard *Basecase* scenario of the adolescent/adult vaccine achieving an incidence rate of 45·3 (39·5–53·8) per 100,000 population, or 80% of the target, and the standard *Accelerated Scale-up* scenario achieving an incidence rate of 43·4 (37·7–51·6) per 100,000 population, or 82% of the target.

Table S10.3 Estimated incidence rate (per 100,000 population) for each vaccine scenario in 2035 to compare to meeting the 2035 End TB target.

	All modelled countries	WHO Region						World Bank Income Group			TB Burden Level	
Scenario		AFR	AMR	EMR	EUR	SEAR	WPR	LIC	LMIC	UMIC	HBC	All other countries
Status Quo No-New-Vaccine baseline	138·8 (114·2–163·6)	196·7 (154·9–240·4)	26·2 (22·3–29·9)	94·8 (76·2–117·4)	31·4 (26·8–36·4)	213·2 (179·1–245·1)	85·2 (70·6–101·5)	126·0 (102·7–151·9)	196·4 (157·4–235·1)	75·4 (66·9–83·7)	169·9 (139·7–200·0)	55·9 (46·0–65·9)
Adolescent/adult vaccine: *Basecase*, 50% efficacy	120·7 (98·9–142·4)	168·4 (131·6–206·8)	22·7 (19·2–26·0)	78·7 (63·1–97·9)	27·9 (23·8–32·5)	189·4 (159·1–217·8)	72·5 (59·7–86·9)	110·7 (89·9–133·5)	170·1 (135·8–204·2)	65·9 (58·4–73·3)	146·9 (120·3–173·1)	50·7 (41·6–60·1)
Adolescent/adult vaccine: *Accelerated Scale-up*, 50% efficacy	103·8 (84·1–123·0)	145·4 (110·5–179·2)	21·2 (18·0–24·4)	69·3 (54·9–86·6)	25·0 (21·3–29·2)	157·2 (130·8–180·4)	67·2 (54·8–80·4)	91·9 (74·0–111·5)	146·4 (115·7–176·2)	57·1 (49·9–64·0)	126·8 (102·7–150·2)	42·2 (34·6–50·6)
Adolescent/adult vaccine: *Routine Only*, 50% efficacy	137·3 (112·8–161·9)	193·5 (151·7–236·6)	26·1 (22·2–29·8)	93·2 (74·8–115·4)	31·3 (26·7–36·3)	212·1 (178·2–243·8)	84·1 (69·6–100·4)	124·6 (101·2–150)	194·2 (155·4–232·5)	74·9 (66·4–83·1)	168·1 (138·0–197·9)	55·5 (45·7–65·5)
Adolescent/adult vaccine: *Basecase*, 75% efficacy	111·5 (91·2–131·6)	154·0 (119·8–189·4)	20·9 (17·7–24·1)	70·7 (56·5–88·2)	26·2 (22·3–30·6)	177·4 (148·8–203·8)	66·1 (54·2–79·4)	102·9 (83·5–124·4)	156·8 (125·0–188·6)	61·0 (54·0–67·8)	135·2 (110·6–159·4)	48·1 (39·4–57·2)

Adolescent/adult vaccine: *Accelerated Scale-up*, 75% efficacy	88·0 (70·8–104·6)	121·9 (91·1–150·6)	18·8 (15·9–21·7)	58·4 (45·7–72·9)	22·1 (18·7–25·8)	132·3 (110·2–153·0)	58·4 (47·4–70·0)	76·8 (61·3–93·6)	124·2 (97·2–149·7)	48·7 (42·2–55·0)	107·5 (86·4–127·7)	36·1 (29·5–43·4)
Infant vaccine: *Basecase*, 80% efficacy	138·0 (113·5–162·7)	194·8 (153·1–237·9)	26·1 (22·2–29·9)	93·8 (75·3–116·2)	31·3 (26·8–36·4)	212·8 (178·7–244·6)	84·6 (70·1–100·9)	125·2 (101·9–150·9)	195·1 (156·3–233·7)	75·1 (66·7–83·3)	168·9 (138·8–198·8)	55·6 (45·8–65·7)
Infant vaccine: *Accelerated Scale-up*, 80% efficacy	133·1 (109·1–157·0)	186·5 (145·6–228·0)	25·8 (22·0–29·6)	89·0 (71·5–110·5)	30·8 (26·3–35·8)	205·8 (172·8–236·1)	82·8 (68·6–98·9)	119·2 (96·8–143·5)	187·9 (150·2–225·4)	73·1 (64·8–81·1)	163·0 (133·4–192·0)	53·7 (44·2–63·7)
2025 End TB No-New-Vaccine baseline	51·5 (44·9–61·2)	70·2 (58·8–85·5)	12·3 (11·1–13·4)	36·4 (28·3–58·2)	17·4 (14·7–21·2)	73·0 (56·7–100·1)	37·1 (30·2–49·2)	44·6 (38·0–53·8)	68·3 (55·5–88·0)	33·4 (30·4–38·3)	62·0 (53·2–75·2)	23·3 (20·7–26·2)
Adolescent/adult vaccine: *Basecase*, 50% efficacy	45·3 (39·5–53·8)	61·3 (51·3–74·0)	10·8 (9·8–11·8)	31·1 (24·2–49·0)	15·5 (13·1–18·8)	65·1 (50·8–88·7)	32·4 (26·5–42·6)	39·8 (34·1–47·3)	60·1 (48·9–77·6)	29·3 (26·7–33·4)	54·2 (46·5–66·0)	21·4 (19·0–24·1)
Adolescent/adult vaccine: *Accelerated Scale-up*, 50% efficacy	43·4 (37·7–51·6)	58·5 (48·5–70·9)	10·6 (9·6–11·6)	30·5 (23·7–45·7)	15·0 (12·6–18·3)	61·7 (47·9–83·2)	31·8 (26·0–41·4)	37·5 (32·0–44·4)	57·5 (46·9–73·7)	28·2 (25·8–32·0)	52·2 (44·7–63·3)	19·9 (17·7–22·2)

Abbreviations: AFR = WHO African Region, AMR = WHO Region of the Americas, EMR = WHO Eastern Mediterranean Region, EUR = WHO European Region, HBC = high burden countries, IRR = incidence rate reduction, LIC = low-income countries, LMIC = lower-middle income countries, MRR = mortality rate reduction, SEAR = WHO South-East Asian Region, UMIC = upper-middle income countries, WPR = WHO Western Pacific Region

References

1 Frascella B, Richards AS, Sossen B, *et al.* Subclinical tuberculosis disease - a review and analysis of prevalence surveys to inform definitions, burden, associations and screening methodology. *Clin Infect Dis* 2020; : ciaa1402.

2 Emery JC, Richards AS, Dale KD, *et al.* Self-clearance of Mycobacterium tuberculosis infection: implications for lifetime risk and population at-risk of tuberculosis disease. *Proc R Soc B Biol Sci* 2021; **288**: 20201635.

3 World Health Organization. Guidelines for treatment of drug-susceptible tuberculosis and patient care: 2017 update. 2017.

4 World Health Organization. Treatment of drug-susceptible tuberculosis: rapid communication. Geneva: World Health Organization, 2021 https://apps.who.int/iris/handle/10665/341729 (accessed Jan 7, 2022).

5 Sutherland I, Svandová E, Radhakrishna S. The development of clinical tuberculosis following infection with tubercle bacilli. 1. A theoretical model for the development of clinical tuberculosis following infection, linking from data on the risk of tuberculous infection and the incidence of clinical tuberculosis in the Netherlands. *Tubercle* 1982; **63**: 255–68.

6 Vynnycky E, Fine PE. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. *Epidemiol Infect* 1997; **119**: 183–201.

7 World Health Organization. Global tuberculosis report 2021. Geneva: World Health Organization, 2021 https://apps.who.int/iris/handle/10665/346387 (accessed Jan 7, 2022).

8 Lee JY. Diagnosis and Treatment of Extrapulmonary Tuberculosis. *Tuberc Respir Dis* 2015; **78**: 47–55.

9 Prem K, Zandvoort K van, Klepac P, *et al.* Projecting contact matrices in 177 geographical regions: An update and comparison with empirical data for the COVID-19 era. *PLOS Comput Biol* 2021; **17**: e1009098.

10 Kwan CK, Ernst JD. HIV and Tuberculosis: a Deadly Human Syndemic. *Clin Microbiol Rev* 2011; **24**: 351–76.

11 Suthar AB, Lawn SD, del Amo J, *et al.* Antiretroviral Therapy for Prevention of Tuberculosis in Adults with HIV: A Systematic Review and Meta-Analysis. *PLoS Med* 2012; **9**: e1001270.

12 Harling G, Ehrlich R, Myer L. The social epidemiology of tuberculosis in South Africa: A multilevel analysis. *Soc Sci Med* 2008; **66**: 492–505.

13 Hoa NB, Tiemersma EW, Sy DN, *et al.* Household expenditure and tuberculosis prevalence in Viet Nam: prediction by a set of household indicators. ; : 7.

14 Hossain S, Quaiyum MA, Zaman K, *et al.* Socio Economic Position in TB Prevalence and Access to Services: Results from a Population Prevalence Survey and a Facility-Based Survey in Bangladesh. *PLOS ONE* 2012; **7**: e44980.

15 Kapata N, Chanda-Kapata P, Ngosa W, *et al.* The Prevalence of Tuberculosis in Zambia: Results from the First National TB Prevalence Survey, 2013–2014. *PLOS ONE* 2016; **11**: e0146392.

16 Migambi P, Gasana M, Uwizeye CB, *et al.* Prevalence of tuberculosis in Rwanda: Results of the first nationwide survey in 2012 yielded important lessons for TB control. *PLOS ONE* 2020; **15**: e0231372.

17 Oxlade O, Murray M. Tuberculosis and Poverty: Why Are the Poor at Greater Risk in India? *PLOS ONE* 2012; **7**: e47533.

18 Singh SK, Kashyap GC, Puri P. Potential effect of household environment on prevalence of tuberculosis in India: evidence from the recent round of a cross-sectional survey. *BMC Pulm Med* 2018; **18**: 66.

19 Siroka A, Law I, Macinko J, *et al.* The effect of household poverty on tuberculosis. *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis* 2016; **20**: 1603–8.

20 van Leth F, Guilatco RS, Hossain S, *et al.* Measuring socio-economic data in tuberculosis prevalence surveys. *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis* 2011; **15 Suppl 2**: 58–63.

21 Yates TA, Ayles H, Leacy FP, *et al.* Socio-economic gradients in prevalent tuberculosis in Zambia and the Western Cape of South Africa. *Trop Med Int Health* 2018; **23**: 375–90.

22 United Nations Department of Economic and Social Affairs. UN Population Projections, 2019 Revision. https://population.un.org/wpp/Download/Standard/Population/.

23 Tiemersma EW, Werf MJ van der, Borgdorff MW, Williams BG, Nagelkerke NJD. Natural History of Tuberculosis: Duration and Fatality of Untreated Pulmonary Tuberculosis in HIV Negative Patients: A Systematic Review. *PLOS ONE* 2011; **6**: e17601.

24 Quaife M, Houben RMGJ, Allwood B, *et al.* Post-tuberculosis mortality and morbidity: valuing the hidden epidemic. *Lancet Respir Med* 2020; **8**: 332–3.

25 World Health Organization. WHO TB Burden Estimates. 2021; published online Dec 17. https://www.who.int/tb/country/data/download/en/.

26 World Health Organization. WHO Case Notifications. 2020. https://www.who.int/tb/country/data/download/en/.

27 Emery J. Subclinical TB disease: lessons and questions from field to lab. 2020.

28 Abu-Raddad L, Sabatelli L, Achterberg JT, *et al.* Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. *Proc Natl Acad Sci U S A* 2009; **106**: 13980–5.

29 Dye C, Williams BG. Eliminating human tuberculosis in the twenty-first century. *J R Soc Interface* 2008; **5**: 653–62.

30 Marx FM, Dunbar R, Enarson DA, *et al.* The Temporal Dynamics of Relapse and Reinfection Tuberculosis After Successful Treatment: A Retrospective Cohort Study. *Clin Infect Dis* 2014; **58**: 1676–83.

31 Gomes MGM, Franco AO, Gomes MC, Medley GF. The reinfection threshold promotes variability in tuberculosis epidemiology and vaccine efficacy. *Proc R Soc B Biol Sci* 2004; **271**: 617–23.

32 Dangisso MH, Woldesemayat EM, Datiko DG, Lindtjørn B. Long-term outcome of smear-positive tuberculosis patients after initiation and completion of treatment: A ten-year retrospective cohort study. *PloS One* 2018; **13**: e0193396.

33 World Health Organization. WHO Treatment Outcomes. 2020. https://www.who.int/tb/country/data/download/en/.

34 Gabriela M. Gomes M, Rodrigues P, Hilker FM, *et al.* Implications of partial immunity on the prospects for tuberculosis control by post-exposure interventions. *J Theor Biol* 2007; **248**: 608–17.

35 Mberi MN, Kuonza LR, Dube NM, Nattey C, Manda S, Summers R. Determinants of loss to follow-up in patients on antiretroviral treatment, South Africa, 2004–2012: a cohort study. *BMC Health Serv Res* 2015; **15**: 259.

36 Cutsem GV, Ford N, Hildebrand K, *et al.* Correcting for Mortality Among Patients Lost to Follow Up on Antiretroviral Therapy in South Africa: A Cohort Analysis. *PLOS ONE* 2011; **6**: e14684.

37 Johansson KA, Robberstad B, Norheim OF. Further benefits by early start of HIV treatment in low income countries: Survival estimates of early versus deferred antiretroviral therapy. *AIDS Res Ther* 2010; **7**: 3.

38 Fatti G, Mothibi E, Meintjes G, Grimwood A. Antiretroviral treatment outcomes amongst older adults in a large multicentre cohort in South Africa. *PloS One* 2014; **9**: e100273.

39 Vazquez F. A systematic review and meta-analysis of the effect of HIV status on the incidence of tuberculosis disease among individuals with latent Mycobacterium tuberculosis infection. 2019.

40 Ackah AN, Coulibaly D, Digbeu H, *et al.* Response to treatment, mortality, and CD4 lymphocyte counts in HIV-infected persons with tuberculosis in Abidjan, Côte d'Ivoire. *Lancet Lond Engl* 1995; **345**: 607–10.

41 Mukadi YD, Maher D, Harries A. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. *AIDS* 2001; **15**: 143–52.

42 Rajagopalan S. Tuberculosis and aging: a global health problem. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2001; **33**: 1034–9.

43 Andrianakis I, Vernon I, McCreesh N, *et al.* History matching of a complex epidemiological model of human immunodeficiency virus transmission by using variance emulation. *J R Stat Soc Ser C Appl Stat* 2017; **66**: 717–40.

44 Andrianakis I, Vernon IR, McCreesh N, *et al.* Bayesian History Matching of Complex Infectious Disease Models Using Emulation: A Tutorial and a Case Study on HIV in Uganda. *PLOS Comput Biol* 2015; **11**: e1003968.

45 Goldstein M. Bayes Linear Analysis for Complex Physical Systems Modeled by Computer Simulators. In: Dienstfrey AM, Boisvert RF, eds. Uncertainty Quantification in Scientific Computing. Berlin, Heidelberg: Springer Berlin Heidelberg, 2012: 78–94.

46 Williamson D, Goldstein M, Allison L, *et al.* History matching for exploring and reducing climate model parameter space using observations and a large perturbed physics ensemble. *Clim Dyn* 2013; **41**: 1703–29.

47 Iskauskas A. hmer: History Matching and Emulation Package. 2022 https://CRAN.R-project.org/package=hmer (accessed April 14, 2022).

48 Jabot F, Faure T, Dumoulin N, Albert C. EasyABC: Efficient Approximate Bayesian Computation Sampling Schemes. 2015 https://CRAN.R-project.org/package=EasyABC (accessed April 12, 2022).

49 Roberts GO, Rosenthal JS. Examples of Adaptive MCMC. *J Comput Graph Stat* 2009; **18**: 349–67.

50 New country classifications by income level: 2019-2020. https://blogs.worldbank.org/opendata/new-country-classifications-income-level-2019-2020 (accessed Sept 26, 2021).

51 World Health Organization. WHO | WHO End TB Strategy. 2015.

52 World Health Organization. WHO Preferred Product Characteristics for New Tuberculosis Vaccines. 2018 DOI:CC BY-NC-SA 3.0 IGO.

53 Country hub. https://www.gavi.org/programmes-impact/country-hub (accessed April 15, 2022).

54 Vaccination and Immunization Statistics. UNICEF DATA. https://data.unicef.org/topic/child-health/immunization/ (accessed March 7, 2022).

55 Harris RC, Sumner T, Knight GM, Zhang H, White RG. Potential impact of tuberculosis vaccines in China, South Africa, and India. *Sci Transl Med* 2020; **12**: eaax4607.

56 Tait DR, Hatherill M, Van Der Meeren O, *et al.* Final Analysis of a Trial of M72/AS01E Vaccine to Prevent Tuberculosis. *N Engl J Med* 2019; **381**: 2429–39.

57 Abubakar I, Pimpin L, Ariti C, *et al.* Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette–Guérin vaccination against tuberculosis. *Health Technol Assess* 2013; **17**. DOI:10.3310/hta17370.

58 Lewnard JA, Grad YH. Vaccine waning and mumps re-emergence in the United States. *Sci Transl Med* 2018; **10**: eaao5945.

59 Blackwood JC, Cummings DAT, Broutin H, Iamsirithaworn S, Rohani P. Deciphering the impacts of vaccination and immunity on pertussis epidemiology in Thailand. *Proc Natl Acad Sci U S A* 2013; **110**: 9595–600.

World Health Organization

Session 7

MR-MAP initial Full Value of Vaccine Assessment (MR-MAP iFVVA)

August 2022

Initial Full Vaccine Value Assessment of MR-MAPs – towards an *initial* public investment case

Intro to IVIR-AC

unicef | for every child

© UNICEF/UNI197921/Schermbrucker

Background

Vaccine MAPs, UNICEF and VIPS

Vaccine containing Microarray patches (MAPs)

Groundbreaking disruptive technology that may contribute to increase immunization coverage:

- Potential for **increased acceptability** by caregivers/vaccinees.
- Increased **ease-of-use** (potential for alternative delivery scenarios and broader coverage).
- Potential for enhanced **thermostabilit**y, which could enable controlled temperature chain use.
- Improved **safety** profile for administration (no reconstitution, sharps-free)
- Fewer components, **simplifying preparation** and supply chain **logistics**.

MAPs are prioritized by

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Gavi · World Health Organization · unicef · Bill & Melinda Gates foundation · PATH

UNICEF Product Innovation Project (PIP) - Goal:

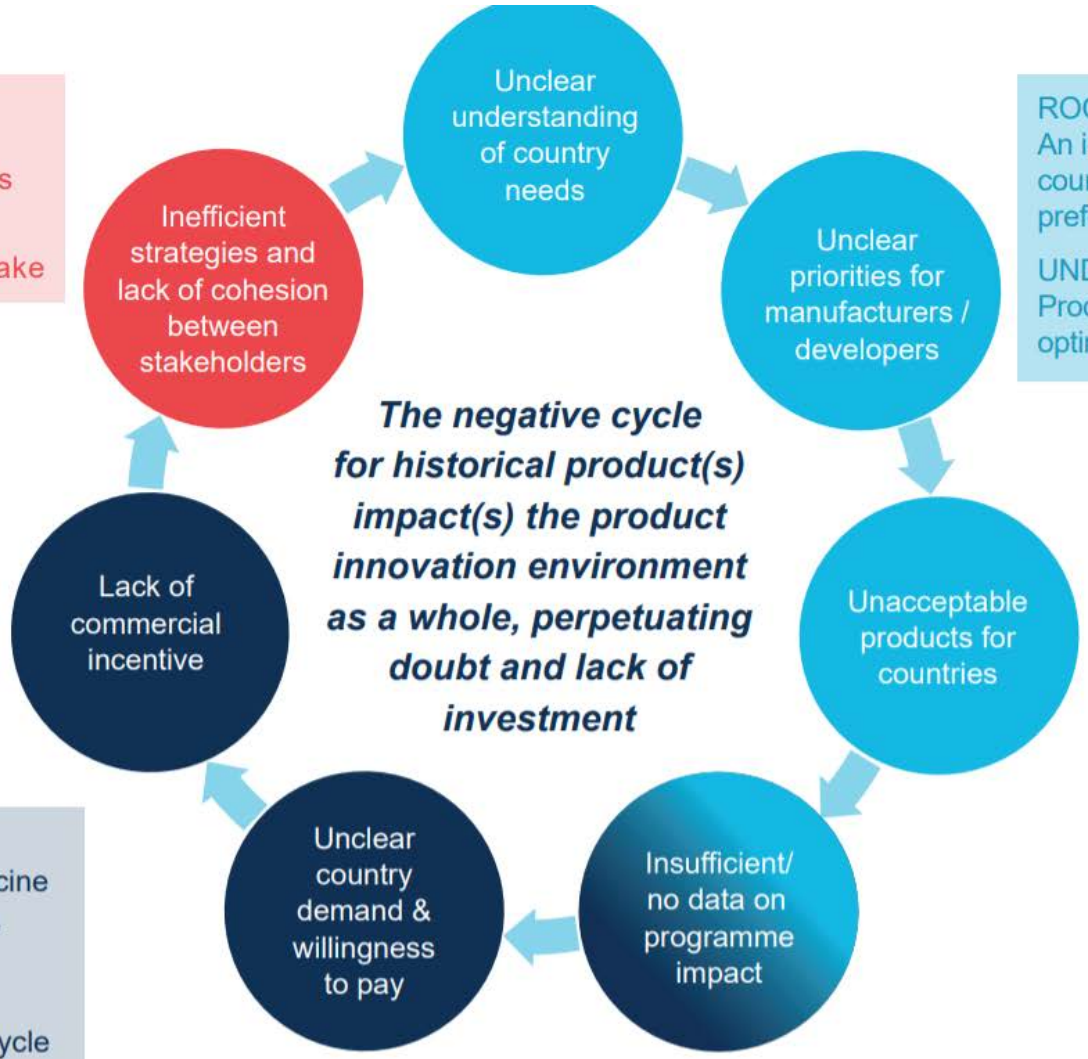
1. **Accelerate** the **introduction** of vaccine microarray patches (VMAPs);
2. **Increase** vaccination **coverage** at the national, sub-national/regional levels to meet or exceed global goals (increase equity and reach zero-dose children)

MR-MAP TPP, developed by MR-MAP-WG

How

- Assess the **cost and benefits** compared to current vaccine presentations using existing frameworks
- Focus on key markets (e.g. Measles & Rubella vaccine market) where this technology is most advanced and **determine** any **potential of investments** for **implementation research** and/or **procurement**
- **Collaborate** with partners (VIPS - Gavi, WHO, BMGF, PATH) for advocacy and provide market, supply and program related input in technical committees (MR-MAP WG, DT WG)

The investment conundrum



ROOT CAUSE:
Lack of alignment across different types of stakeholders

UNDESIRABLE OUTCOME:
Stagnant development or uptake

ROOT CAUSE:
An insufficient understanding of country needs, priorities and preferences

UNDESIRABLE OUTCOME:
Products not developed or not optimal for LMICs

ROOT CAUSE:
Lack of clear articulation of vaccine innovations' value for countries, funders and manufacturers

UNDESIRABLE OUTCOME:
A broken demand-investment cycle

VIPS VACCINE INNOVATIO PRIORITISATIO STRATEGY

VIPS & MAPs

VIPS Alliance **Action Plan for MAPs**

- Identified activities and defined target outcomes (TOs) for the VIPS Alliance and other organizations to undertake (2021-2025) to accelerate development and future uptake of vaccine MAP products for LMIC use

Target outcomes:

- TO 1: Provide guidance to industry, funders and countries by clarifying the needs and demand for, and the value of, vaccine MAPs.
- TO 2: Create an enabling environment for vaccine MAPs by understanding the need for market incentives, and addressing the challenges linked to the business case for vaccine MAPs for LMICs.
- TO 3: Expand the evidence base to demonstrate the potential of MAPs as a platform technology for delivering vaccines, including for pandemic preparedness and response.
- TO 4: Advance at least one LMIC vaccine MAP product to phase 3 clinical trials.
- TO 5: Cross-cutting (shared with Action Plans for other VIPS priority innovations): secure resources and set-up engagement and coordination mechanisms with key stakeholders and establish a continuous learning environment.

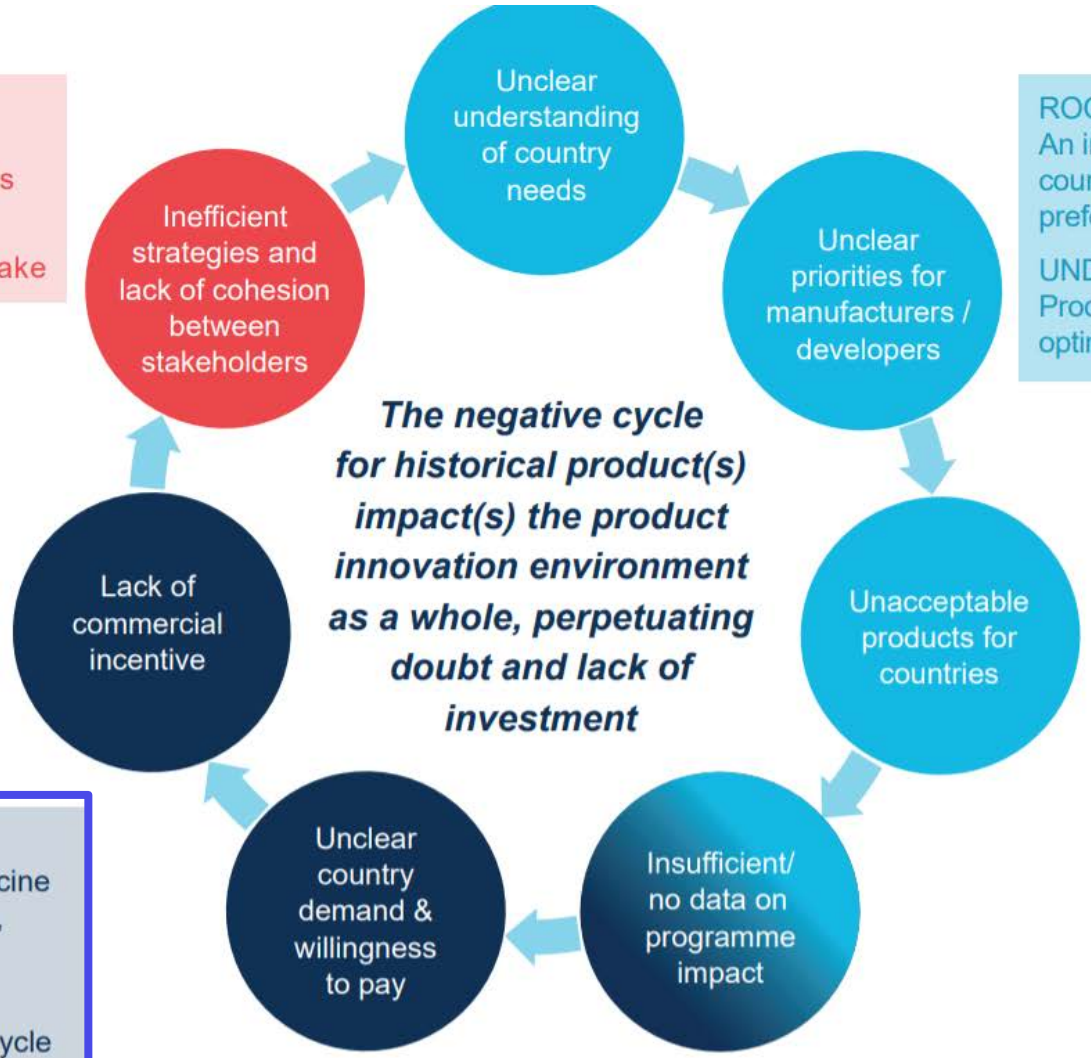
Full Value of Vaccines Assessment (FVVA) for MAPs

- Activity under TO1: **Develop and communicate FVVAs for MAPs for at least two vaccines relevant to LMICs**
  - To provide guidance on the vaccines that global health funders, countries and procurement agencies consider of value for use with MAPs, so that appropriate products for LMICs are developed.
  - Components of WHO's format of FVVAs include analyses of potential use-cases and preferred product attributes, demand forecasting and economic modelling.

FVVA & The investment conundrum for MR-MAPs

ROOT CAUSE:
Lack of alignment across different types of stakeholders

UNDESIRABLE OUTCOME:
Stagnant development or uptake



ROOT CAUSE:
An insufficient understanding of country needs, priorities and preferences

UNDESIRABLE OUTCOME:
Products not developed or not optimal for LMICs

Full Value of Vaccine Assessment (FVVA)
– focus: public perspective (countries & funders)

ROOT CAUSE:
Lack of clear articulation of vaccine innovations' value for countries, funders and manufacturers

UNDESIRABLE OUTCOME:
A broken demand-investment cycle

Business case
– focus: commercial perspective (manufacturers)

VIPS VACCINE INNOVATIO PRIORITISATIO STRATEGY

initial Full Value of Vaccine Assessment for MR-MAPs

Development of cost benefit analysis from public health perspective (donor/procurement) to prepare for potential future procurement and identify any investment opportunities for implementation research and/or procurement.

© UNICEF/UNI111450/Asselin

Overview of topics covered*

- Chapter 1: Executive summary
- Chapter 2: Methodology
- Chapter 3 and 4: Public health need
- Chapter 5: Stakeholder analysis
- Chapter 6: Key issues for development
- Chapter 7: Assessment of development pipeline
- Chapter 8: Potential MR-MAP markets
- Chapter 9: Disease burden for Measles and Rubella
- Chapter 10: Impact of MR-MAPs on disease burden
- Chapter 11: Economic analysis of MR-MAPs
- Chapter 12: Financing the development of MR-MAPs
- Chapter 13: Conclusions

* Final iFVVA has a different order/ structure of presented content

Overview of the iFVVA approach

Three organizations are partnered* to support the development of the MR-MAP iFVVA

- Implementation and market expertise; experience with MR-MAPs and Use Cases
- Project lead, responsible for project management and all deliverables

- Disease burden modelling expertise
- Responsible for articulating measles burden, estimating measles burden and health and economic impact of MR-MAPs

- Advocacy and comms expertise
- Responsible for professional layout and ensuring compelling language, final slide deck to stakeholders and fact sheet to donors

* MMGH has been contracted by UNICEF for the project

MR-MAPs *initial* Full Vaccine Value assessment – an *initial* public investment case | Scope and key outputs

PUBLIC HEALTH NEED AND RISK

- Articulate public health needs, how MR-MAPs can address those needs, and potential risks to implementation
- Map key stakeholders

IMPACT & COST

- Describe MR burden
- Estimate MR-MAP impact on Measles burden and economic benefits, high level estimates of Rubella burden
- Strategize on barriers for immunization as identified by VIPS

INCEPTION

- Define methodology, including identification of key areas with knowledge gaps and solutions to address knowledge gaps
- Establish external advisory group

MARKET

- Develop demand forecast and assess how MR-MAPs will be used
- Understand the MR-MAP or vaccine-MAP pipeline
- Describe potential business models to commercialize MR-MAPs

FINALIZE

- Finalize a compelling ***initial*** Full Vaccine Value Assessment with stakeholder feedback
- Develop slide deck and fact sheet

- Each phase is used to also define key (implementation) research / knowledge gaps re: MR-MAPs & immunization barriers
- Touchpoints with existing cross-organizational groups, such as MR-MAP WG, M&RI Management Team and VIPS has been used.

unicef

for every child

Thank You

© UNICEF/SUDA2014-XX228/Noorani

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

Classified as Internal

Title: Estimating the future global dose demand for Measles-Rubella microarray patches

Authors (in order):

Name	Email	Affiliation	Highest degree
Melissa Ko	kom@mmglobalhealth.org	MMGH Consulting GmbH, Geneva, Switzerland	MsPH
Stefano Malvoti	malvoltis@mmglobalhealth.org	MMGH Consulting GmbH, Zurich, Switzerland	MPH, MSE
Thomas Cherian	cheriant@mmglobalhealth.org	MMGH Consulting GmbH, Geneva, Switzerland	MD
Carsten Mantel	mantelc@mmglobalhealth.org	MMGH Consulting GmbH, Zurich, Switzerland	MD, MPH
Robin Biellik	rbiellik@gmail.com	Independent Consultant, La Rippe, Switzerland	DrPH
Courtney Jarrahian	cjarrahian@path.org	PATH Seattle, USA	MS
Marion Menozzi-Arnaud	mmenozziarnaud@gavi.org	Gavi, The Vaccine Alliance, Geneva, Switzerland	MD
Jean-Pierre Amorij	jamorij@unicef.org	UNICEF, Copenhagen, Denmark	PhD
Hans Christiansen	hchristiansen@unicef.org	UNICEF, Copenhagen, Denmark	PhD
Mark Papania	myp7@cdc.gov	Centers for Disease Control and Prevention, Atlanta, USA	PhD
Martin I. Meltzer	qzm4@cdc.gov	Centers for Disease Control and Prevention, Atlanta, USA	PhD
Balcha Girma Masresha	masreshab@who.int	Vaccine Preventable Diseases AFRO/WHO	PhD

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

Desiree Pastor	dpastor@paho.org	Immunization Unit/FPL PAHO/WHO Washington DC, USA	MD, MPH
David N. Durrheim	David.Durrheim@health.nsw.gov.au	Medicine and Public Health, University of Newcastle, Callaghan, NSW, Australia	MD
Birgitte Giersing	giersingb@who.int	Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland	PhD
Mateusz Hasso-Agopsowicz	hassoagopsowiczm@who.int	Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland	PhD

Corresponding Author

Mateusz Hasso-Agopsowicz, hassoagopsowiczm@who.int

Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland

Alternate Author

Melissa Ko, kom@mmglobalhealth.org

MMGH Consulting GmbH, Geneva, Switzerland

Contribution of the authors:

MK, SM, TC, CM, BG and MHA were responsible for the design and implementation of the research. MK and SM analysed the results. MK and MHA wrote the article, and all authors reviewed the article. MHA, BG, and MK supervised the work. MHA and BG secured funding for the research.

Conflict of interest: all authors declare no conflict of interest

Keywords: Measles, Rubella, microarray patch, microneedle, demand forecast, programmatic doses required

Key points: the delivery of measles and rubella vaccines with microarray patches (MR-MAPs) could disrupt the immunization landscape. We estimated the demand for MR-MAPs

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

between 2030-2040 at 4.05 billion doses. This analysis will inform the size of investment required to manufacture MR-MAPs.

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

Abstract

Background: Progress towards measles and rubella (MR) elimination has stagnated as countries are unable to reach the required 95% vaccine coverage. Microarray patches (MAPs) are anticipated to offer significant programmatic advantages to needle and syringe (N/S) presentation and increase MR vaccination coverage. A demand forecast analysis of the programmatic doses required (PDR) could accelerate MR-MAP development by informing the size and return of the investment required to manufacture MAPs.

Methods: Unconstrained global MR-MAP demand for 2030-2040 was estimated for three scenarios, for groups of countries with similar characteristics (archetypes), and four types of uses of MR-MAPs (use cases). The base scenario 1 assumed that MR-MAPs would replace a share of MR doses delivered by N/S, and that MAPs can reach a proportion of previously unimmunised populations. Scenario 2 assumed that MR-MAPs would be piloted in selected countries in each region of the World Health Organization (WHO); and scenario 3 explored introduction of MR-MAPs earlier in countries with the lowest measles vaccine coverage and highest MR disease burden.

Results: For the base scenario (1), the estimated global PDR for MR-MAPs was forecasted at 30 million doses in 2030 and increased to 220 million doses by 2040. Compared to scenario 1, scenario 2 resulted in an overall decrease in PDR of 18%, and scenario 3 resulted in a 21% increase in PDR between 2030-2040.

Conclusions: Significant demand is expected for MR-MAPs between 2030-2040, however, efforts are required to address remaining data quality, uncertainties and gaps that underpin the assumptions in this analysis.

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
Classified as Internal
All rights reserved. No reuse allowed without permission.

Introduction

Prior to widespread vaccination, major epidemics of measles occurred every two to three years and measles caused an estimated 2.6 million deaths globally each year, while four babies for every 1,000 live births worldwide were born with congenital rubella syndrome (CRS).[1, 2] Measles and rubella remain a major cause of worldwide morbidity and mortality with an estimated 7.5 million measles cases and more than 60,700 measles-related deaths in 2020, and around 100,000 infants born with CRS each year.[1, 3] To eliminate transmission and prevent outbreaks of measles and rubella at least 90-95% of all children must receive both measles and rubella first (MCV1) and second vaccine doses (MCV2)[4].

While the global coverage of MCV1 increased from 72% to 84% between 2000 and 2020, it has stagnated at around 83-85% for the past 10 years.[5] MCV2 coverage has been steadily increasing as countries introduce the second dose into their routine schedules but has now also plateaued at around 70%.[5] Furthermore, countries and regions are struggling not only to achieve but sustain their measles elimination status through high and widespread levels of vaccination. [6] The impact of the SARS-CoV-2 pandemic and its disruptions to routine immunization services and supplemental immunization activities (SIA) have highlighted the precarious situation with regards to measles control and elimination, with the reduction in global MCV1 coverage likely to 'fuel a resurgence of measles'.[5, 7, 8]

Efforts to increase coverage and reduce measles and rubella burden could be assisted by the application of innovative technologies such as microarray patches (MAPs) to help reach those communities that are currently under-immunized or completely missed by vaccination (un-immunized). A microarray patch (MAP) consists of hundreds to thousands of tiny projections that deliver vaccine just below the skin surface. Measles-Rubella MAPs (MR-MAPs) are anticipated to be easier to administer than needle-and-syringe (N/S) and be less burdensome on vaccinators and the immunization system, given that they would not require reconstitution, they come as a single dose presentation, have the potential for increased thermostability, and reduced weight. Further the needleless presentation could address some vaccine hesitancy due to an increasing number of painful injections administered during an immunization session. MAP characteristics required for maximum impact in low- and middle-income countries (LMICs) have been described in the MR-MAP Target Product Profile.[9] Given these product characteristics, MR-MAPs are anticipated to be delivered by less trained personal and together with the attributes noted above, facilitate reaching the un- (zero-dose) and under-immunized populations by minimizing delivery challenges. This improved reach is anticipated to ultimately contribute to increasing MCV1 and MCV2 coverage and achieving MR elimination goals. Previous studies have demonstrated MAP

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

acceptability to care givers, its suitability for paediatric use, and preference over N/S administration.[10, 11]

While two MR-MAP products have entered Phase I clinical development in 2021 (NCT04394689 and ACTRN12621000820808), they continue to face several hurdles impeding development and slowing licensure timelines. The path to commercialization and uptake is critical since MR-MAP developers or their commercialization partners will need to invest in building and validating MAP manufacturing facilities, and this has not yet been achieved for any vaccine-MAP. Programmatic Doses Required (PDR) are defined as the average estimated number of doses required to meet immunization program needs, whether these are routine or campaign. The PDR includes wastage, which is dependent on the vaccine presentation, and buffer stock. Clarity on the potential demand of PDR and how countries plan to use MR-MAPs could help to inform manufacturing investment decisions. A recent analysis estimates that MR-MAPs could be available to all countries by 2030.[12]

This article summarises the demand estimates for MR-MAPs between 2030-2040. It aims to inform analyses such as cost-effectiveness, willingness to pay, size of manufacturing investment required to manufacture MR-MAPs; as well as other decisions like preparation of appropriate policies, communication or training material to allow for rapid MR-MAP introduction.

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

Methodology

To forecast the global MR-MAP demand from 2030-40, a five-step approach was used. This forecast was unconstrained from programmatic, supply, and price perspectives. The methodology described here is a high level, non-technical summary of the approach. A detailed summary of the methodology can be found in Annex A, together with an Excel file "annex.xls" that contains data, sources, all assumptions used in this analysis, and a model to estimate the year of introduction of MR-MAPs. Additional sensitivity analyses can be found in Annex B.

First, **a demand expressed in PDR was estimated for measles- containing vaccines (MCV) for the years 2030-2040** by leveraging the methodology of the WHO's Market Information for Access to Vaccine's (MI4A) MCV Global Market Study, which contains global MR PDR estimates up to 2030.[13] MI4A is a study that provides a global perspective on vaccine markets, including for measles monovalent, MR, and Measles, Mumps, and Rubella (MMR) or Measles, Mumps, Rubella, and Varicella (MMRV), until 2030 using a population-based methodology, with protocols and assumptions established and reviewed by experts.[13] Briefly, the size of the target population, MCV1 and MCV2 coverage, frequency of SIAs, and buffer and stock wastage in 2030-2040 were used to estimate the MCV PDR demand for these years (annex A, step 1).

Second, **estimates of the number of N/S doses calculated in step 1 that would be replaced by MR-MAPs** were made. To achieve this, a set of criteria were identified to predict the year in which a country would adopt MR-MAPs. Then, a market penetration rate of MR-MAPs was applied. Market penetration is defined as the percentage of PDR utilizing MR-MAPs and assumes that MR-MAPs are delivered alongside the N/S presentation. Countries with similar patterns of MR use, or location, were grouped into four archetypes and 16 key countries (text box 1; annex A, step 2).

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

Text box 1: Country archetypes

A: Countries exclusively using MMR or MMRV

B: Countries using MMR or MMRV in routine schedules but utilizing Measles monovalent and MR for SIA activities

C: Countries using MR located in WHO's African & Eastern Mediterranean Region

D: Countries that use M or MR in WHO's Southeast Asian & Western Pacific Region

16 Key Countries: Afghanistan, Bangladesh, Brazil, Chad, Democratic Republic of the Congo, Ethiopia, India, Indonesia, Mozambique, Nigeria, Pakistan, Philippines, South Africa, Tanzania, Uganda, United States of America

Third, **additional PDR was estimated given the anticipated increased reach of MR-MAPs** to zero-dose or under-immunized populations, including remote rural, security compromised, urban slums and missed opportunity for vaccination (MOV) populations. This included defining and developing a set of assumptions concerning definitions, size and vaccine coverage of these additional populations, recommended buffer stocks, and anticipated wastage rates (annex A, step 3).

Fourth, to understand who would administer MR-MAPs and where, **the total MR-MAP PDR from steps 2 and 3 was allocated to the previously defined MR-MAP Use Cases (UCs)** using the dimensions of delivery location and service provider (text box 2). The UCs were developed through consultations with National Immunization Programme managers as well as regional and national WHO focal points, and through desk reviews of published and unpublished literature on their potential feasibility and acceptability. These UCs were leveraged to develop an initial estimate of MR-MAP PDR from 2030-40. This exercise estimated the global PDR only for MR-MAPs delivered in a fixed health post or through outreach with or without cold chain capacity (UC1, UC2, and UC3/4), while additional research is currently being conducted to estimate PDR for self-administered MR-MAPs (UC5 and UC6), (annex A, step 4).

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

Text box 2: Description of the MR-MAP Use Cases

UC1: Delivery in a fixed health post with full cold chain capabilities by health worker or community health worker.

UC2: Outreach delivery with reduced cold chain capabilities or no cold chain by health worker.

UC3: Outreach delivery with reduced cold chain capacities by community health worker.

UC4: Outreach delivery with no cold chain by community health worker in their 'home' community.

UC5: Self-administration with health worker or community health worker supervision.

UC6: Self-administration without health worker or community health worker supervision, but may include supervision by another individual (e.g., school teacher, community leader, etc). for monitoring purposes.

Finally, given the level of uncertainty for key assumptions that could significantly impact MR-MAP PDR, three scenarios were explored. The base scenario 1 assumed that MR-MAPs would replace a share of MR doses delivered by N/S, and that MAPs could reach a proportion of previously unimmunised populations. Scenario 2 assumed that MR-MAPs would be first piloted in selected countries in each WHO region prior to wider scale use in countries; and scenario 3 explored earlier introduction of MR-MAPs in countries with the lowest measles vaccine coverage and highest MR disease burden (annex A, step 5).

Throughout the development of the demand forecast, the Working Group of Experts on MR-MAPs, the MI4A Advisory Group and key country experts were consulted on the methodology and assumptions utilized.

Figure 1 provides an overview of the five-step process.

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
Classified as Internal
All rights reserved. No reuse allowed without permission.

Results

Scenario 1 (Base) results

All numbers presented in this section are approximate. We estimated the PDR for MCV between 2030-2040 at 4.05 billion doses, with 3.05 billion doses delivered through routine immunization, and ~1 billion doses delivered through SIAs. After applying additional steps including country adoption and market penetration rates (see methods), we estimated the PDR for MR-MAPs between 2030-2040 at 1.46 billion doses. We calculated the additional MR-MAP PDR to reach populations not receiving MCV vaccines due to MOV or living in hard-to-reach areas (urban slums, remote rural, and security compromised populations) at 0.25 billion doses between 2030-2040. This resulted in a total PDR for MR-MAPs between 2030-40 of 1.71 billion doses.

The initial MR-MAP PDR in 2030 is estimated at 30 million doses, expected to peak in 2036 at 250 million doses, and level out at 220 million doses in 2040. We estimated that MAPs will deliver a total of 9% (30 million doses) MR PDR in 2030, and steadily increase to approximately 76% (220 million doses) by 2040.[13] Figure 2 provides an overview of the total number of MR PDR delivered by MAPs and N/S in countries forecasted to use MR in their national immunization schedules.

The majority of the 2030 estimated MR-MAP PDR is from 16 key countries (37%) and Group A countries (50%) with Group B, C, and D accounting for 12% of total PDR. However, by 2040, the percentages are estimated to shift with the 16 key countries accounting for the largest share (61%) of total global PDR, followed by countries in Group C (27%) and countries in Group A, B, and D accounting for 3%, 5% and 4%, respectively.

Figure 3 and table S1 in Annex C provide an overview of the estimated global MR-MAP PDR by country group.

In 2030, 61% of MR-MAP PDR is forecasted to be delivered at fixed health posts with full cold chain capabilities by health workers or community health workers (UC1). The remaining 39% of MR-MAP PDR is anticipated to be used as part of outreach activities or UC2 and UC3/4, i.e., when there is limited or no cold chain availability and MAPs will be administered by health workers or community health workers. By 2040, 52% of MR-MAP PDR is forecasted to be used in UC1 and 47% in UC2 and UC3/4, showing a slight shift in how

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

doses may be used once most countries have adopted MR-MAPs. Figure 4 and table S2 in Annex C provide an overview of the estimated MR-MAP PDR by UC.

Exploring uncertainty of global MR-MAP demand with scenarios

In addition to scenario 1 (baseline), two other scenarios were developed to investigate the uncertainty in the trajectory of MR-MAP demand between 2030 and 2040.

Scenario 2 explores the use of **regional MR-MAP pilots** and results in lower MR-MAP PDR estimates (130 million doses) over the first five years compared to the 290 million doses in Scenario 1 (Base) and in a 18% reduction of MR-MAP PDR over the 2030-40 period.

Scenario 3 explores more **accelerated MR-MAP adoption in countries with the greatest needs** and estimates an increase in PDR of 186% (830 million doses) in the first five years and an overall increase of 21% in PDR over the 2030-40 period compared to Scenario 1.

While the MR-MAPs PDR estimates for each of the scenarios vary, particularly in the first half of the forecasting period, the PDR estimates ultimately converge towards the latter part of the forecasting period. Figure 5 and table S3 in Annex C provide an overview of the estimated MR-MAP PDR by scenario.

Limitations

The limitations of this unconstrained demand forecast are largely driven by the limited evidence and data to inform key assumptions, including on how those data may evolve over the next 20 years. We conducted sensitivity analyses to measure the impact of data uncertainty on the estimates of MR-MAP demand between 2030-2040 and report the results in annex B.

In particular the data estimating the size of hard-to-reach populations as well as those prone to MOV that could be reached by using MR-MAPs was scarce with substantial uncertainty in how the situation will evolve over the next 20 years. However, sensitivity analyses revealed that even major changes in the assumptions of estimated population size (e.g., a decrease by 20%) only had a minor impact on the global PDR estimates with a decrease of 1 million doses (see supplemental Annex B for additional information on the methodology and results of the sensitivity analyses). In contrast, the sensitivity analyses revealed that assumptions around the anticipated reach or coverage of MR-MAPs, particularly in the hard-to-reach and MOV populations, and the market penetration of MR-MAPs significantly impacted the estimated PDR. These assumptions are currently being driven by limited data up to 2020, and gaps were filled by expert opinion and extrapolations made to 2040. Further revisions will require research and consultation to generate a stronger evidence-base.

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

Other assumptions relating to the delivery of MR-MAPs by less trained individuals (e.g., community health workers) may not be valid due to prevailing and future legal and policy constraints in some countries. These assumptions could also considerably impact global PDR, particularly the split of PDR between the different UCs. Additional evidence is required to understand if and how lesser trained individuals could administer MR-MAPs.

Finally, all assumptions are subject to the perceived benefit, operational feasibility, and cost-effectiveness of switching to MR-MAPs in different country situations. We have assumed that MR-MAPs will have desirable product characteristics based on the Target Product Profile .[9] However, uncertainties remain (e.g., thermostability, wear time, vaccine price, ability to reach zero-dose and under-immunized, and impact on cold chain) and these characteristics will likely contribute to country decision making on the adoption and use of MR-MAPs.

As MR-MAPs proceed through the clinical trial phases and the product attributes and operational feasibility become clearer, it will be important to re-visit the applied assumptions and update the demand forecast.

Discussion

This work represents a first attempt to estimate the unconstrained global PDR of MR-MAPs while considering potential UCs, to inform global discussions and decision making about the investment in, development, introduction, and use of MR-MAPs. As additional information becomes available, the current assumptions should be adjusted to improve the accuracy of the estimates.

We estimate that MR-MAPs PDR will stabilize by 2038 at approximately 210 million doses per year and will account for approximately 76% of total MR PDR. In 2040, approximately 53%, 27%, and 20% of total MR-MAP PDR will be contributed by UC1, UC2, and UC3/4, respectively (Figure 4). This demand forecast indicates that there will be a substantial and sustainable role for MR-MAPs as part of national immunization programmes. Finally, we estimate that a significant portion of MR-MAP PDR will be used as part of routine immunization (73%) compared to SIAs (27%) by 2040.

Given that MR-MAPs are a new vaccine presentation, a pilot implementation strategy may be the most realistic scenario for their roll-out (Scenario 2). If designed appropriately this strategy could provide valuable evidence on vaccine acceptability and feasibility of uptake and identify best practices to assist countries with their decision making while demonstrating and communicating the benefits of MR-MAPs. Pilot strategies have previously proven useful for countries with the introduction of vaccines using different immunization strategies and

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

varying delivery costs a (e.g., Human papillomavirus (HPV) vaccination demonstration projects and malaria vaccine pilots).

Scenario 3, which forecasts the use of MR-MAPs in countries with the greatest needs, reflects the global public health community's ambition to urgently utilize MR-MAPs as a critical tool to overcome the limitations of current N/S presentations and close coverage gaps. This scenario highlights the potential role that MR-MAPs could play in achieving MR elimination goals.

Additional data and evidence will need to be gathered to refine these estimates, particularly exploring how countries are making decisions on the adoption of MR-MAPs, and how quickly countries could adopt MR-MAPs. Finally, this demand forecast was considered independent of price assumptions to investigate the full potential of demand, which can ultimately impact Cost of Goods Sold and price. There is a need to further explore how a potential increase in price will be off-set by cost savings in the immunization system and a potentially increased health and economic impact, including the ability of MR-MAPs to reach zero-dose and under-immunized children, which would result in reduced morbidity and mortality. This could play an important role in informing decisions by countries on adopting MR-MAPs.

Conclusions

While MR-MAPs have recently entered Phase I clinical trials, questions on their anticipated use and impact remain (text box 3), which could influence the demand forecast and ultimately affect investment decisions, clinical development strategies and timelines. The use of MAP presentations could potentially change the immunization landscape by addressing some of the current barriers that countries face related to zero-dose and under-immunized children. Thus, it is imperative that these outstanding issues are addressed through open dialogue with countries and manufacturers. As these issues are resolved, the global demand forecasting methodology and assumptions for MR-MAPs will need to be continuously revised to reflect the latest data and information. This can improve the accuracy and reliability of the estimates of MR-MAP demand, which can play an important role in providing confidence to manufacturers of their investments.

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

Classified as Internal

Text box 3: Key questions that can impact the demand forecast

- What is the anticipated reach or coverage of MR-MAPs in hard-to-reach and MOV populations?
- What is the market penetration of MR-MAPs and whether they will replace the N/S presentation?
- Can MR-MAPs can be delivered by lesser trained individuals?
- What is the quantification of the perceived benefit, operational feasibility, and cost effectiveness of using MR-MAP in different country situations and contexts?
- Will a potential price increase be offset by other cost savings related to cost savings in logistics, transportation, use of lesser trained individuals, etc?

Funding: This work was supported by Bill & Melinda Gates Foundation grant to World Health Organization [INV-005318].

Acknowledgements

The authors thank the Working Group of Experts on MR-MAPs and MI4A Advisory Group who provided invaluable guidance and feedback on the development of the methodology and scenarios. The authors acknowledge immunization experts in countries who shared their expertise and feedback to review the methodology and develop country or regional assumptions.

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

Supplemental Annex A: Additional information on the methodology and assumptions

Step 1: Estimate MCV PDR for 2030-2040

Estimate the size of the target population, its characteristics, and immunization strategies

Data: annex.xls, sheets 2a-2g

To calculate the size of the future target populations, and the MCV PDR for 2030-2040, the medium estimates for the number of surviving infants and nine to 59 month old children were obtained from the United Nations World Population Prospectus (WPP) for years 2030-2040, which provides population estimates for 183 of the 194 UN countries.[13] Two delivery strategies were considered: (i) two MCV doses delivered in routine immunization at nine to 12 months and at 15-18 months of age; and (ii) one MCV dose delivered as part of supplemental immunization activities (SIAs) to children aged nine to 59 months of age every two to five years until optimal immunity in the target population can be achieved.[4, 14, 15] We assume that all countries in the analysis will have introduced MCV2 by 2030 (e.g., N/S introduction date).[13]

Forecast MCV1 and MCV2 coverage estimates

Data: annex.xls, sheets 4a-4b

The changes in MCV1 and MCV2 coverage between 2030 and 2040 were estimated using the 2019 WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) MCV coverage estimates, leveraging the MI4A methodology, and based on the following assumptions: (i) if coverage is less than 70%, then an annual growth of 3% would be applied; (ii) if coverage was between 70-85% then an annual growth of 1% would be applied; and (iii) finally if coverage was greater than 85%, then an annual growth of 0.5% would be applied.[13] Coverage was capped at 95% or higher if a country has ever achieved greater than 95% in MCV1 or MCV2 coverage. Uptake is a variable that estimates how quickly a country is able to introduce a routine vaccine into its national immunization system. Uptake of MCV1 and MCV2 vaccine was not considered a relevant variable as all countries were forecasted to introduce prior to 2030. [5] The coverage rate and growth were calculated on a yearly basis. A 100% coverage for SIAs was applied to estimate the PDR for SIA; such an assumption was also based on MI4A methodology, which considers the standard practice to

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
Classified as Internal
All rights reserved. No reuse allowed without permission.

procure SIA doses for the entire population.[13] SIAs were assumed to be implemented in one single year (e.g., uptake at 100%) with the exception of countries that have historically implemented SIAs over 2-3 years, including Democratic Republic of Congo, Egypt, Ethiopia, Indonesia, Nigeria, Pakistan, and Philippines. This is in line with the MI4A methodology.[13]

Forecast the frequency of SIAs

Data: annex.xls, sheets 8a-8b

The frequency of the SIAs targeting 9–59-month-old children were forecasted until 2040 based on the forecasted MCV2 coverage using MI4A methodology: (i) if countries had a MCV2 coverage of <60%, they were projected to conduct an SIA every 2 years; (ii) if countries had an MCV2 coverage between 60-80%, they were assumed conducting an SIA every 3 years; and (iii) if countries had a MCV2 coverage of > 80%, SIA were foreseen every 4-5 years.[13] Countries were forecasted to stop conducting SIAs when their MCV2 coverage reached 90% for 3 consecutive years.[4]

Calculate buffer stock and wastage

Data: annex.xls, sheet 5

WHO guidance was followed to estimate buffer stock and wastage rates for the N/S MR vaccine.[16, 17] Annual buffer stock was calculated as 25% of the difference in demand from the current and the prior year of vaccine routine use, negative values were transformed to zero. The following wastage rates were applied for N/S vaccines to be delivered routinely in infants: 1-dose vial 5%, 5-dose vial 15%, and 10-dose vial 40%. The following wastage rates were applied for N/S vaccines to be delivered in SIAs: 1-dose vial 1%, 5-dose vial 10%, 10-dose vial 10%. [16, 17] The wastage rate for MR-MAPs was set at 1% due to their assumed increased thermostability, single dose presentation, and shelf life.[16, 17]

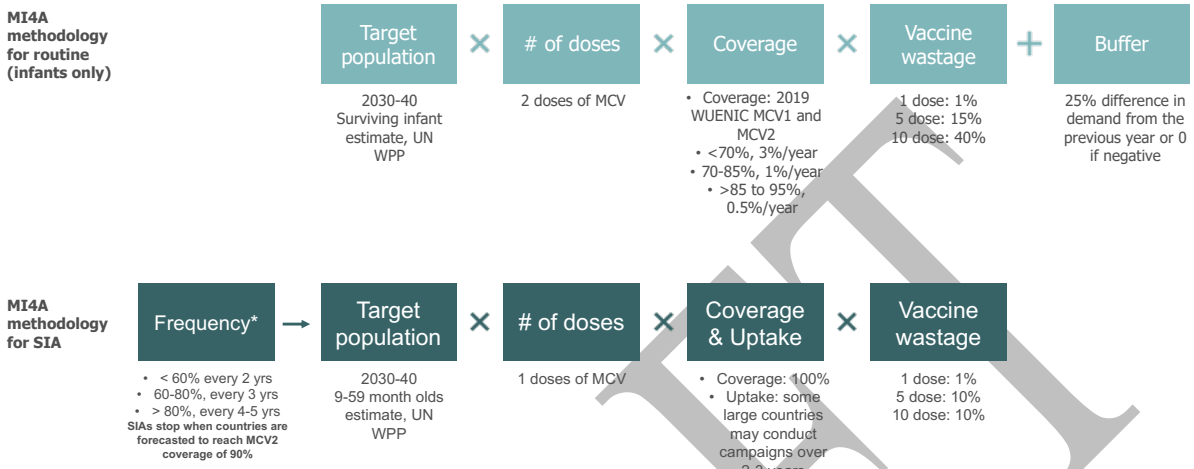
Figure S1 provides an overview of the methodology and assumptions to extrapolate MCV routine immunization doses to 2040.

Figure S1: Methodology and assumptions to estimate MCV routine immunization and SIA PDR for 2030-2040 (Step 1). MR: measles and rubella; SIA: supplementary immunization activities; PDR: programmatic doses required; MI4A: Market Information for Access to Vaccines; UN: United Nations; WPP: World Population Prospectus; WUENIC:

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

WHO/UNICEF Estimates of National Immunization Coverage; MCV1: 1st dose of a measles containing vaccine; MCV2: 2nd dose of a measles containing vaccine.



*95% or the country's historical high coverage

Step 2: Estimate MR-MAP PDR

Create country archetypes

Data: annex.xls, sheet 1a

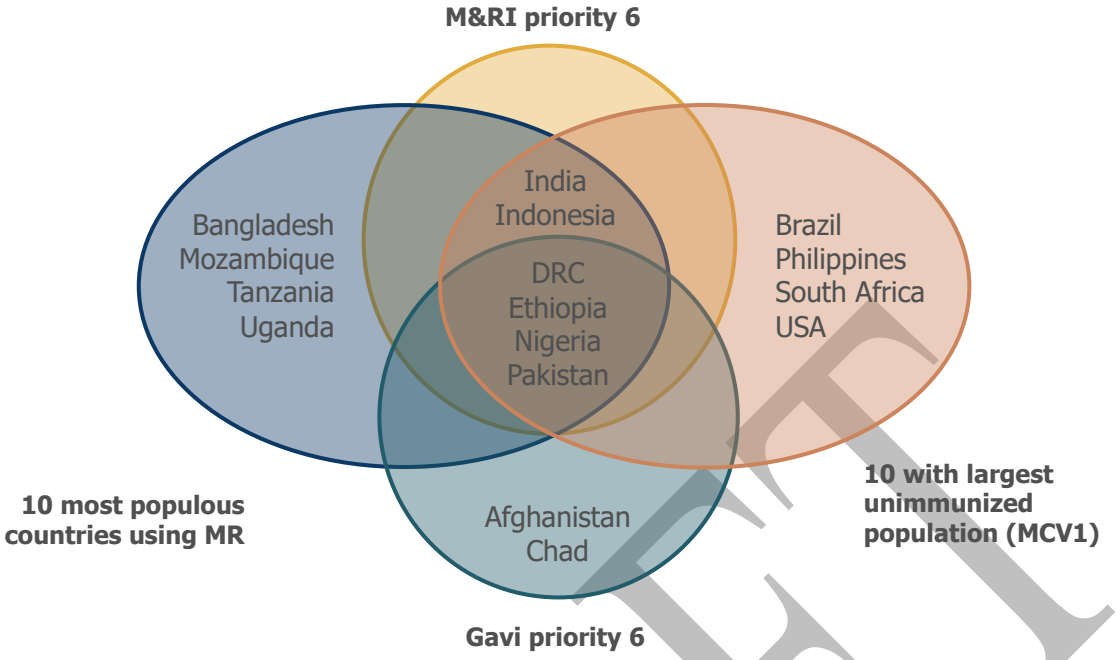
The MR-MAP demand forecast utilized a hybrid method where assumptions were developed for four country archetypes, and individually, for 16 key countries. These countries included the ten countries with the largest populations, the ten countries with the largest number of unimmunized children based on MCV1 coverage, and six countries that are judged high priority by the Measles and Rubella Initiative (M&RI) and/or Gavi, the Vaccine Alliance (Gavi). Using these criteria, 16 key countries were identified, and these countries account for approximately 50% of the under 5 year old population.[18] (Figure S2).

Figure S2 Identification of 16 key countries. M&RI: Measles And Rubella Initiative; MR: measles and rubella; DRC: Democratic Republic of the Congo; USA: United States of

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

385 America; MCV1: 1st dose of a measles containing vaccine.



386

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
Classified as Internal
All rights reserved. No reuse allowed without permission.

The remaining 167 countries were grouped based on their forecasted MCV use and their WHO regions to reflect potential differences in health systems and how vaccines are delivered. This resulted in four country archetypes:

A. Countries that exclusively use MMR / MMRV
B. Countries that use MMR / MMRV in routine immunization but may use MR / M for SIAs
C. Countries that use M or MR in WHO's African & Eastern Mediterranean Region
D. Countries that use M or MR in WHO's Southeast Asian & Western Pacific Region

Where country assumptions were unavailable, the weighted average estimated for the group which included that country was applied.

Estimate country adoption year of MR-MAPs

Data: annex.xls, sheet 8d

To estimate the proportion of global MCV demand delivered by MAPs, a framework to predict the year of country adoption of MR-MAPs was developed, based on the following three parameters: (i) the year of introduction of MCV2, rubella, pneumococcal conjugate, rotavirus, and human papillomavirus vaccines; (ii) the total disease burden of measles and rubella (2019 reported annual cases and deaths of measles, 2019 measles incidence rate, and 2010 number of estimated rubella cases), and (iii) the percentage of total expenditure on vaccines funded by the government (%) for the last available year or the forecasted Gavi eligibility status in 2030. [19-23]

The predictive framework considers the variables and assigns points distributed by quartiles using the data for each country. For example, the introduction of rotavirus vaccines occurred between 2006 to the present day; thus, those countries that introduced the vaccine within the first quartile or 25th percentile of all years 2006-2022, i.e. years 2006 to 2011, were assigned 4 points, second quartile (i.e., years 2011 to 2014) were assigned 3 points, third quartile (i.e., years 2014-2017) were assigned 2 points, and fourth quartile (i.e., 2017-present day) were assigned 1 point. The quartiles were calculated for each variable with the points assigned in a similar fashion. Then, the scores for each variable were totalled by country, and based on this score, the countries were assigned an adoption year which was equally spread across the 11-year time period of 2030-40. This resulted in ~16 countries adopting MR-MAPs each year. This framework predicts that countries would adopt MR-MAPs earlier if they had a history of early introduction of new vaccines, had a high level of measles and rubella burden, and had sufficient financial resources devoted to immunization

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

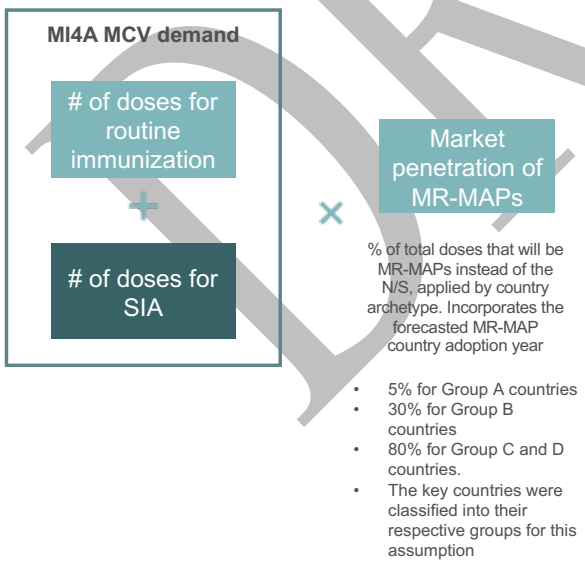
or were anticipated to receive donor support. The variables were considered equally for the base estimates.

Market penetration of MR-MAPs

To estimate the proportion of global MCV demand delivered by MAPs, an MR-MAP market penetration rate, varied by country groups, was applied to the total MCV PDR calculated from Step 1. A market penetration of 5% was assumed for Group A as these countries would largely continue using MMR and MMRV for the majority of their programmes, but potentially utilize MR-MAPs to vaccinate special and vulnerable populations, such as migrants. A market penetration of 30% was used for Group B countries based on the historical use of MR vaccines in MMR/MMRV countries, which estimated that MR N/S accounted for approximately 30% of total MCV demand for these countries.[24] Finally, a market penetration of 80% was applied for Groups C and D based on the assumption that these countries would unlikely switch fully to MR-MAPs.[24] In the absence of available data, the market penetration of MR-MAPs was discussed and agreed upon by a group experts and consulted with country immunization experts.

Figure S3 provides an overview of the methodology and assumptions for Step 2.

Figure S3: Step 3 Split global MCV PDR by presentation and vaccine type. SIA: supplementary immunization activities; MI4A: Market Information for Access to Vaccines; MR: measles rubella; MR-MAP: measles and rubella microarray patches; N/S: needle and syringe.



DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

Step 3: Estimate additional PDR due to increased reach of MR-MAPs

Characterise the considered target population and immunization strategies

Data: annex.xls, sheets 3a-3e

To estimate the full PDR of MR-MAPs, we calculated the size of additional populations that could be reached by MR-MAPs, including wastage and buffer stock. These populations included those who are not receiving MCV vaccines due to missed opportunities for vaccinations (MOV) or living in hard-to-reach areas. We used data from published and unpublished data sources, such as country comprehensive multi-year plans, EPI reviews, Gavi joint appraisal reports, World Bank estimates for population living in urban slums and rural areas, and 2019 United Nations High Commissioner for Refugees estimates for population of concern.[18, 25-30]

To estimate the size of the hard-to-reach populations, the children between 0-2, and 2-15 years old, who lived in urban slums, remote rural, and security compromised settings were included. The relevant data was obtained using the above data sources and then stratified by age based on United Nations World Population Prospectus.[18, 25, 26, 28, 29] The estimates for hard-to-reach populations were held constant for the entire forecasting period given the high level of uncertainty in how these estimates may evolve over the next 20 years.

An MOV refers to any contact with health services by a child or adult who is eligible for vaccination, which does not result in the person receiving one or more of the vaccine doses for which he or she is eligible. The estimated size of the MOV population was calculated as 2% of children under 2 years of age per United Nations World Population Prospectus from 2030-40. This percentage was derived from published MOV literature and validated by expert opinion which considered the timeliness of vaccination and methodology to develop WUENIC estimates to avoid overestimating the MOV population.[18, 28, 29, 31] The MOV percentage was held constant for the forecasting period.

The following immunization strategies were used to reach the MOV and hard-to-reach populations: (i) two doses delivered as part of additional routine immunization for children less than two years of age in MOV and hard-to-reach populations (e.g., security compromised, remote rural, and urban slum populations); and (ii) two doses delivered through SIAs in children between the ages of two to 15 years in hard-to-reach populations.[18, 25-29]

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

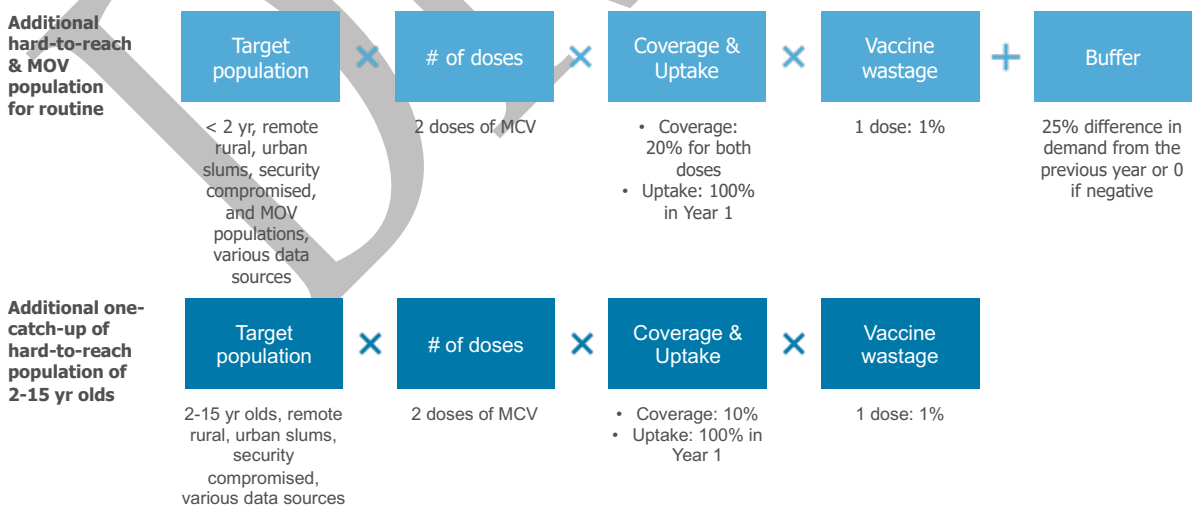
Forecast coverage of hard-to-reach and MOV populations

Data: annex.xls, sheets 4c-4d

For the hard-to-reach and MOV populations, the coverage was estimated based on the expert opinion of members of the Working Group of Experts on MR-MAPs and MI4A Advisory Group. While MR-MAPs were assumed to increase the MR reach in hard-to-reach and MOV populations, their ability to fully address all programmatic barriers was considered unlikely. Hence, for the hard-to-reach and MOV populations, a coverage of 20% was applied in a routine immunization setting for both doses, and 10% was applied for the SIAs. These estimates are conservative given the lack of information on the MAP reach of hard-to-reach and MOV populations. These estimates were also held constant for the forecasting period given the lack of data available to inform this assumption. Uptake of MR-MAPs was assumed to be 100% for both routine and the one-time catch-up campaign of MOV and hard-to-reach populations.

Figure S4 provides an overview of the methodology and assumptions to calculate the additional PDR due to the use of MAPs.

Figure S4: Methodology and assumptions utilized to calculate additional reach of MR-MAPs in the hard-to-reach and MOV population. MR-MAPs: measles and rubella microarray patches; MOV: missed opportunities for vaccination; MCV: measles containing vaccines; yr: years.



Step 4: Estimate the proportion of MR-MAP PDR delivered by Use Cases

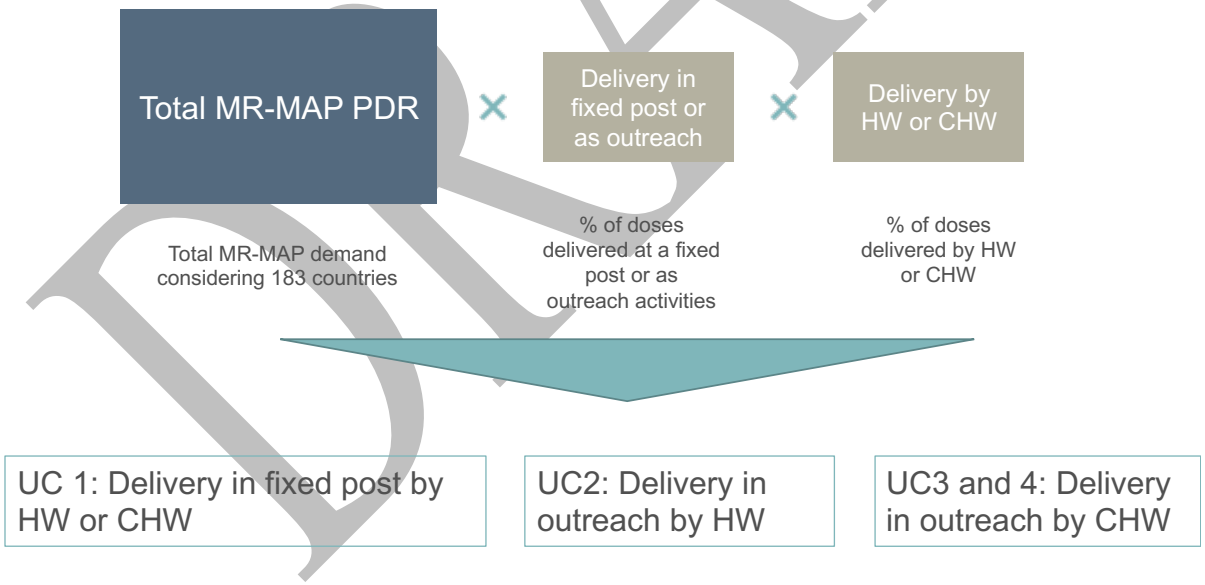
Data: annex.xls, sheets 6a-6c

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

To estimate where MR-MAPs would be delivered (fixed post with full cold chain capabilities versus limited or no cold chain capabilities) and by whom (health workers, community health workers), we have applied the previously developed Use Cases 1-4 (text box 2) to the MR-MAP PDR developed in step 3. We applied assumptions about the proportion of vaccines delivered in the mentioned locations and by the mentioned personnel. The assumptions relating to the number of nurses or midwives and community health workers were obtained from the Global Health Workforce statistics and supported by unpublished literature, such as country comprehensive multi-year plans. The assumptions related to vaccine delivery in fixed posts or during outreach were largely obtained from unpublished literature such as from country comprehensive multi-year plans, Expanded Programme on Immunization (EPI) reviews, Gavi joint appraisal reports, validated during interviews with country EPI managers and immunization focal points. [32] The data was not adjusted for the period 2030-2040, nor it was changed to reflect the introduction of MAPs. Figure S5 provides an overview of the methodology and assumptions.

Figure S5: Splitting MR-MAP PDR by Use Case. MR-MAP: measles and rubella microarray patches; PDR: programmatic doses required; HW: health workers; CHW: community health workers; UC: use case.



DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

Step 5: Explore uncertainty of MR-MAP PDR with scenarios

Data: annex.xls, sheet 8e

Given the high level of uncertainty in how global PDR will evolve for MR-MAPs between 2030-2040, three scenarios were explored (text box 4).

Text box 4: Description of the scenarios

- Scenario 1: **Base**: utilizes 5-step demand forecasting methodology described above.
- Scenario 2: **Regional MR-MAP pilots**: Five countries in each WHO region conduct sub-national pilots with MR-MAPs for 2 years prior to national implementation. All other countries do not adopt MR-MAPs until the regional pilots are completed.
- Scenario 3: **Accelerated adoption in countries with the greatest need**: Countries with the lowest MCV1 coverage and highest disease burden for measles and rubella are forecasted to adopt MR-MAPs earlier.

Note that there were no constraints applied to any of the scenarios.

The scenarios were developed based on the input of the Working Group of Experts on MR-MAPs and MI4A Advisory Group. Scenario 1 serves as the **base scenario** and utilizes the forecasting methodology described above to estimate PDR and is described in Steps 1-4. Scenario 2, **regional MR-MAP pilots**, considered if MR-MAPs would be rolled out as 'sub-national pilots' in the first five countries in each WHO region targeting only 5% of the surviving infant population for the first two years. These countries would introduce MR-MAPs nationally in year 3 while all other countries would delay the introduction of MR-MAPs until the regional pilots were completed (5 years from the beginning of the pilot). Scenario 3 explored if MR-MAPs were adopted first in countries that had the **greatest need** based on their MCV1 coverage and their disease burden of measles and rubella. This was achieved by utilizing the same predictive framework to forecast adoption year, but instead of the variables being equally weighted, the variables for MCV1 coverage and measles and rubella burden were given twice the weight compared to the other variables. Based on the revised weights, a new adoption year was calculated.

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

Supplemental Annex B: Methodology and results of sensitivity analyses

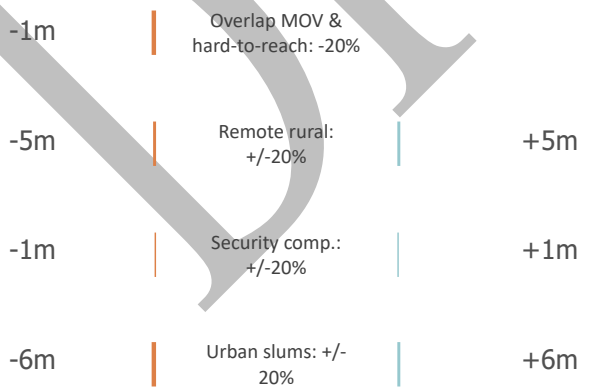
Sensitivity analyses were conducted on specific variables where no or limited data existed or if there were concerns regarding the quality of the data highlighted by the Expert group on MR-MAPs and the MI4A Advisory Group. Four types of sensitivity analyses were conducted on (i) additional hard-to-reach and MOV populations, (ii) proportion of additional hard-to-reach and MOV populations reached by MR-MAPs, (iii) delivery location, and (iv) service provider.

These analyses aimed to identify which variables have the highest impact on the demand forecast so that efforts could be focused on filling the most impactful evidence gaps to improve the accuracy and reliability of the demand forecast.

For simplicity, the variables were considered independently and explored using a plus or minus 20% change. 20% was chosen as the MI4A MCV analysis shows an annual change in total MCV routine and SIA PDR of ~22-28%.[13]

The first sensitivity analysis conducted reviewed the estimated hard-to-reach and MOV populations. Based on expert feedback, there were concerns that the definition of these hard-to-reach and MOV populations may either over or underestimate the population and/or there may be overlap between the different populations. Figure S6 provides an overview of the results of the sensitivity analyses for these populations.

Figure S6: Overview results of sensitivity analyses on hard-to-reach and MOV populations. MOV: missed opportunities for vaccination



f

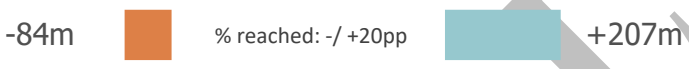
The estimated hard-to-reach and MOV populations could have an impact of 1 to 6 million PDR on the overall demand forecast. As this accounts for less than 2% of the total annual PDR once a steady state is reached, it is unlikely that inaccuracies in these population estimates will have significant impact on the overall demand forecast.

DRAFT

medRxiv preprint doi: https://doi.org/10.1101/2022.08.11.22278665; this version posted August 12, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.
Classified as Internal

Next, we reviewed the proportion of the hard-to-reach and MOV populations that could be reached by a MR-MAP but not a N/S presentation for routine immunization and a one-time catch-up campaign. In contrast, the coverage did have a significant impact on the estimated PDR impacting demand by -84 million doses or by +207 million doses. This highlights the importance in understanding whether MR-MAPs, given their innovative product characteristics, can actually close immunization gaps and reach the zero-dose or under-vaccinated populations. Figure S7 provides the results of this sensitivity analysis.

Figure S7: Results of the +/-20% sensitivity analysis on the proportion of hard-to-reach and MOV populations that could be reached by a MR-MAP but not a N/S. MOV: missed opportunities for vaccination; MR-MAP: measles and rubella microarray patches; N/S: needle and syringe; pp: percentage points; m: millions.



Next, we looked at how percentage changes impacted the UC dimensions of delivery location and service provider. While this sensitivity did not change the total estimated PDR for MR-MAPs, it did change how countries would be utilizing the MR-MAPs and the proportion of doses delivered in different UCs.

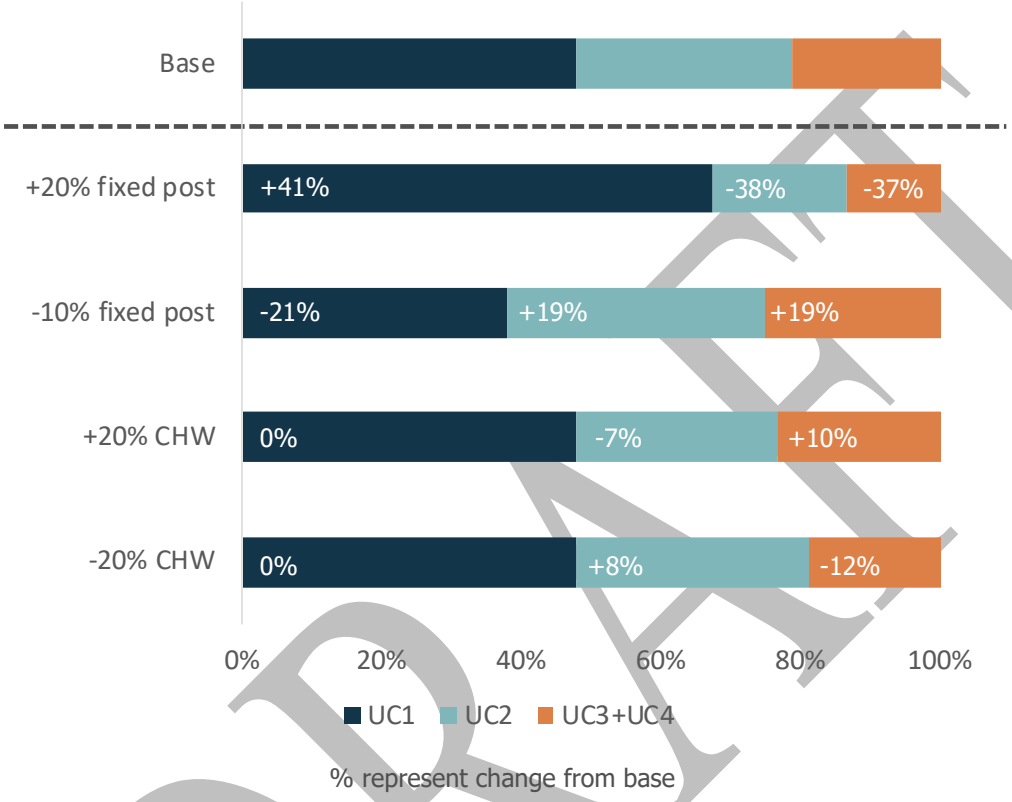
An increase in the delivery at fixed post by 20% resulted in an increase in UC1 (+41%) with decrease of UC2 and UC3+4 (-38% and -37%, respectively), which focus more on outreach activities. In contrast a decrease of 10% delivery in fixed post resulted in a decrease in UC1 (-21%) and increase in UC2 and UC3+4 (+19% for both). The delivery location implies a certain level of stability with the PDR and shows that there is interest for MR-MAPs to be delivered in various locations not only in certain settings.

Finally, considering a +/-20 percent change in whether community health worker could deliver MR-MAPs impacted the PDR between UC2 and UC3+4. If 20% more community health workers are able to deliver MR-MAPs this could create an increase in UC3+4 of ~10% and a decrease in UC2 of -7%. In comparison, if community health workers are unable to deliver MR-MAPs, then this may place more importance on UC2 (+8%) compared to UC3+4 (-12%). Country consultations have indicated that there could be legal and technical hurdles to allowing community health workers to deliver MR-MAPs. These hurdles may reduce a MR-MAP's value proposition to expand the potential vaccination workforce to reach the zero-dose and under-immunized as it will not allow for differentiation from the N/S presentation. Given that these sensitivity analyses show ~10% change in the UCs, it highlights the importance of understanding where MR-MAPs will be used and who can deliver MR-MAPs

DRAFT

as this could impact the anticipated value of a MR-MAP ultimately affecting investment decisions. Figure S8 provides an overview of the results of the sensitivity analyses on the UC dimensions.

Figure S8: Results of the +/- 20% sensitivity analysis on UC dimensions of delivery location and service provider. UC: use case; CHW: community health worker.



DRAFT

Supplemental Annex C: Summary tables of the demand forecasting results

Table S1: Estimated programmatic doses required of MR-MAPs by country archetype and year in millions. M: measles; MR: measles, rubella; MMR: measles, mumps rubella; MMRV: measles, mumps, rubella, varicella; SIA: supplementary immunization activities; WHO: World Health Organization.

	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040
16 key countries	12	21	38	90	92	156	160	126	138	142	134
Group A – Countries exclusively using MMR or MMRV	16	6	5	5	5	5	6	6	6	6	6
Group B – Countries using MMR or MMRV in routine programmes but measles monovalent or MR for SIA activities	2	1	2	2	4	4	6	5	12	11	11
Group C – Countries using M or MR located in WHO's African & Eastern Mediterranean Region	2	12	33	37	31	36	66	38	48	47	60
Group D – Countries using M or MR located in WHO's Southeast Asian & Western Pacific Region	-	2	1	2	2	5	8	8	8	8	8
Total	30	40	80	140	130	210	250	180	210	210	220

DRAFT

618 **Table S2: Estimated programmatic doses required of MR-MAPs by use cases and year in millions. UC: use case.**

	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040
UC1 – Delivery in a fixed post by health worker or community health worker	20	30	50	71	74	111	125	100	117	117	117
UC2 - Outreach delivery by health worker	5	7	18	37	36	51	68	46	55	54	58
UC3+UC4 - Outreach or community delivery by community health worker	7	5	11	28	25	44	52	36	40	43	45
Total	30	40	80	140	130	210	250	180	210	210	220

619

620 **Table S3: Estimated programmatic doses required of MR-MAPs by scenario and year in millions.** MR-MAP: measles and rubella
621 microarray patches.

	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040
Scenario 1 - Base	30	40	80	140	130	210	250	180	210	210	220
Scenario 2 - Regional MR-MAP pilots	1	1	30	100	130	150	190	180	210	200	200
Scenario 3 - Accelerated adoption in countries with greatest need	120	130	200	210	170	210	230	170	210	200	200

622

DRAFT

Bibliography

1. Rubella: Fact Sheet. Accessed May 6.
2. Measles fact sheet. Accessed 24/11.
3. Dixon MG, Ferrari M, Antoni S, et al. Progress Toward Regional Measles Elimination - Worldwide, 2000-2020. MMWR Morb Mortal Wkly Rep **2021**; 70(45): 1563-9.
4. World Health Organization. Measles vaccines: WHO position paper. Weekly Epidemiological Record **2017**; 92(17): 205-27.
5. WHO/UNICEF coverage estimates for 1980-2020. Geneva, **2021**.
6. Measles and Rubella Strategic Framework, 2021–2030. Geneva, Switzerland: World Health Organization, **2020**.
7. Durrheim DN, Andrus JK, Tabassum S, Bashour H, Githanga D, Pfaff G. A dangerous measles future looms beyond the COVID-19 pandemic. Nat Med **2021**; 27(3): 360-1.
8. Maltezou HC, Medic S, Cassimos DC, Effraimidou E, Poland GA. Decreasing routine vaccination rates in children in the COVID-19 era. Vaccine **2022**; 40(18): 2525-7.
9. Measles-Rubella microarray patch (MR-MAP) target product profile. Geneva: World Health Organization and the United Nations Children's Fund (UNICEF), 2020, **2019**.
10. Marshall S, Sahm LJ, Moore AC. Microneedle technology for immunisation: Perception, acceptability and suitability for paediatric use. Vaccine **2016**; 34(6): 723-34.
11. Griffin P, Elliott S, Krauer K, et al. Safety, acceptability and tolerability of uncoated and excipient-coated high density silicon micro-projection array patches in human subjects. Vaccine **2017**; 35(48 Pt B): 6676-84.
12. Hasso-Agopsowicz M, Crowcroft N, Biellik R, et al. Accelerating the Development of Measles and Rubella Microarray Patches to Eliminate Measles and Rubella: Recent Progress, Remaining Challenges. Front Public Health **2022**; 10: 809675.
13. Global Market Study, Measles-containing vaccines. Geneva: World Health Organisation, Market Information for Access to Vaccines (MI4A) Initiative, **2020**.

DRAFT

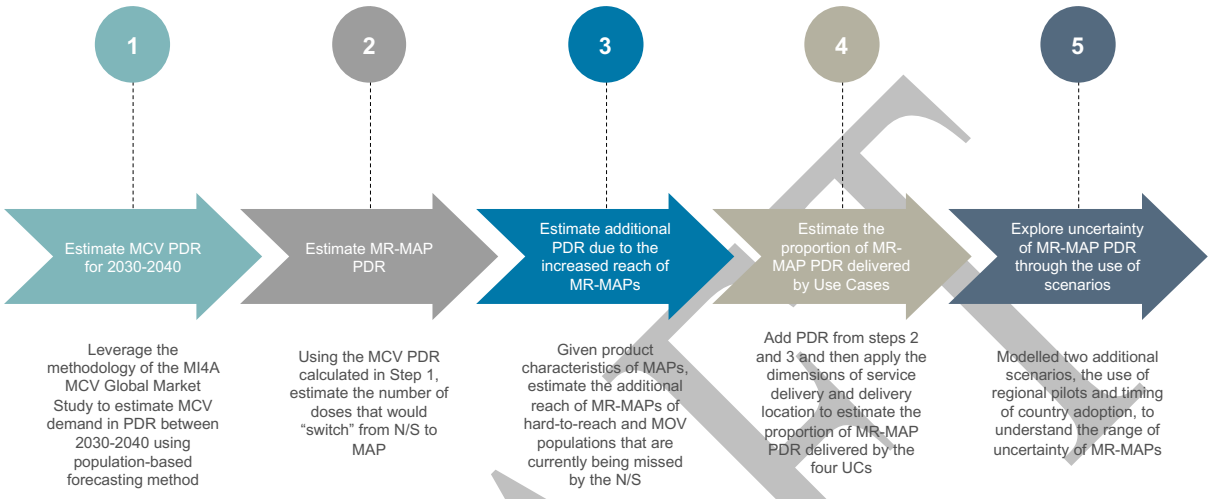
14. Gavi The Vaccine Alliance. Measles and measles-rubella vaccine support. Accessed August 13.
15. World Health Organization. Rubella vaccines: WHO position paper. Weekly Epidemiological Record **2020**; 95(27): 306 - 24.
16. How to calculate vaccine volumes and cold chain capacity requirements. Geneva, Switzerland: World Health Organization, **2017**.
17. Vaccine Wastage Rates Calculator. Geneva, Switzerland: World Health Organization, **2021**.
18. United Nations, Department of Economic and Social Affairs, Division P. World Population
Prospects 2019. Geneva, Switzerland, **2019**.
19. Global Burden of Disease Collaborative Network. Global Burden of Disease study 2019 (GBD 2019) Results.
20. World Health Organization. Immunization Data, vaccine introduction. Accessed May.
21. World Health Organization. Immunization data, provisional measles and rubella data. Accessed May.
22. World Health Organization. Immunization expenditure. Accessed May.
23. Vynnycky E, Adams EJ, Cutts FT, et al. Using Seroprevalence and Immunisation Coverage Data to Estimate the Global Burden of Congenital Rubella Syndrome, 1996-2010: A Systematic Review. PLoS One **2016**; 11(3): e0149160.
24. Summary Measles-Rubella Supplementary Immunization Activities, 2000-2020. World Health Organization, **October 2020**.
25. Rural population. In: Prospects UNPDsWU. New York: World Bank, **2018 Revision**.
26. Population living in slums (% of urban population). World Bank.
27. Affairs - Population Division of the U. N. Department of Economic and Social. 2018 Revision of World Urbanization Prospects. **2018**.
28. Magadzire BP, Joao G, Shendale S, Ogbuanu IU. Reducing missed opportunities for vaccination in selected provinces of Mozambique: A study protocol. Gates Open Res **2017**; 1: 5.

DRAFT

29. Sridhar S, Maleq N, Guillermet E, Colombini A, Gessner BD. A systematic literature review of missed opportunities for immunization in low- and middle-income countries. Vaccine **2014**; 32(51): 6870-9.
30. End of the year Population of Concern. United Nations High Commissioner for Refugees **2020**.
31. The percentage of children aged 12–23 months who have received at least one dose of measles-containing vaccine in a given year. Global Health Observatory. Geneva: WHO, **2019**.
32. Global Health Workforce Statistics. Geneva: World Health Organization, **2018 update**.

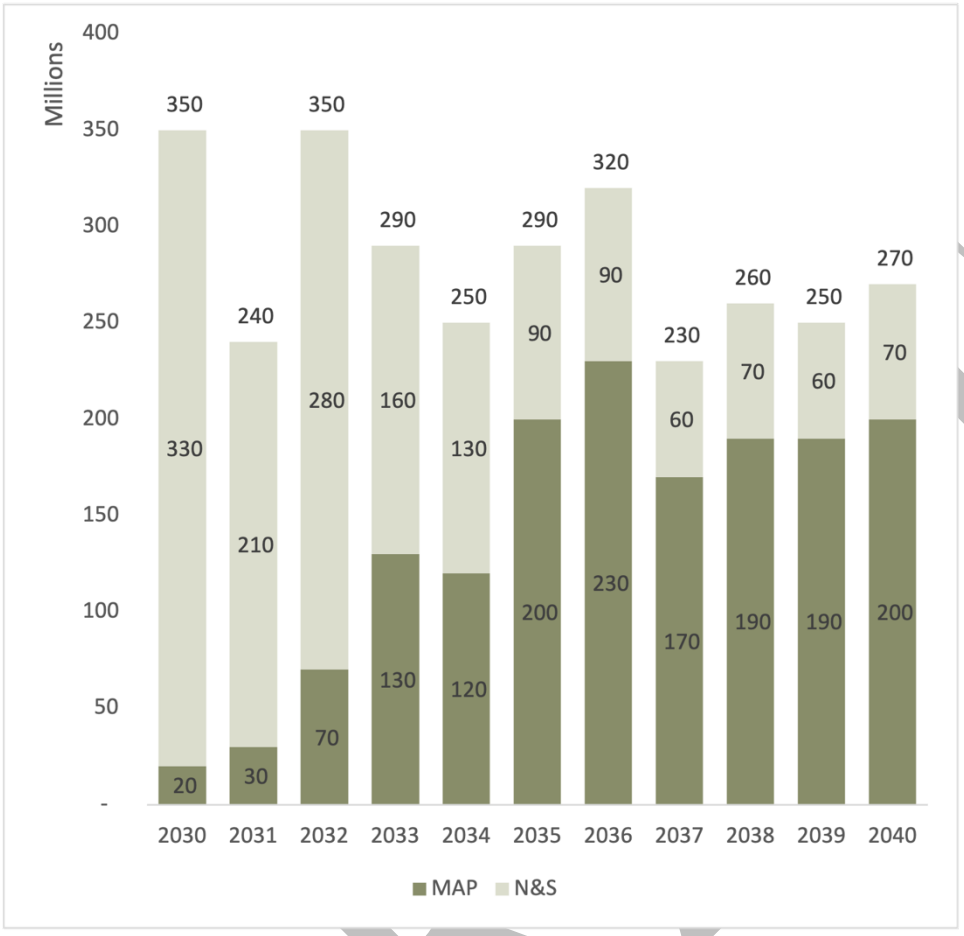
DRAFT

Figure 1: Overview of the four-step approach to develop MR-MAP demand forecast.
MR-MAP: measles and rubella microarray patches; MCV: measles containing vaccines; PDR: programmatic doses required; N/S: needle and syringe; MOV: missed opportunities for vaccination; UCs: use cases.



DRAFT

706 **Figure 2: Estimated MR PDR delivered by MAPs and N/S for countries using MR in**
707 **their national immunization schedules, between 2030-2040.** MR: measles rubella; PDR:
708 programmatic doses required; MAPs: microarray patches; N/S: needle and syringe.

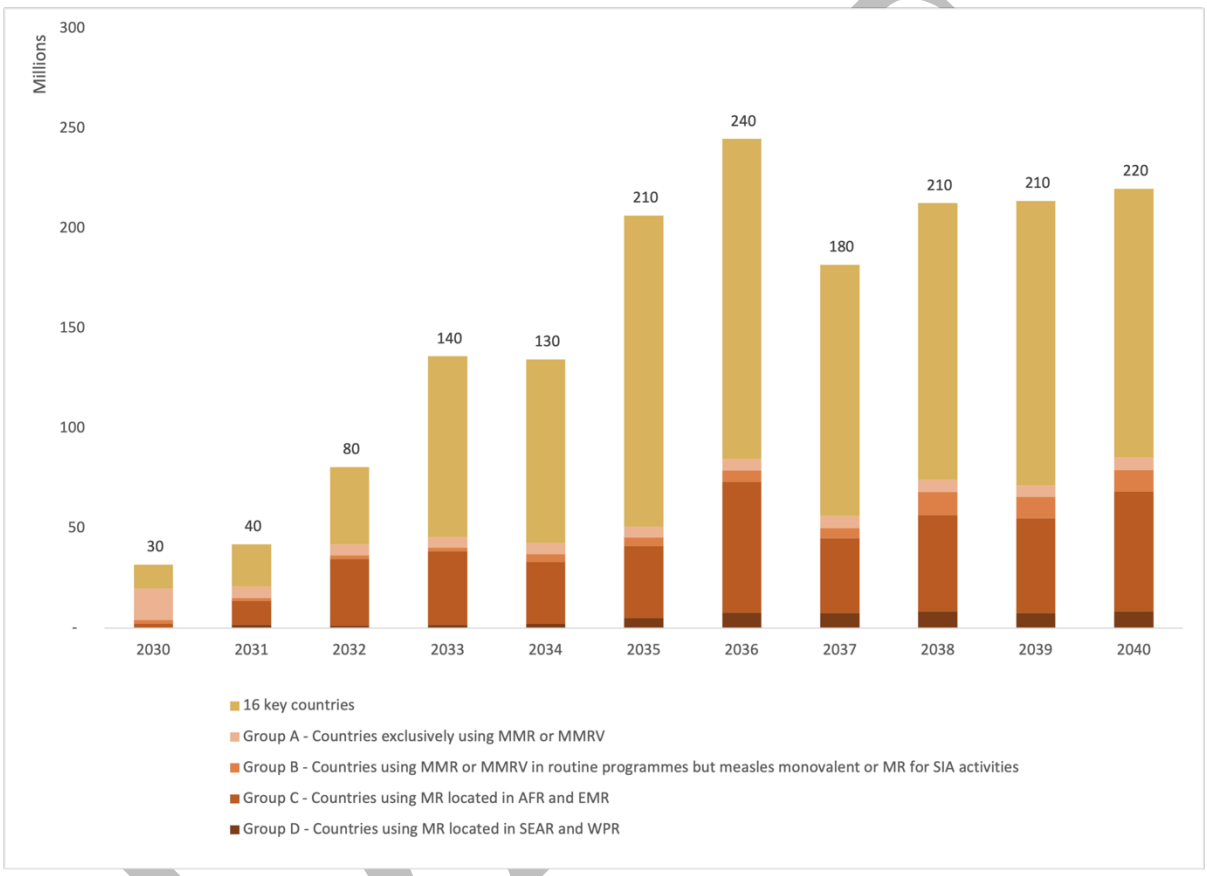


709

710

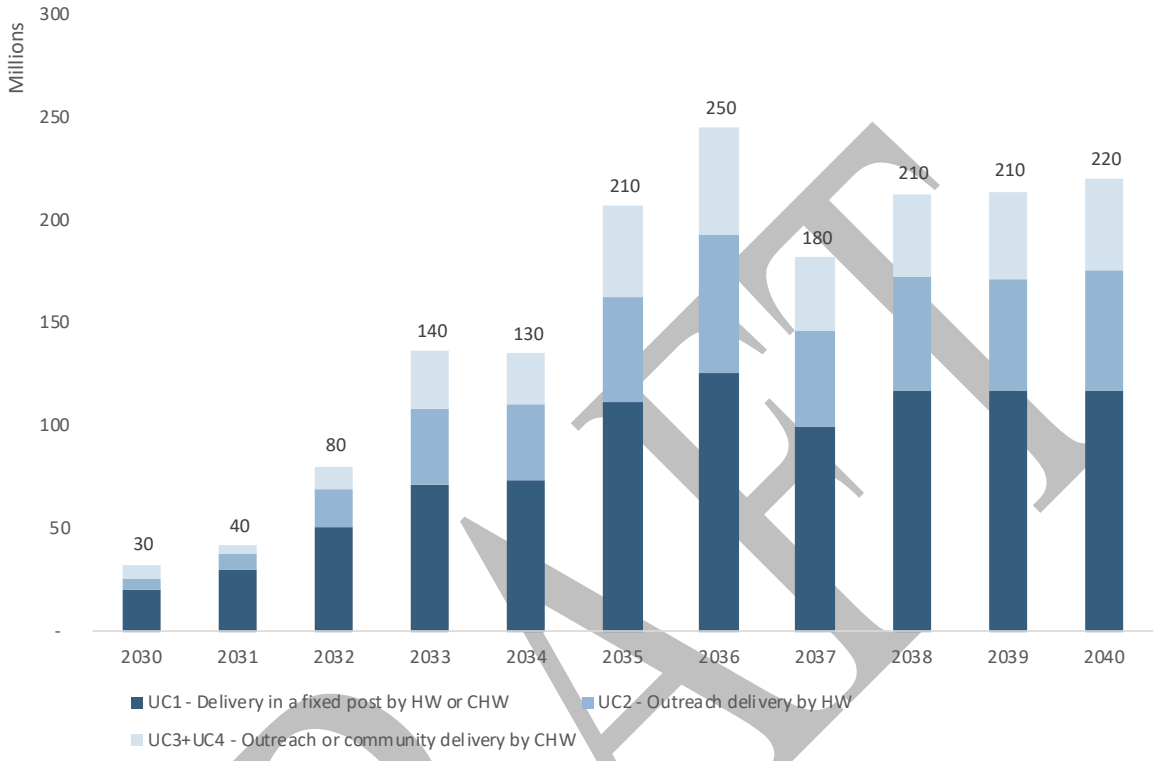
DRAFT

Figure 3: Estimated Global MR-MAP PDR – by country group, between 2030-2040. MR: measles and rubella; MAP: microarray patches; PDR: programmatic doses required; SEAR: WHO South East Asia Region; WPR: WHO Western Pacific Region; AFR: WHO African Region; EMR: WHO Eastern Mediterranean Region; MMR: measles, mumps, rubella; MMRV: measles, mumps, rubella, varicella; SIA: supplementary immunization activities.



720 **Figure 4: Estimated global PDR for MR-MAPs from 2030 to 2040 by UC.** PDR:
721 programmatic doses required; MR: measles and rubella; MAPs: microarray patches; UC:
722 use case; HW: health worker; CHW: community health worker.

723



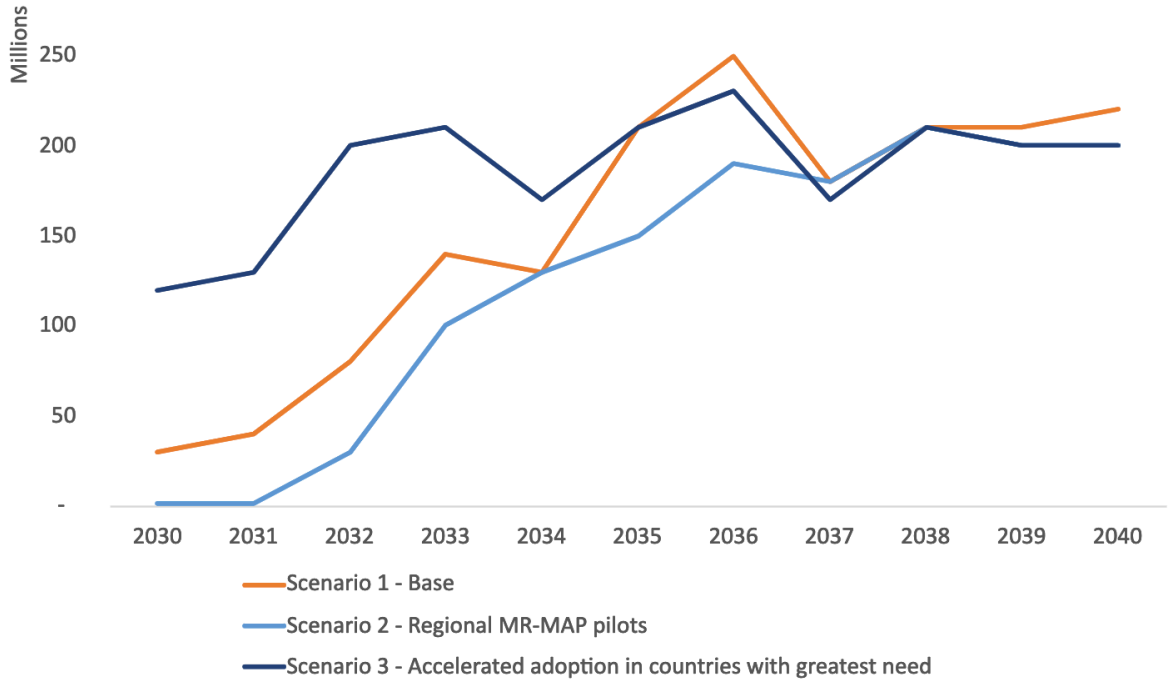
724

725

DRAFT

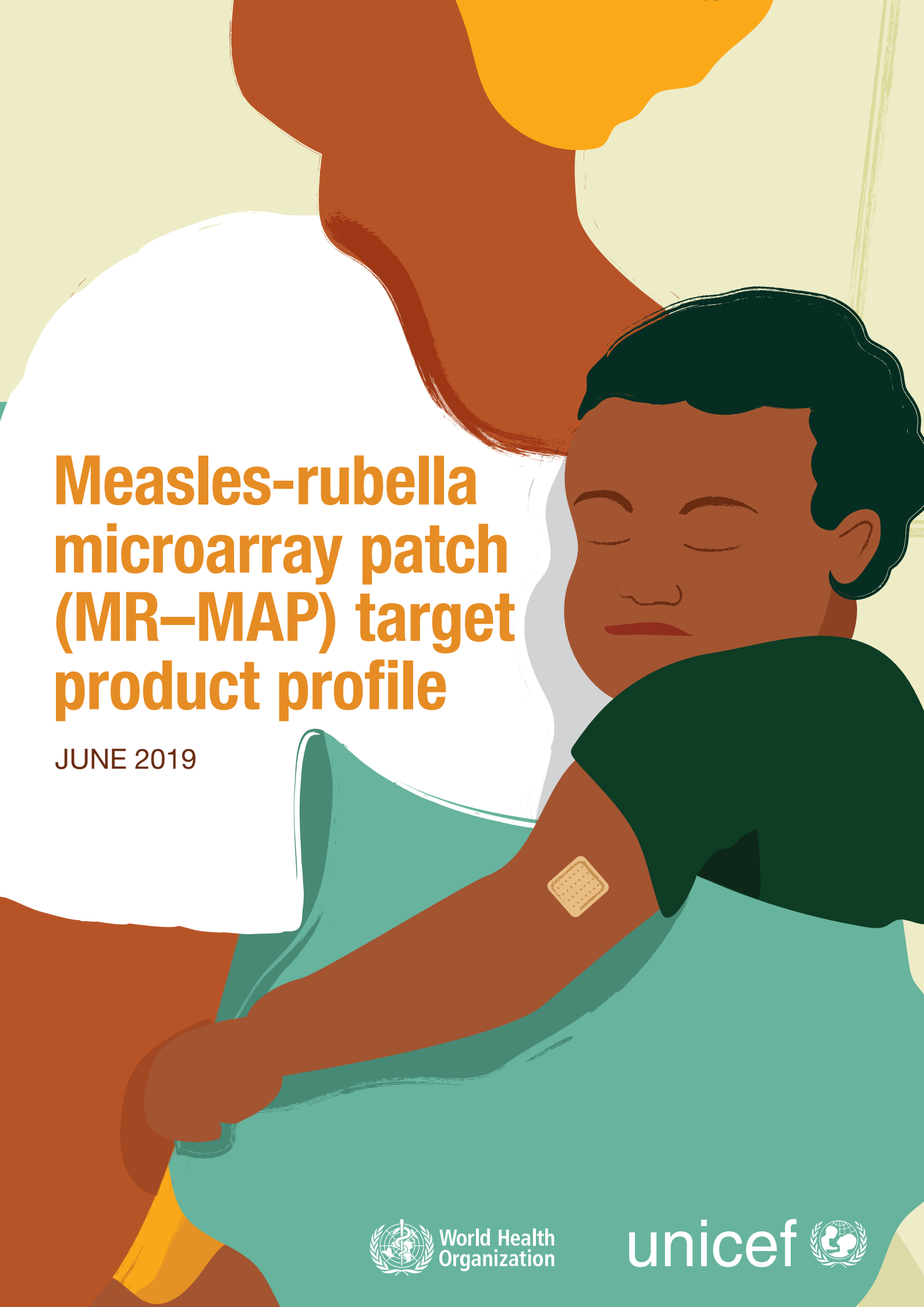
726 **Figure 5: Comparison of global MR-MAP PDR by scenario, between 2030-2040.** PDR:
727 programmatic doses required; MR: measles and rubella; MAPs: microarray patches.

728



729

DRAFT



Measles-rubella microarray patch (MR–MAP) target product profile

JUNE 2019

World Health Organization

unicef

Measles-rubella microarray patch (MR–MAP) target product profile

JUNE 2019

World Health Organization

unicef

Measles-rubella microarray patch (MR–MAP) target product profile

ISBN 978-92-4-000020-9 (WHO)

© World Health Organization and the United Nations Children's Fund (UNICEF), 2020

This joint report reflects the activities of the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF).

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; https://creativecommons.org/licenses/by-nc-sa/3.0/igo).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO or UNICEF endorses any specific organization, products or services. The unauthorized use of the WHO or UNICEF names or logos is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO) or the United Nations Children's Fund (UNICEF). Neither WHO nor UNICEF are responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization (http://www.wipo.int/amc/en/mediation/rules).

Suggested citation. Measles-rubella microarray patch (MR–MAP) target product profile. Geneva: World Health Organization and the United Nations Children's Fund (UNICEF), 2020. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see http://www.who.int/about/licensing.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO or UNICEF concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO or UNICEF in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO and UNICEF to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO or UNICEF be liable for damages arising from its use.

Design and layout by Lushomo www.lushomo.net

Printed in Switzerland.

Contents

Contents iii

Preface iv

Acknowledgements v

Abbreviations vi

1. Introduction 1

2. General considerations for an mr vaccine delivered by MAPs 2
- Indication 2
- Use-case scenarios 2
- Dose regimen and schedule 3
- Formulation 3
- Presentation 3

3. Generic product characteristics for an MR vaccine on solid coated or in dissolvable MAPs 4
- Target population 4
- Target countries 4
- Safety 5
- Immunogenicity 5
- Stability 6
- Vaccine vial monitors (VVM) 6
- Dosage 7

4. Generic product characteristics for MAPs for delivery of MR vaccines 8
- Product registration path 8
- Dose presentation 8
- Primary and secondary packaging 9
- Tertiary packaging 9
- Labelling 9
- Route of administration 10
- Human factors (HF) 10
- Application 10
- User training requirements 11
- Delivery time: time required to apply the map 11
- Wear time: minimal time that the map must be worn for the entire dose of the vaccine to be successfully delivered 11
- Delivery: indication of a successful vaccination 12
- Delivery: application site 12
- Reactogenicity 12
- Cost per immunized child 13
- Disposal 13

Preface

This target product profile (TPP) describes the minimal and optimal product characteristics for a measles and rubella (MR) microarray patch (MAP) vaccine, with a particular focus on delivery considerations for low- and middle-income countries (LMICs). It is intended to inform MAP developers, vaccine developers, procurement agencies and funders on MR–MAP research and public health priorities, and to facilitate the most expeditious development of MR–MAP candidates that would address the greatest and most urgent public health need in LMICs.

The document is based on an initial MR–MAP TPP developed by PATH and the World Health Organization (WHO) in 2016. It has been updated following input from a WHO working group of independent subject matter experts from diverse areas of expertise, including epidemiology, immunology, manufacturing and clinical development, regulatory affairs, health economics and policy. Specific aspects of the TPP were refined through consultations with various immunization stakeholders including the Immunization Practices Advisory Committee (IPAC) and the TechNet-21 community.

A draft was disseminated widely for public consultation in December 2018 among relevant stakeholders including MAP developers and vaccine manufacturers. The comments received were reviewed by the WHO MR–MAP working group and, where appropriate, incorporated into the TPP. This updated version is endorsed by the United Nations Children's Fund (UNICEF) and co-published with WHO.

While this document contains assumptions concerning regulatory considerations to help frame the rationale for the proposed characteristics, this TPP should not be considered as a regulatory document. The TPP will be updated as product development of MAP technology evolves, or as other changes in the identified need or research and development landscape emerge.

The document is divided into three major sections:

1. General considerations comparing the attributes of an MR vaccine delivered by MAP with those of the current, lyophilized MR vaccine;

2. Generic product characteristics for an MR vaccine on solid coated or dissolvable MAPs; and

3. Generic product characteristics for MAPs for delivery of MR vaccines.

Sections 2 and 3 describe the minimally acceptable and optimal targets for MR–MAP product attributes. However, these attributes are not currently listed in order of priority or importance; should an MR–MAP profile be sufficiently superior to the minimal characteristics under one or more categories, this may outweigh deficiencies in meeting a specific minimal characteristic in the suitability of product procurement.

The primary target audience for this TPP is any entity intending to develop a vaccine for national immunization programme use, including in low resource settings, and eventually to seek WHO prequalification and UNICEF procurement following licensure of its product. However, it is important to note that while this TPP defines aspirational goals for MR–MAP vaccine attributes, it does not supersede the evidence-based assessment by WHO's Strategic Advisory Group of Experts on Immunization (SAGE) for policy recommendation on use; other existing WHO guidance on vaccine development or prequalification; or assessments conducted by national regulatory authorities (NRAs), the European Medicines Agency (EMA), or the United States Food & Drug Administration (FDA).

Acknowledgements

The Department of Immunization, Vaccines and Biologicals at WHO, and UNICEF would like to thank the many individuals who contributed to the development of this document. Particular appreciation is extended to the members of the WHO MR–MAP working group for their assistance with drafting and review: Jean-Pierre Amorij, UNICEF focal point, Copenhagen, Denmark; Robin Biellik, Consultant, Lausanne, Switzerland, chair of the Programmatic Suitability for Prequalification (PSPQ) Steering Committee; Shanda Boyle, Consultant, Seattle WA, United States of America (USA); David Durrheim, University of Newcastle, Newcastle, Australia; Michael J. Free, Consultant and member of IPAC, Seattle WA, USA; Birgitte Giersing, WHO focal point, MR–MAP working group coordinator, secretariat of the WHO Product Development for Vaccines Advisory Committee (PDVAC), Geneva, Switzerland; Mateusz Hasso-Agopsowicz, WHO, Geneva, Switzerland; Katrina Kretsinger, WHO, Geneva, Switzerland; Martin I. Meltzer, United States Centers for Disease Control and Prevention (CDC), Atlanta GA, USA; William Moss, Johns Hopkins University, Baltimore MD, USA; Mark Papania, CDC, Atlanta GA, USA (PDVAC member); Nicolas Peyraud, Médecins sans Frontières, Geneva, Switzerland; Pieter Neels, Consultant, Antwerp, Belgium; David Robinson, Bill & Melinda Gates Foundation, Seattle WA, USA; James M. Robinson, Consultant, St Augustine FL, USA; Marian Wentworth, Management Sciences for Health, Arlington VA, USA (PDVAC member); Darin Zehrung, PATH, Seattle WA, USA.

We would also like to extend our thanks to Marion Gruber, United States Food and Drug Administration (US FDA), members of IPAC for their review and input, as well as the many individuals and institutions who provided comments on the draft at the public consultation stage.

Abbreviations

$CCID_{50}$	50% cell culture infectious dose
COGS	cost of goods sold
CTC	controlled temperature chain
EMA	European Medicines Agency
gPPP	generic Preferred Product Profile
HCW	health care worker
HF	human factors
ID	intradermal
IPAC	Immunization Practices Advisory Committee
IQR	inter-quartile range
LMIC	low- and middle-income countries
MAP	microarray patch
MCV1	measles-containing vaccine first dose
MCV2	measles-containing vaccine second dose
MMR	measles–mumps–rubella
MMRV	measles–mumps–rubella-varicella
MR	measles–rubella
NRA	national regulatory authority
NS	needle and syringe
ORI	outbreak response immunization
PDVAC	Product Development for Vaccines Advisory Committee
PQ	prequalified
PSPQ	Programmatic Suitability for Prequalification
PTTI	peak temperature threshold indicator
RI	routine immunization
SAGE	Strategic Advisory Group of Experts on Immunization
SC	subcutaneous
SIAs	supplementary immunization activities
$TCID_{50}$	50% tissue culture infective dose
TPP	target product profile
UNICEF	United Nations Children's Fund
VPPAG	Vaccine Presentation and Packaging Advisory Group
VVM	vaccine vial monitor
VVM–TI	vaccine vial monitor with an integrated threshold indicator
WHO	World Health Organization

1. Introduction

The potentially favourable product attributes of microarray patches (MAPs, also known as microneedle patches) render them of considerable interest for delivery of measles–rubella (MR) vaccines, particularly within low- and middle-income countries (LMICs). MAPs possess perceived operational advantages that could ultimately increase equitable coverage and facilitate vaccine administration in inaccessible areas, especially if they contain thermostable vaccine. The MR–MAP would constitute a new vaccine product, based on a potentially disruptive technology (i.e. an innovation that creates demand, eventually disrupting an existing market). For this reason, the product attributes of MR–MAPs need to be competitive with those of existing licensed MR vaccines that require a stringent end-to-end cold chain, reconstitution followed by storage in the dark at 2-8°C and administration with an auto-disable (AD) needle and syringe (NS)[1] by a trained health care worker (HCW).

In order to rationalize the product development, procurement and introduction costs that will be required for implementation, MR–MAPs should have all or some of the following properties, in addition to comparable safety and equivalent immunogenicity with a currently prequalified (PQ) MR vaccine: less costly to deliver (thermostable, small footprint, administered with minimal instruction); easier and safer to administer (remove the need for and risks associated with reconstitution); easier to dispose of (free of sharps); and be considered acceptable by recipients and vaccinators (pain- and/or needle-free).

The following is a target product profile for a MAP presentation based on dry vaccine formulations of a live-attenuated MR vaccine. It articulates preferences for both solid coated and dissolvable microneedle formats but is not relevant for hollow microneedle arrays intended to deliver liquid or reconstituted vaccines. Delivery of combination MR vaccines has been identified as a priority public health use case for MAPs, to help achieve the measles and rubella elimination targets set by the Global Vaccine Action Plan.[2] The MR combination was selected for the likelihood that it will be used widely by the time that MR–MAP products are expected to be available for programmatic use in LMICs in the late 2020s.

[1] World Health Organization, United Nations Children's Fund, United Nations Population Fund. Safety of injections: WHO-UNICEF-UNFPA joint statement on the use of auto-disable syringes in immunization services. Geneva: World Health Organization; 2003.
[2] Global vaccine action plan 2011–2020. Geneva: World Health Organization; 2013.

2. General considerations for an MR vaccine delivered by MAPs

Indication

Current, lyophilized MR vaccine

Prophylactic vaccination against both measles and rubella virus infection of susceptible infants, children, adolescents and adults.

Guidance for MR–MAP

Same as for the currently lyophilized MR vaccine.

Notes: Measles–mumps–rubella (MMR) or measles–mumps–rubella–varicella (MMRV) vaccines are typically delivered as measles-containing vaccines for high-income countries, but these vaccine combinations are unlikely to be widely used in low-income countries.

Use-case scenarios

Current, lyophilized MR vaccine

For use in routine immunization (RI) service delivery, supplementary immunization activities (SIAs), outbreak response immunization (ORI) and vaccine stockpiling of MR vaccine.

Guidance for MR–MAP

Same as for the currently lyophilized MR vaccine. In addition, with its potential ease of use and improved thermostability profile, MR–MAP could be used in "house-to-house" campaigns and temporary or fixed post sites, potentially enlisting an expanded cadre of vaccinators.

Notes: The WHO position paper states that *all children with 2 appropriately timed doses of measles vaccine should be the standard for all national immunization programmes. Countries aiming at measles elimination should achieve ≥95% coverage with both doses equitably to all children in every district (regardless of measles-containing vaccine first dose (MCV1) coverage rates).*[3]

To reach this goal, countries should take all measures to increase delivery of two doses of MCV through routine services. In addition, SIAs in a variety of targeted age groups are utilized in most LMICs, in addition to vaccination offered through RI.

MR–MAPs are ideally suited for delivery through RI, SIAs and ORI due to ease of use. MR–MAPs have a strong comparative advantage in the context of weak health systems such as fragile and rural/remote settings, and nomadic and urban poor populations. In situations without health support, such as refugee camps and post-disaster communities, in which trained HCW may not be available, the potential for vaccine administration by community health volunteers becomes essential.

In certain settings, nationwide immunization campaigns may not be programmatically efficient, cost-effective or feasible (e.g. due to variations in subnational RI coverage, civil unrest, political instability, or financial constraints) and targeted subnational SIAs may be implemented to reduce the accumulation of susceptible individuals. The number of doses administered in national or subnational SIA settings is dependent on the coverage of MCV1 and measles-containing vaccines second dose (MCV2) achieved through routine immunization; thus, projections are possible for different RI performance scenarios.

[3] Measles vaccines: WHO position paper. Wkly Epidemiol Rec. 2017;92(17):205–27.

Dose regimen and schedule

Current, lyophilized MR vaccine

First dose (MCV1): aged 9 months and above.

Second dose (MCV2): ideally delivered at 15–18 months, or in accordance with WHO recommended schedules.

The minimal interval between MCV1 and MCV2 is 4 weeks.[3]

Children as young as 6 months may receive a dose of MCV in special circumstances[3] (called MCV0 and not counted toward the two recommended doses).

All commercially available live attenuated measles vaccines, either as monovalent vaccine or in combination with rubella, mumps, or varicella vaccines, or some combination of these, can be used interchangeably to protect against measles.[3]

Guidance for MR–MAP

Same as for the currently lyophilized MR vaccine.

MR–MAP may be used interchangeably with currently available measles and rubella vaccine.

Notes: MR–MAP requires safety data from 9 months of age, and data to demonstrate a short-interval repeat dosing (i.e. 4 weeks between doses) is acceptable providing the immunogenicity is comparable with conventional vaccines.

For more information on inclusion of additional age groups, please refer to the "Target Population" in section 3.

As for the current vaccine, MR–MAP vaccines should be able to be co-administered at different anatomical sites and with other vaccines including Japanese encephalitis, yellow fever, DTP-containing vaccines, meningococcal vaccine, hepatitis B, inactivated poliovirus, Haemophilus influenzae type b conjugate vaccine, and pneumococcal vaccines.[3]

Formulation

Current, lyophilized MR vaccine

Formulation contains MR vaccine as the active ingredient. Current formulation requires an end-to-end cold chain and reconstitution at the point of use.

Guidance for MR–MAP

Additional or alternative excipients/additives might be needed depending on MAP format (solid coated or dissolvable), particularly to improve thermostability and light sensitivity.

Notes: It will be imperative that MR–MAPs are compliant with relevant quality and manufacturing attributes to ensure safety, quality and efficacy as well as programmatic suitability. These will be defined during development of the product and assessed by regulatory experts to ensure license of the products.[4] All the necessary excipients/additives/stabilizers would be evaluated as part of the final formulation, to be approved for parenteral administration and within the acceptable limits.

Presentation

Current, lyophilized MR vaccine

Current presentation consists of multi-dose vial of lyophilized MR vaccine that must be stored at 2–8°C. It is reconstituted with diluent prior to injection and stored in the dark at 2–8°C for up to 6 hours before discarding.

Guidance for MR–MAP

A single dose presentation, composed of an integrated MR-vaccine delivery device in which MR vaccine is presented as a solid coated or dissolvable microarray format.

Notes: Because of the possible dose-sparing advantages of MAPs for intradermal (ID) delivery, there is the potential for a reduced dose of virus compared to current MR doses.[5] This will be based on confirmed non-inferiority studies of immune response with supporting evidence of virus replication after MR–MAP delivery. It should be noted, however, that to date, there are no data from studies in humans or non-human primates to suggest that ID or MAP delivery of measles or rubella vaccine results in dose-sparing.[6–8]

[4] Requirements for measles, mumps and rubella vaccines and combined vaccines (live). In: WHO Expert Committee on Biological Standardization: forty-third report. Geneva: World Health Organization; 1994: Annex 3 (WHO Technical Report Series, No. 840).

[5] Moon S et al. Dose sparing and enhanced immunogenicity of inactivated rotavirus vaccine administered by skin vaccination using a microneedle patch. Vaccine.2013;doi:10.1016/j.vaccine.2012.11.027.

[6] Cutts FT, Clements CJ, Bennett JV. Alternative routes of measles immunization: a review. Biologicals. 1997;doi:10.1006/biol.1997.0103.

[7] Edens C, Collins ML, Goodson J L, Rota PA, Prausnitz MR. A microneedle patch containing measles vaccine is immunogenic in non-human primates. Vaccine 2015;doi:10.1016/j.vaccine.2015.02.074.

[8] Joyce JC et al. A microneedle patch for measles and rubella vaccination is immunogenic and protective in infant rhesus macaques. J Infect Dis.

3. Generic product characteristics for an MR vaccine on solid coated or in dissolvable MAPs

Two targets (minimally acceptable and optimal) have been assigned for each of the following MR–MAP attributes, according to the current understanding and development status of this technology.

- Minimally acceptable target: This case represents the "should meet" requirements necessary for suitability of the MAP technology within current MR delivery settings in LMICs. If these criteria are not met, the MR–MAP technology is likely to be considered unsuitable for programmatic delivery of MR vaccine.
- Optimal target: This case represents the "should aim for" recommendations. The criteria represent a potential scenario that would be a significant improvement over the current presentation of lyophilized multi-dose vials that require administration by a trained HCW, resulting in a quantifiable reduction in total systems cost and increased reach of the MR–MAP vaccine.

Target population

Minimally acceptable target

Routine Immunization: infants aged from 9 months for the first dose, and at least 1 month later for the second dose.

Campaigns (i.e. SIAs and ORIs): children aged 9 months and above, adolescents and adults at risk.

Optimal target

Same as minimal, with the addition of infants aged 6–9 months, if supported by effectiveness data post-licensure.

Notes: WHO recommends that in countries with ongoing transmission in which the risk of measles mortality among infants remains high, MCV1 is administered at 9 months of age, with the routine dose of MCV2 at age 15–18 months.

WHO recommendations, unless otherwise stated, are global, and based on epidemiological analysis that may target wide age groups, such as adolescents and susceptible adults, that are beyond the current age range targeted by funding agencies. Thus, the target population is not restricted to infant/child age groups but includes all susceptible individuals above 9 months of age.

For MCV0 recommendation, see "dose regimen and schedule" in section two. Immunogenicity and safety data in 6 month-old infants immunized with MR–MAPs should be collected as part of post-licensure studies to support a licence indication in this population; however, preclinical data suggest that maternal antibodies in infant rhesus macaques cannot be overcome by MR–MAP administration.[9]

Target countries

Minimally acceptable target

All countries currently providing MR vaccines.

Optimal target

Availability and use of MR–MAP in all countries, including those where MMR and MMRV are recommended.

Notes: According to the Global Measles and Rubella Strategic Plan: 2012–2020,[10] all six WHO regions have committed to measles elimination, four of which have also set rubella control or elimination targets.

Countries using MR or MMR in their national schedule should use the combined vaccine rather than measles-only formulations in all children, including those aged 6 months to <1 year.[11]

Ideally, the MAP manufacturing platform would support production of MCV for the global market (i.e. including MMR and MMRV vaccines).

[9] Joyce JC et al. A microneedle patch for measles and rubella vaccination is immunogenic and protective in infant rhesus macaques. J Infect Dis. 2018;doi:10.1093/infdis/jiy139.
[10] Global measles and rubella strategic plan 2012–2020. Geneva: World Health Organization; 2012.
[11] Measles vaccines: WHO position paper. Wkly Epidemiol Rec. 2017;92(17):205–27.

Safety

Minimally acceptable target

Adverse events should be no more serious than those of the current NS delivery using the subcutaneous (SC) route.

Optimal target

Adverse events should be less frequent and less serious than those for current NS MR vaccination using the SC route.

Notes: The safety of MR–MAPs would need to be established in prelicensure safety studies in the target population for whom this product is indicated. With the current MR vaccine, adverse reactions following measles vaccination are generally mild and transient. Within 24 hours of vaccination, vaccine recipients may experience sensation and tenderness at the site of injection, which usually resolve in 2–3 days. Approximately 7–12 days after vaccination, systemic reactions occur in about 5–15% of recipients including fever of >39 °C for 1–2 days. A transient rash may occur in about 2% of recipients. Adverse events, with the exception of anaphylactic reactions, are less likely to occur after MCV2 vaccination.

The application of a dissolvable MAP coated with an inactivated influenza vaccine resulted in a mild and transient reactogenicity, mostly reported as tenderness (66% recipients), erythema (40% recipients), and pruritus (82% recipients), lasting on average between 2-3 days. Of participants scored, 80% indicated they experienced no pain.[12] No serious adverse events have been recorded with MAP vaccine delivery to date, but few vaccine delivery studies have been undertaken (refer also to the reactogenicity paragraph in section 4).

Risks related to reconstitution with wrong, or incorrect use of diluents will be eliminated, and risks related to other types of operational errors should be reduced.

Immunogenicity

Minimally acceptable target

Seroconversion rates should be non-inferior to a currently prequalified SC MR vaccination when given at 9 or10 months of age (reported seroconversion 92.2%, inter-quartile range (IQR) 84–96).[13]

Optimal target

Same as minimal target.

Notes: Antibodies to H and F measles proteins contribute to virus neutralization and are the best correlates of protection against measles virus infection. The presence of neutralizing antibodies demonstrated by appropriate standardized serologic assays and validated by WHO is considered the most reliable correlate of protection (protective level, >120 IU/mL).[14] Other assays such as commercial enzyme immunoassay (EIA) kits have been used previously to measure immunogenicity.[15] The choice of assay will need to be agreed with the relevant NRA.

Non-inferiority should be demonstrated in comparison to the immune response with NS administered vaccine. The 5% margin has been used previously in a non-inferiority trial of an aerosolized measles vaccine.[16] However, the appropriate non-inferiority margin needs to be selected in consultation with regulatory agencies, and the established seroconversion rate of the licensed SC vaccine considered,[13] as well as statistical analysis and clinical judgement in accordance with established protocols.[17,18]

Frequently cited figures show that 89.6% (IQR 82–95) of children seroconvert when vaccinated at 8–9 months of age; 92.2% (IQR 59–100) seroconvert when vaccinated at 9–10 months of age; and 99% (IQR 95.7–100) of children seroconvert when vaccinated at 11–12 months of age.[13]

In a review of field studies, rubella vaccination induced a seroconversion rate of >95% after a single dose in susceptible individuals aged 12 months and older.[19]

[12] Rouphael NG, Paine M, Mosley R, Henry S, McAllister D V., Kalluri H, et al. The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch (TIV-MNP 2015): a randomised, partly blinded, placebo-controlled, phase 1 trial. Lancet 2017. doi:10.1016/S0140-6736(17)30575-5.
[13] The immunological basis for immunization: measles. Geneva: World Health Organization; 2009.
[14] Chen RT et al. Measles antibody: reevaluation of protective titers. J. Infect. Dis. 1990:doi:10.1093/infdis/162.5.1036.
[15] Wiedmann RT et al. M-M-R®II manufactured using recombinant human albumin (rHA) and M-M-R®II manufactured using human serum albumin (HSA) exhibit similar safety and immunogenicity profiles when administered as a 2-dose regimen to h. Vaccine. 2015;doi:10.1016/j.vaccine.2015.03.017.
[16] Low N et al. A randomized, controlled trial of an aerosolized vaccine against measles. N Engl J Med. 2015;372:1519–29.
[17] Guideline on the choice of the non-inferiority margin. Brussels: European Medicines Agency; 2005.
[18] Center for Drug Evaluation and Research. Non-inferiority clinical trials to establish effectiveness: FDA guidance. Washington (DC): United States Food and Drug Administration; 2016.
[19] Rubella vaccines: WHO position paper. Geneva: World Health Organization; 2011

Stability

Minimally acceptable target

Vaccine potency stability profiles should be superior to current MR vaccine stability, i.e. vaccine vial monitor 14 (VVM14) when stored at 2–8°C (24 months), and must be amenable to controlled temperature chain (CTC), i.e. a single excursion for at least 3 days at 40°C.[20]

Optimal target

Stability profiles should have enhanced thermostability, i.e. use under CTC conditions for at least 2 months.[21,22]

Shelf life to be longer than 24 months at 2–8°C, particularly if to be considered for stockpiling.

MR–MAP should offer improved storage conditions over current MR vaccine requirements.

Doses should be formulated to prevent risk of damage from freezing.

Notes: Stability condition definitions:

Condition	Temperature	Stability timeline minimum
Full cold chain ("shelf life")	2–8ºC	24 months
CTC	At least 40ºC	≥ 3 days, 2 months preferred

CTC applies to vaccines capable of tolerating at least 40ºC for a minimum of 3 days prior to use, designated for use in campaign or special strategy settings, labelled with specific use conditions, and licensed for this use by the relevant regulatory authorities. Testing and validation of MR–MAP stability characteristics should be implemented according to WHO guidance on extended controlled temperature conditions (ECTC).[22] Based on assessment of common supply chain structures, up to 2 months thermostability would remove reliance on cold chain equipment and logistics at health posts and stocking of vaccines at unequipped facilities. This would also offer the potential for house-to-house delivery.[21,23] This target was proposed by immunization programme experts including IPAC members. However, the cold chain would still be required for the majority of other EPI vaccines at the current time.

Vaccine vial monitors (VVM)

Minimally acceptable target

Individual MR–MAPs should be labelled with an appropriate VVM.

Optimal target

Individual MR–MAPs should be labelled with an appropriate VVM and accompanied by a peak temperature threshold indicator (PTTI), or a VVM with an integrated threshold indicator (VVM–TI).

Notes: The creation of a new VVM type may be needed to fit the thermostability characteristics of the product if thermostability exceeds 30 days at 40°C.[24] VVM or VVM–TI should be placed on the primary packaging of the individual MR–MAP.

PTTI could accompany the vaccine or be placed on either primary or secondary packaging depending on the delivery strategy and microplanning.

[20] Controlled temperature chain: frequently asked questions. Geneva: World Health Organization; 2016 (www.who.int/immunization/programmes_systems/supply_chain/resources/CTC_FAQ_English_November_2016.pdf?ua=1, accessed 5 March 2019).
[21] Karp CL et al. Evaluating the value proposition for improving vaccine thermostability to increase vaccine impact in low and middle-income countries. Vaccine. 2015;doi:10.1016/j.vaccine.2015.05.071.
[22] Guidelines on the stability evaluation of vaccines for use under extended controlled temperature conditions. Geneva: World Health Organization; 2016.
[23] Kahn A-L, Kristensen D, Rao R. Extending supply chains and improving immunization coverage and equity through controlled temperature chain use of vaccines. Vaccine. 2017:doi:10.1016/j.vaccine.2016.10.091.
[24] What is VVM and how does it work? Geneva: World Health Organization; 2011.

Dosage

Minimally acceptable target

Target dosage should be defined by the quantity (i.e. virus potency on product release) of vaccine required to give a non-inferior immune response to the currently available injectable vaccine delivered in 0.5 mL by the SC route (≥ 1000 of 50% cell culture infectious dose ($CCID_{50}$) of each virus per dose) throughout projected shelf life of product.[25]

Optimal target

MR–MAP should require a reduced quantity (potency on product release) of active biologic ingredient compared with amount of active biologic ingredient contained in 0.5 mL of injectable MR vaccine without reduction in induced immunogenicity throughout projected shelf life of MR–MAP product.

Notes: Endpoint dilution assays such as the 50% tissue culture infective dose ($TCID_{50}$) or $CCID_{50}$ are used to measure the infectious virus titre. These assays measure the amount of virus required to kill 50% of inoculated tissue culture cells, and are recommended in the manufacturing process and production control for measles and rubella by WHO.[26]

WHO recommends a minimal potency for measles vaccine of 1000 viral infective units (3.0 log10 $TCID_{50}$). Vaccines with potencies between 3.0 and 4.6 log10 are considered to be standardtitre vaccines, and vaccines with potencies above 4.7 log10 are defined as high-titre vaccines.[26]

Measures of potency using methods other than $TCID_{50}$ are in development and may be considered as a future basis for licensure, subject to approval by relevant NRAs.

[25] Measles vaccines: WHO position paper. Wkly Epidemiol Rec. 2017;92(17):205–27.
[26] Requirements for measles, mumps and rubella vaccines and combined vaccines (live). In: WHO Expert Committee on Biological Standardization: forty-third report. Geneva: World Health Organization; 1994: Annex 3 (WHO Technical Report Series, No. 840).

4. Generic product characteristics for MAPs for delivery of MR vaccines

Product registration path

Minimally acceptable target

Following licensure by a WHO listed authority, MR–MAPs should be eligible for prequalification by WHO; and should comply with its programmatic suitability for prequalification (PSPQ) guidelines.

Optimal target

Same as minimal target.

Notes: MR–MAPs would be considered a novel vaccine product and need to be evaluated for regulatory approval.

WHO PQ would be needed for UNICEF procurement of MR–MAPs. The PQ process would include discussion with a relevant WHO listed authority and the Standing Committee on PSPQ, as the MAP vaccine product would fall into the category of 'unique' characteristics.[27]

Article 58 of Medicines for use outside the European Union,[28] including vaccines, aims to facilitate patient access to essential medicines in LMICs, including new or improved therapies for unmet medical needs, which are intended to prevent or treat diseases of major public health interest. The procedure combines EMA's scientific review capabilities with the local epidemiology and disease expertise of WHO and national regulators in the target countries, to provide a unique development and assessment pathway.

Experience with some analogous technologies (such as transdermal patches with small or large molecule non-vaccine medicines) may be useful for drafting initial regulatory guidelines.

Dose presentation

Minimally acceptable target

Product should be provided in an integrated (vaccine and patch combination) single dose, single-use (disposable) MAP format.

Optimal target

Same as minimal target. The size of MR–MAP should be driven by the minimal surface required to achieve the optimal antigen dose.

Notes: MR–MAPs do not require diluent nor the step of vaccine reconstitution. Relevant MAP formats are either dissolvable or vaccine coated onto a solid or porous substrate.

[27] Joyce JC et al. A microneedle patch for measles and rubella vaccination is immunogenic and protective in infant rhesus macaques. J Infect Dis. 2018;doi:10.1093/infdis/jiy139.

[28] Medicines for use outside the European Union. Brussels: European Medicines Agency; 2015 (www.ema.europa.eu/en/human-regulatory/marketing-authorisation/medicines-use-outside-european-union).

Primary and secondary packaging

Minimally acceptable target

Primary packaging (in direct contact with vaccine) should seclude patch projections to prevent intervention resulting in damage and/or contamination of projections during shipping and storage.

For patches that require storage at 2–8°C: product should be contained within suitable secondary packaging compatible with the immunization supply chain, with a cold-chain storage volume per dose no greater than a single dose vial of injectable MR vaccine (21.09 cm^3).

Optimal target

Primary package requirements same as the minimal target.

For patches that require storage at 2–8°C: product should be contained within suitable secondary packaging that is compatible with the immunization supply chain and require less cold-chain storage volume per dose than a 10-dose vial of injectable MR vaccine (2.11 cm^3).

Notes: Suitable secondary packaging for MR–MAPs will protect them against damage, moisture transfer, and sunlight exposure if deemed necessary. If the patches require an applicator (single use or re-usable), it should be integrated or shipped together with the patches, and ideally not in the cold chain.

Secondary packaging configuration should minimize volume, weight and the need to repackage for in-country distribution, as defined by the Vaccine Presentation and Packaging Advisory Group's (VPPAG) generic Preferred Product Profile (gPPP) for vaccines.[29]

Current packing vial volumes per dose:[30]

Storage volume of single dose vaccine (diluent)	Comparison MR product
2.11 cm^3 (3.14 cm^3)	10-dose glass vial
4.22 cm^3 (5.48 cm^3)	5-dose glass vial
21.09 cm^3 (12.53 cm^3)	1-dose glass vial

Note: Diluent is not stored in the cold chain but is to be kept cool. Currently, UNICEF only supplies 5- and 10-dose vials, as countries have not expressed a preference for smaller presentation volumes. For patches that do not require cold storage, comparator volume for total packaging (CTC and out of cold chain) is vaccine vial with diluent (33.62 cm^3) + syringe (~60 cm^3).

Secondary packaging that allows the vaccinator to visualize the number of remaining doses should be considered.

Tertiary packaging

Minimally acceptable target

Product should be contained within suitable tertiary packaging that is compatible with the existing immunization supply chain.

Optimal target

Same as minimal target.

Notes: Tertiary packaging should comply with the VPPAG's gPPP recommendations. Compatible packaging is defined as that which minimizes weight and volume and limits the need for repackaging for in-country supply chain distribution.[29]

Labelling

Minimally acceptable target

Primary container labelling should meet recommendations outlined by the VPPAG's gPPP for vaccines, and WHO's PSPQ guidelines as outlined by the Committee on Biological Standardization (ECBS).

Optimal target

Same as minimal target.

Notes: The VPPAG's gPPP for vaccines outlines recommendations for minimal labelling content, conventions and font. If CTC is indicated, additional labelling is required (see section 3, Vaccine Vial Monitors). MAPs can be labelled on their primary package (e.g. foil pouch) as well as on the secondary packaging (e.g. carton).

[29] Generic preferred product profile for vaccines. Geneva: World Health Organization; 2015.
[30] WHO prequalified vaccines [Extranet]. Geneva: World Health Organization.

Route of administration

Minimally acceptable target

Product should be suitable for delivery to dermis or epidermis in an anatomic site that is acceptable to immunization programmes.

Optimal target

Same as minimal target.

Administration should not result in visible external serum leakage onto a disposable component.

Notes: The term ID has been used for the delivery route and target tissue for MR–MAPs. Some patches might deliver primarily ID, but others might deliver to both the epidermis and dermis. There are insufficient data to specify the optimal depth or target tissue within the skin.

Human factors (HF)

Minimally acceptable target

A summative usability evaluation must demonstrate that safety-related use errors related to the device, applicator (if needed), labelling, and training have been identified and mitigated.

Optimal target

Same as minimal target.

Notes: For intended users and the scenarios of use for MR–MAP (section 2, Use–Case Scenarios), HF of the device must be assessed in the relevant target population (children and adults) and geography. The usability engineering process in IEC 62366-1:2015 Medical devices – Part 1: Application of usability engineering to medical devices should be followed in order to verify and validate the final MR–MAP design and applicator (if required for use). This includes establishing a usability engineering file. HF principles outlined in ANSI/AAMI HE75 Human factors engineering – Design of medical devices should be adhered to. Key components of HF for an MR–MAP are described in other sections of this TPP, including labelling, packaging, user training requirements, application site, delivery time, wear time, applicator, indication of successful vaccination, and disposal.

Application

Minimally acceptable target

MAP delivery requires a single-use applicator (while maintaining compliance with packaging requirements).

Applicator (if required) should fixate to the skin and provide an impact for penetration. Minimal force to be required for the application reproducibly ensuring complete delivery.

Any patient-contact surfaces of an applicator should be disposable to prevent cross-contamination among vaccinees.

Optimal target

MAP should be able to be delivered onto the skin consistently and successfully without the need for a separate applicator.

Notes: If an applicator is required, packaging the applicator(s) and MAPs together, or integrating them, would be preferable from a usability and logistics perspective, provided this has no unacceptable negative impact on cost or cold chain storage volume.

User training requirements

Minimally acceptable target

Minimal device training is required; HCW or trained lay health worker with printed instructions should be able to administer MAP correctly after minimal training.

Optimal target

No device training required; HCW, trained lay health worker or caregiver should be able to administer MR–MAP correctly using printed pictorial instructions.

Notes: Some studies have shown that people with minimal training can apply MAPs.[31,32] Ideally, MR–MAPs are to be used by minimally trained HCWs in routine vaccination settings or by lay health workers with printed instructions in campaign settings after training. The MR–MAP should be simple, intuitive, and easy enough to use in clinic-based or outreach vaccination settings since it is expected that MAPs will be used in both rural and urban settings (particularly in fragile contexts in low-resource settings).

Printed instructions must be made available in at least one of the recognized languages of the destination country, pre-tested for comprehension, and revised as needed.

Delivery time: time required to apply the MAP

Minimally acceptable target

For SIAs, total time for delivery of one MR–MAP should be comparable to that of one SC MR injection with NS, including time for reconstitution from a vial.

For routine settings, delivery time should be acceptable to the immunization system in question (informed by usability evidence).

Optimal target

For SIAs, total time for delivery of 10 MR–MAPs should be comparable to that of 10 SC MR injections, including time for reconstitution from a 10-dose vial.

Notes: "Total delivery time" consists of preparation and administration. Because MR- MAPs are to be used in both routine activities and SIAs, decreasing the time required to deliver each dose would have a significant impact on overall programme logistics and capacity.

Preparation and application of MAP should be comparable to the estimated time required for reconstitution and delivery of a lyophilized vaccine from a 10-dose vial in routine settings (approximately 70 seconds for reconstitution and delivery of the first dose and 20 seconds for each subsequent dose; after the assessment of the vaccinee and vaccine-related paperwork).[33]

Wear time: minimal time that the MAP must be worn for the entire dose of the vaccine to be successfully delivered

Minimally acceptable target

Up to 5 minutes, under observation, before removal of MAP by HCW, trained lay health worker or caregiver.

Optimal target

Less than 1 minute, under observation, before removal of MAP by HCW, trained lay health worker or caregiver.

Notes: Specifying and monitoring acceptable "wear time" of the patch is likely to be critical to ensure effective immunization as some MAP technologies might require extended (and monitored) wear time after patch application for reliable antigen delivery: from seconds to several minutes. Wear time is determined by clinical studies to evaluate the immune response induced by the MR–MAP in the appropriate target groups; desirable and acceptable wear times have been solicited from experts in the immunization field, including members of IPAC. Operational research will be needed to determine the acceptable time in the context of MR–MAP RI and SIAs.

RI is often performed alongside other vaccinations and health interventions and so an extended wear time for the MR–MAP might not extend the total time per vaccinee. A wear time of up to 5 minutes is deemed acceptable, given the recommendation to observe vaccinees post vaccination (including those administered by NS).

Appropriate systems for verification of the 5-minute period will need to be established. As a general principle, reduction of MAP wear time should be prioritized by developers to further reduce the risk of removal by infants and toddlers. There should be minimal safety concerns associated with leaving the patch on for longer periods.

[31] Donnelly RF et al. Hydrogel-forming microneedle arrays can be effectively inserted in skin by self-application: a pilot study centred on pharmacist intervention and a patient information leaflet. Pharm Res. 2014;doi:10.1007/s11095-014-1301-y.
[32] Norman JJ et al. Microneedle patches: usability and acceptability for self-vaccination against influenza. Vaccine. 2014;doi:10.1016/j.vaccine.2014.01.076.
[33] Pentavalent Vaccine in the UnijectTM Injection System: A Time and Motion Study. Seattle WA: PATH; 2014.

Delivery: indication of a successful vaccination

Minimally acceptable target

The design should include at least one functional, auditory or visual cue during or after application of a single dose as an indicator of successful MAP application.

Optimal target

The design should include more than one functional, auditory or visual cue during or after application of a single dose as an indicator of successful MAP application.

Notes: The specific indicator for a successful vaccine delivery depends on the tolerance of the system for over- or under-application pressure and the subsequent effect on immunogenicity and adverse events. Some delivery systems might include a visual (such as patch colour change, dye transfer or intrinsic change in skin colour) or auditory or pressure cue (such as a click) for correct application. Note that the cue indicates the correct skin application (penetration) of the MAP but not necessarily confirmation of vaccine delivery, which depends on skin penetration and correct wear time.

Effectiveness of visual cues may be dependent on skin tone/ texture and end-user acceptability concerns with this method may need to be assessed.

Cue must only be able to be activated once per MAP; failure to activate the cue will indicate the MAP has already been used or the application process was faulty.

MR–MAPs that are integrated with an applicator for successful delivery are prevented from being repeatedly applied by an MR–MAP spring mechanism, i.e. once activated, they are disabled.

Delivery: application site

Minimally acceptable target

Site of application should not impede efficacy of vaccination.

Optimal target

Same as minimal target.

Notes: Whether the MR–MAP would be dislodged during application by the vaccinee (or person administering) is unknown and resistance to this should be designed into the device. Ideally, the patch and applicator should be of minimal visual interest, particularly for paediatric vaccines. Locations on infants and toddlers that are less likely to be disturbed and/or removed (such as the scapular region), and the upper arm in older children are likely to be more favourable, assuming they are not detrimental to immunogenicity. Some MAPs in development are being tested on other anatomical sites such as the wrist, forearm, shoulder and thigh.

Minimal patch size is a consideration for application to infants.

Reactogenicity

Minimally acceptable target

Local reactogenicity is expected to be more serious or frequent than that associated with SC MR vaccination, albeit with less perception of pain.

Optimal target

Same as minimal target

Notes: Visible erythema is expected to occur post vaccination with MR–MAP and may take weeks to fully resolve. The frequency and severity of such reactions should be assessed in prelicensure clinical safety trials and prior to introduction to assess vaccine acceptability, taking into consideration other benefits of the MR– MAP vaccine and the NS comparator.

Cost per immunized child

Minimally acceptable target

Incremental increase (to be decided) to cost of goods sold (COGS) should be acceptable if MAPs offer sufficient additional programmatic benefits, including reducing vaccine hesitancy, which could enable greater vaccine reach.

Optimal target

Total cost to immunize a child (COGS plus delivery) should be lower than standard SC injection delivery methods.

Notes: Any incremental increase in COGS should reasonably be able to be offset by costs associated with delivery, such as cold chain, administration and disposal, assuming acceptability to end user, resulting in the ability to reach a greater proportion of the target population, i.e. as measured by the total systems effectiveness approach.

Disposal

Minimally acceptable target

Product should allow for safe disposal as biohazard or sharps waste, at a health care facility, with similar sharps waste volume compared with NS delivery and reconstitution.

Optimal target

Product should not be considered sharps waste and thus be acceptable as biohazardous waste. It should also have lower clinical waste volumes compared with NS delivery and reconstitution.

Notes: After application, the MR–MAP will need to be disposed of, either at the immunization setting itself or, in the event of extended wear, in a community setting.

Both dissolvable and solid coated patches can carry residues of live attenuated virus and should be considered as biohazardous waste and need to be disposed of within the clinical waste system. If the MR–MAP is not capable of penetrating or lacerating the skin without an applicator, it could be considered as non-sharps waste, but consultation with appropriate regulatory and programmatic agencies will be needed to confirm this based on field data.

The degree of risk to the vaccinator and community is likely to be much less than for traditional NS application (and previous reconstitution), if the MAP and its packaging have been suitably designed or if studies demonstrate that accidental exposure is not possible. In a survey of IPAC and TechNet-21 members, both dissolvable and solid patches were considered biohazardous waste.

In line with the VPPAG's gPPP, materials used in delivery devices, primary containers, and secondary and tertiary packaging should be chosen to minimize the environmental impact of waste disposal for resource-limited systems. MAPs and disposable applicators need to be made of a material that can be safely treated and be compatible with available waste treatment methodologies in health centres (incineration and/or disinfection) without causing harm directly or indirectly to the environment and health.

For further information please contact:

Initiative for Vaccine Research
Immunization, Vaccines, and Biologicals
World Health Organization

Avenue Appia 20
CH-1211 Geneva 27
Switzerland
Email: vaccineresearch@who.int

9789240000209

Table of Contents

Acknowledgements *3*

Abbreviations and acronyms *4*

I. Executive summary *6*

A. Key stakeholders **6**

B. Methodology **6**

C. The global need for improved MR vaccines **7**

D. MR-MAPs as a solution to address barriers **8**

E. The findings on the potential benefits and costs of MR-MAPs **8**

1. Estimating MR-MAP demand and populations reached 8
2. Estimating the impact of MR-MAPs 9
3. Estimating commodity and delivery costs of MR-MAP 10
4. Estimating the cost effectiveness of MR-MAPs 11

F. The pathway from development to delivery in countries **11**

1. Estimating the financial viability and sustainability for a vaccine manufacturer or MAPs developer 11

G. Conclusion and call to action **12**

II. Introduction *14*

A. Objectives of initial Full Value Vaccine Assessment **14**

B. Target audiences **14**

C. Methodology to develop the iFVVA **14**

III. The global need for improved MR-vaccines *15*

A. Disease overview of Measles and Rubella **15**

B. Overview of MR vaccines **15**

C. Estimation of disease burden and transmission **16**

D. MR vaccination coverage in MICs/LMICs **17**

E. Barriers to MR programme goals in MICs/LMICs **17**

IV. MR-MAPs as a solution to address barriers *19*

A. MAPs as a strategic priority **19**

B. Key product characteristics of MR-MAPs[50] **21**

V. Estimating the benefits and costs of MR-MAP delivery *21*

A. Potential market segments considering the MR-MAP Use Cases **21**

B. Estimating MR-MAP demand and population immunized for MR-MAPs **23**

C. Estimating the impact of MR-MAPs **27**

1. If MR-MAPs are available and implemented starting in 2030 27
2. If MR-MAPs are available and prioritised in 2030 to countries with the greatest need 28
3. Estimated number needed to vaccinate if MR-MAPs were available in 2030 30
4. Key takeaways on the impact modelling 30

D. Benchmarking potential MR-MAP prices 30
1. Estimated MR-MAP price benchmarks 31

E. Estimating commodity and delivery cost of MR-MAPs 33
1. Costs for routine immunization 34
2. Costs for SIAs 36
3. Key takeaways on the cost analysis 36

F. Cost-effectiveness of MR-MAPs analysis 37
1. Cost effectiveness of introducing MR-MAPs 37
2. Key takeaways on the cost effectiveness of MR-MAPs 41

VI. The pathway from development to delivery in countries 41
1. Status of MR-MAP development 41
2. Key product characteristics important for decision makers 42
3. Key questions hindering the delivery of MR-MAPs 43
4. Technical challenges to the development process 44
5. Financial sustainability of development and production of MR-MAPs 46

VII. Conclusions and call to action 51

VIII. Bibliography 54

Acknowledgements

UNICEF developed this report as part of its continued efforts with partners to advance and implement prioritized innovations to contribute to bettering the health of children in low- and middle-income countries. The project team consisted of UNICEF, MMGH Consulting GmbH, London School of Hygiene and Tropical Medicine, and Global Health Visions. The preparation of this document was made possible with generous support and funding from Alwaleed Philanthropies. The project team warmly thanks the experts who provided their time and valuable input throughout the entire development process. These experts spanned across 21 countries in all the regions, as well as, a variety of institutions and perspectives, including:

- Adjuvant Capital
- Bill & Melinda Gates Foundation
- Biomedical Advanced Research and Development Authority (BARDA)
- Chinese Center for Disease Control and Prevention
- Coalition for Epidemic Preparedness Innovations (CEPI)
- Gavi, the Vaccine Alliance
- Georgia Institute of Technology
- GlaxoSmithKline
- Harro Höfliger
- International Vaccine Institute (IVI)
- Jhpiego
- Merck
- Médecins Sans Frontiers
- Micron Biomedical
- National Immunization Technical Advisory Group Chairs and members
- NRL Enterprise Solutions
- Regional Immunization Technical Advisory Group Chairs
- Sanofi Pasteur
- Serum Institute of India
- PATH
- PT Bio Farma
- University of Newcastle
- U.S. Centers for Disease Control and Prevention
- Vaxxas
- Vaxess Technologies
- Verndari, Inc.
- Working in Tandem Ltd.
- World Health Organization

The project team wishes to thank PATH for providing the Vaccine Technology Impact Assessment (VTIA) model for estimating the costs associated with introducing MR-MAPs in low- and middle-income countries.

Their contributions of all the experts listed above resulted in the development of MR-MAPs as an initial public health investment case and the identification of key actions that need to be taken to ensure the development, delivery, uptake, and utilization of MR-MAPs.

Abbreviations and acronyms

2021-2030 MRSF	Measles and rubella strategic framework 2021-2030
AFR	WHO African region
AMR	WHO Americas region
BARDA	Biomedical Advanced Research and Development Authority
BLA	Biologics License Application
CEPI	Coalition for Epidemic Preparedness Innovations
CHW	Community health worker
CMC	Chemistry, manufacturing, and controls
COGS	Cost of goods sold
COVID-19	Coronavirus disease 2019
CRS	Congenital rubella syndrome
CTC	Controlled temperature chain
DALY	Disability-adjusted life years
DCF	Discounted cash flow
DynaMICE	Dynamic Measles Immunisation Calculation Engine
EMR	WHO Eastern-Mediterranean region
EPI	Expanded Programme for Immunization
FVP	Fully vaccinated persons
GMP	Good manufacturing practices
GSK	GlaxoSmithKline plc
HIC	High income country
HPV	Human papillomavirus vaccine
HR	Human resources
HW	Health worker
IA2030	Immunization Agenda 2030
ICER	Incremental Cost-Effectiveness Ratio
iFVVA	initial Full Value Vaccine Assessment
IPV	Inactivated Poliovirus vaccine
IVI	International Vaccine Institute
LIC	Low-income country
LMIC	Lower middle-income country
LSHTM	London School Hygiene and Tropical Medicine
MAP	Microarray patch
MCV	Measles containing vaccine
MCV1	First dose of measles-containing vaccine
MCV2	Second dose of measles-containing vaccine
MDV	Multi-dose vial
MI4A	Market Information for Access to Vaccines Initiative
MMGH	MMGH Consulting GmbH
MMR	Measles, Mumps, and Rubella vaccine
MMRV	Measles, Mumps, Rubella, and Varicella vaccine
MN	Microneedle

MOV	Missed opportunities for vaccination
MR	Measles-Rubella
MSIA	Measles supplementary immunization activities
N/S	Needle and syringe
NITAG	National Immunization Technical Advisory Group
NNV	Number needed to vaccinate
NPV	Net present value
NRA	National regulatory authority
PAHO RF	Pan-American Health Organization Revolving Fund
PCV	Pneumococcal conjugate vaccine
PDR	Programmatic doses required
PFS	Pre-filled syringe
PHC	Primary health care
PIRI	Periodic Intensification of Routine Immunization
PQ	WHO pre-qualification
QA/QC	Quality assurance/quality control
RI	Routine immunization
RITAG	Regional Immunization Technical Advisory Group
ROI	Return on investment
RSV	Respiratory syncytial virus
S&GA	Sales, general, and administrative expenses
SAGE	WHO Strategic Advisory Group of Experts on Immunization
SDG	Sustainable development goals
SDV	Single dose vial
SEAR	WHO Southeast Asian region
SIA	Supplementary immunization activity
SII	Serum Institute of India
SP	Immunization Agenda 2030's strategic priorities
TIP	Tailoring immunization programmes
TPP	Target product profile
UC	Use Case
UHC	Universal health coverage
UMIC	Upper middle-income country
UN	United Nations
UNICEF	United Nations Children's Fund
USD	U.S. Dollars
VIPS	Vaccine Innovation Prioritization Strategy
VTIA	Vaccine Technology Impact Assessment
WACC	Weighted average cost of capital
WB	World Bank
WHO	World Health Organization
WPR	WHO Western Pacific region
WUENIC	WHO/UNICEF Estimates National Immunization Coverage

I. Executive summary

The Measles-Rubella vaccine is estimated to provide the highest return on investments (ROI) in public health.(Sim et al., 2020) However, routine vaccination coverage in infants and young children has plateaued during the past decade, leading to a delay in establishing a global eradication goal for measles.(*Global eradication of measles: report by the Secretariat, 63rd World Health Assembly*, 2010) The current vaccine requires a needle and syringe (N/S) for delivery, is demanding on the cold chain, and requires reconstitution. In addition, since the presentation used in most low- and middle-income countries is in a multi-dose vial presentation and the reconstituted vaccine must be discarded at the end of the session or after six hours, the open vial wastage of the N/S presentation is high. These limitations create operational barriers that contribute to low coverage, especially among the hard-to-reach communities. Measles-Rubella microarray patches (MR-MAPs) with their single dose, lighter and easy-to-use needle-free presentation, and potential thermostability, have been identified as a potential solution. Therefore, an initial Full Value of Vaccine Assessment (iFVVA) was launched to assess the public health and market value of MR-MAPs. The iFVVA aims to define the key factors influencing the MR-MAP value proposition as well as the open questions that are hindering the advancement and implementation of MR-MAPs.

A. Key stakeholders

The project team conducted an iFVVA for MR-MAP by combining data from different analyses to evaluate the benefits and costs of development and delivery. This document is intended for three main stakeholders:

- **MAP developers and vaccine manufacturers** are responsible for the clinical development of MR-MAP and ensuring supply is appropriately scaled-up. They may use the iFVVA to identify the product characteristics that will affect country adoption decisions, inform efforts to secure financial support to develop and produce MR-MAPs, and understand the drivers impacting ROI.
- **Donors** play a vital role in supporting MR-MAP development and ensuring that this innovative technology is made available to countries**.** They may use the iFVVA to better understand the use cases and potential public health and equity impacts of MR-MAPs, as well as the potential gaps in the financial landscape to ensure the sustainable development, commercialization, and delivery of MR-MAPs.
- **Policy and decision makers at global, regional, and country levels** will review evidence and data to provide recommendations for the inclusion of MR-MAPs into national immunization programmes. They may use the iFVVA to assess the cost, impact, and public health benefit of MR-MAPs for national immunization programmes. Further, they may utilize the iFVVA to highlight research or evidence gaps that can influence their decisions on adopting MR-MAPs.

B. Methodology

The development of the MR-MAPs iFVVA spanned 14 months and applied a mixed method approach using desk review, consultations, and qualitative and quantitative analyses.

- An extended **desk review** of published and unpublished literature was conducted to identify barriers currently being faced by MR programmes as well as to support the qualitative and quantitative analyses, including the assessment of MR-MAP development timelines, the generation of population-based **demand forecasts** assuming better reach of hard-to-reach populations and reducing missed opportunities for vaccination (MOV) with MAP compared to N/S, and the execution of the **financial analysis,** including a **price benchmarking analysis** and **Discounted Cash Flow (DCF) analysis.**

- **Consultations** were conducted with 34 experts across a wide range of topics, including Measles and Rubella epidemiology and disease prevention, vaccine implementation in low-income (LIC) and lower-middle-income countries (LMIC), drivers of decision making at global, regional, and national levels, MAP development, clinical development and manufacturing of vaccines. Similarly, to the desk reviews, the consultations supported the barrier analysis, MR-MAP development timelines, demand forecasts, and the financial analyses
- Finally, the iFVVA estimates the **cost, impact, and cost effectiveness** of introducing and implementing MR-MAPs. To do so, the iFVVA uses the following existing models: **PATH's Vaccine Technology Impact Assessment** (VTIA) assessed cost and **London School of Hygiene and Tropical Medicines' (LSHTM) Dynamic Measles Immunisation Calculation Engine (DynaMICE)** assessed impact and cost effectiveness.(Fu et al., 2021; Mvundura et al., 2019)

The methodology is further detailed in the relevant sections and annexes of the iFVVA. Lastly, the iFVVA relied on an Expert Advisory Group consisting of 19 experts to discuss the methodology and assumptions used, and to endorse the key findings.

C. The global need for improved MR vaccines

Measles and rubella vaccination prevents the highest number of vaccine-preventable deaths in children and has the highest ROI.(Sim et al., 2020) Despite its impact, deficiencies in the coverage of measles and rubella vaccination are estimated to have resulted in more than 200,000 deaths globally in 2019.(M. K. Patel et al., 2020) The gaps in population measles and rubella immunity profiles in many LMICs and LICs sustain a costly cycle of outbreaks and the required public health responses, which have only worsened during the COVID pandemic. Inequities in measles immunization delivery in many countries resulted in over twenty-five million unvaccinated children in 2021.(*Progress and challenges with achieving universal immunization coverage: 2020 WHO/UNICEF Estimates of National Immunization Coverage*, 2021; *WHO/UNICEF coverage estimates for 1980-2020*, 2021) This is the highest number of unvaccinated children in over a decade and these children live disproportionately in under-served communities, particularly in remote rural, fragile, or conflict-affected areas.

Measles and rubella vaccines require **achieving and maintaining** high coverage to avoid outbreaks and ultimately achieve eradication-- WHO recommends that countries strive for 95% coverage of two measles containing vaccine (MCV) doses.(World Health Organization, 2017) When vaccination coverage for measles or rubella falls below the necessary threshold, outbreaks occur.(Wallinga et al., 2005) Furthermore, a decrease in coverage can result in the re-establishment of measles virus circulation as seen in countries that have lost their elimination status. This illustrates the challenges and difficulties that countries face in maintaining high vaccination coverage for two doses of MCV.(Moss et al., 2021)

From 2000 to 2010, estimated global MCV1 coverage increased from 72% to 84% but since then has plateaued and decreased.(M.K. Patel et al., 2020) Due to the global pandemic of SARS-CoV-2, the global coverage for MCV1 decreased by 5 percentage points, respectively, leaving 5 million additional children unvaccinated compared to 2019.(*WHO/UNICEF coverage estimates for 1980-2021*, 2022)

Furthermore, it is estimated that ten countries accounted for more than half of the world's unprotected children (~13 million).(*Progress and challenges with achieving universal immunization coverage: 2020 WHO/UNICEF Estimates of National Immunization Coverage*, 2021) The SARS-CoV-2 pandemic highlighted the tenuous gains achieved by the programme and the difficulty in achieving and maintaining the elimination and equity goals.

The product characteristics of the current N/S vaccine have been linked with several barriers that may affect the ability to effectively deliver vaccines. Using a desk review, 15 barriers were identified and categorized into four groups: (i) high human resource requirements, (ii) ineffective administration procedures, (iii) poor total system performance and negative impacts on the environment, and (iv) an increase in hesitancy. Based on this evidence, the **barriers affecting the programme most frequently and most profoundly were related to the high labor costs and the challenges associated with equitably delivering injectable vaccines**. However, more research will be needed to better understand the barriers and root causes of the operational challenges associated with equitably delivering the N/S MR vaccine as well as research to quantify their frequency and magnitude of the impact. This research will help to further articulate the key barriers impacting MR programmes and potential solutions that could address these barriers.

D. MR-MAPs as a solution to address barriers

As immunization stakeholders strive to reach the under- and un-immunized populations, they are increasingly focusing on people-centered interventions that address the specific needs of each community. The Vaccine Innovation Prioritization Strategy (VIPS) aims to coordinate and align vaccine product innovation efforts among global immunization stakeholders, including UNICEF, WHO, Gavi, the Vaccine Alliance, the Bill and Melinda Gates Foundation, and PATH, to meet country needs and achieve global immunization goals("VIPS update to the Delivery Technologies Working Group ", 2020). VIPS conducted in-depth country consultations to align vaccine product innovation efforts, which **rated MAPs as the most promising innovation to help address immunization programme challenges and improve coverage and equitable access to vaccines**(Organization, 2017).

A MR-MAP is designed to have an **integrated vaccine and delivery mechanism as well as a single-dose delivery method.** Resulting, in a simplified process for preparing and administering vaccines that could expand the workforce to community health workers, teachers, and/or others. MR-MAPs are also expected to be **smaller and lighter in weight** than both the 5-dose or 10-dose vials and diluent, as well as potentially having **thermostability characteristics** (e.g., 3 days at 40 degrees Celsius). **Its needleless presentation** could benefit many areas such as reducing waste disposal requirements, reducing the environmental impact, allowing for easier integration with other vaccines in a N/S presentation, and facilitating vaccination compliance if individuals are fearful of the N/S and pain.

E. The findings on the potential benefits and costs of MR-MAPs

1. Estimating MR-MAP demand and populations reached

MR-MAPs are estimated to become available in 2030 and provide several benefits and savings over time. A demand forecast serves as a key input in estimating the MR-MAP's total public health impact and potential cost savings. To estimate the global programmatic doses required (PDR) from 2030-40, a population-based forecasting model estimated the global demand requirements.(Amarasinghe et al., 2010; Cernuschi et al., 2018; Zuber et al., 2009) In the forecast, MR-MAPs are projected to reach additional hard-to-reach populations and reduce the missed opportunity for vaccination (MOV) that cannot be reached by the current N/S presentation(Ko et al.). Furthermore, given the uncertainty regarding the adoption timing of MR-MAPs and the current stagnation in coverage, the forecast examined six scenarios that explored alternative adoption timings, as well as high and low growth coverage assumptions over 2030-40.

The range of scenarios estimated that the annual MR-MAP dose requirements begin between ~30-140 million doses in 2030 and stabilizes at ~230-280 million doses by 2040. MR-MAPs represent ~9% of total MR demand in 2030 but increases to ~76% by 2040. Based on the analysis of the dose distribution by the MR-MAP use cases from 2030-2040, ~55% of the total doses will be delivered by health workers or community health workers in a fixed post and 45% will be delivered as part of the outreach activities by health workers or community health workers.

Lastly, depending on the assumptions taken, the different scenarios illustrated MR-MAPs' contribution to closing the gap of unvaccinated children. With estimates that MR-MAPs will reach an additional 80-110 million children (8-10%) between 2030-40 compared to the scenarios where MR-MAPs are not made available to countries. Key questions that could significantly impact the demand forecast include countries' interest and willingness to adopt MR-MAPs as well as the speed and size of the uptake of MR-MAPs.

2. Estimating the impact of MR-MAPs

The DynaMICE model evaluated the global impact of MR-MAPs on measles burden. the full potential of this product. Depending on the scenario modelled, the adoption of MR-MAPs could result in a reduction of up to 37 million measles cases (35%), up to 397,000 measles deaths (35%), and up to 25.9 million measles related disability-adjusted life years (DALYs) (35%) over the 11-year period. Further, the number needed to vaccinate (NNV) to avert one measles case showed that the highest dose efficiency was observed in LMICs and LICs as they required only an additional 2.3 to 3.5 doses to avert one measles case across all scenarios.

Demand and pricing scenarios were aligned with other iFVVA analyses; and, demand was assumed as unconstrained from supply, programmatic, and demand perspectives, to capture Considering the procurement cost[1] and the estimated measles DALYs averted in LIC and LMICs only, the estimated cost per DALY averted is $85-$2,310, which is comparable to HPV ($91-$928), Rotavirus ($202-$428), and RSV maternal vaccine ($70-$270).(Debellut et al., 2019; *Gavi Vaccine Investment Strategy*, 2018; Jit et al., 2014) If only the low coverage growth scenarios were considered the range of cost per DALY averted would be further narrowed to $85-$255.

Based on this analysis, MR-MAPs may positively impact measles disease burden compared to the N/S presentation, however, the scale of this impact is dependent on the assumptions regarding the numbers of doses required by countries – as related to the future trends in coverage, the ability to increase routine vaccination coverage among hard-to-reach and MOV populations using MR-MAP. Lastly, as these estimates are unconstrained, the availability of sufficient supply to meet demand.

[1] Estimated MR-MAP price multiplied by total MR-MAP doses for LIC and LMICs

Text Box- Additional indirect benefits: In addition to having up to 66% reduction in measles cases, up to 73% reduction in measles deaths and DALYs, MR-MAPs will have additional benefits. First, reconstitution errors and their impact were shown to significantly impact immunization coverage and one country witnessed a 40% decrease in coverage and 70 deaths due to a reconstitution error. This would have been completely avoided with MR-MAPs given its integrated presentation. Second, if countries utilizing 10-dose vials were to adopt MR-MAPs, which will likely have a much lower wastage rate, they would experience ~39% decrease in the number of doses to be purchased, while countries utilizing 5-dose vials could experience a decrease of 14%.[1] Thus, MR-MAPs can greatly reduce the number of doses in countries needed ultimately impacting vaccine

3. Estimating commodity and delivery costs of MR-MAP

The VTIA model was used to estimate the commodity and delivery costs for the immunization programme by examining key cost categories. Given the uncertainties in the MR-MAP product characteristics of price, volume, HR time for administration, and controlled temperature chain (CTC) properties (3 days at 40 degrees Celsius), four scenarios were developed to explore these uncertainties.

For routine immunization, under the best-case scenario where MR-MAPs have an estimated price of $1.29, a low packed volume of 3cm^3, and the shortest human resource time for administration of 20 seconds results in a lower weighted average cost per dose administered of $1.65 as compared to the N/S presentation of $1.87.[2] This result suggests that the pricing and delivery characteristics levels in this scenario provide a competitive alternative to the current N/S presentation. Assuming MR-MAPs had CTC properties, then the weighted average cost per dose administered would further decrease by 3.6% to $1.59. This suggests that the use of CTC may result in additional cost savings when delivering MR-MAPs. However, in the other MR-MAP scenarios explored, MR-MAPs were estimated to incur a higher weighted average cost per dose administered compared to the N/S presentation.

For the administration of SIAs, MR-MAPs did not have a lower weighted average cost per dose administered than the N/S across all the scenarios explored. This is different from routine administration and driven by the lower indicative wastage rates applied during SIAs and the larger target populations for SIAs.

As a breakdown of the costs, **vaccine costs, including MR-MAP price, wastage, and international shipping, always make up the largest portion of total costs**, regardless of whether the MR-MAP was provided in routine immunization or in an SIA. Other factors that may influence cost include the packaged volume of MR-MAPs and wastage rates which impacts the number of doses to be procured and cold chain costs as well as the number of individuals receiving vaccination through outreach or mobile delivery. As vaccine cost is often the largest driver of total costs, this highlights the **critical role that MR-MAP price plays in the cost of introducing MR-MAPs as well as the need to ensure an appropriate price that balances the potential impact of reaching un- and under-immunized children and the use of an innovative product to meet programmatic goals**.

[2] Weighted average cost per dose administered is defined as the commodity and delivery costs considering vaccine wastage and target population

4. Estimating the cost effectiveness of MR-MAPs

A cost effectiveness analysis was conducted including costs from: (i) the cost of illness; (ii) the cost of procuring a vaccine; and (iii) the cost of administering the vaccine, combined with effectiveness estimates of averted DALYs from the health impact modelling.

Introducing MR-MAPs would be a cost-effective strategy across many countries, based on relative comparisons of health opportunity costs. However, **the cost-effectiveness of the MR-MAP introduction in LICs and LMICs is sensitive to the assumptions on forecasted coverage growth**. Indicating that if MR vaccination coverage stagnates, then MR-MAPs would be cost-effective to adopt in all countries regardless of the estimated MR-MAP price.

The results of this analysis indicate that it will be **cost-effective to introduce MR-MAPs, despite the heterogeneity of a country's health systems and fiscal space, coverage assumptions, and cost uncertainties.** When the MR-MAP introduction is considered for individual countries, additional local data on burden and cost impact estimates will be useful for decision-making and policy planning.

F. The pathway from development to delivery in countries

Two MR-MAP candidates are presently in Phase I development with estimated timelines for receiving WHO pre-qualification (PQ) in 2029 assuming that at-risk investments in the construction and validation of an initial small-scale facility are completed during Phase I and Phase II trials. Without these at-risk investments, WHO PQ for MR-MAPs may be delayed another four years to 2033.

In addition to investment constraints, technical questions remain. These questions are likely to be addressed as MR-MAPs progress through clinical development and include understanding the optimization of bulk MR antigen for use in MAPs (e.g. further bulk concentration and/or the identification of the right excipients), generation of evidence on immunogenicity, safety, and reactogenicity data in comparison to the N/S presentation, assessing the need for aseptic manufacturing, defining the appropriate scale for the MAP manufacturing lines including a better understanding of the automation of the line, developing new quality assurance or quality control processes for MR-MAPs, and defining an efficient regulatory pathway taking into account the interactions between the MAP device and MR vaccine.

Regarding the development, the relevant evidence and data must be generated and gathered for decision makers, particularly on the programmatic viability of MR-MAPs. To determine the key data and evidence needed to make recommendations for the inclusion of MR-MAPs in national immunization programs, regional and national immunization technical advisory group chairs and members were consulted. Among the key data needs identified were **cost per immunized child, safety, efficacy, immunogenicity, human factors, and SAGE or other NITAG recommendations.**

1. Estimating the financial viability and sustainability for a vaccine manufacturer or MAPs developer

A DCF analysis was conducted to assess the ROI for a vaccine manufacturer or MAPs developer that assumes the risk of taking on the clinical development and the construction of the manufacturing facility. Depending on risk assessment of the development and commercialization of MR-MAPs, ROI expectations will be different. For the higher hurdle rate[3] of 18%, the Net Present Value (NPV) was positive, indicating a good investment for the developer/manufacturer, only for the highest tiered pricing (ranging from $2.92 to $5.20 for

[3] Hurdle rate is the minimum rate of return.

LICs to UMICs) and lowest manufacturing investment (e.g., where existing antigen bulk production facilities can be leveraged and the cost for the initial small-scale plant is not incurred by the developer). The acceptance of a lower hurdle rate at 10.5% allowed also for the scenario with a reduced COGS[4] to yield a positive NPV.

The analysis highlights two key facts. **First, the importance of clarifying the manufacturing partner choice and the manufacturing setup and its costs. Second, and similarly to the analysis on the cost of introducing MR-MAPs, the critical influence of an appropriate price on the financial sustainability and on demand**. Those findings stress the importance of establishing a mechanism of risk-sharing between private and public stakeholders given the public health importance of MR-MAPs as what was done for the development and manufacture of COVID-19 vaccines. This risk sharing will have to act at two levels (i) to finance some clinical development and initial small-scale facility costs, in exchange for a reduced ROI for the developers; and (ii) to subsidize price to ensure that countries can maintain a degree of parity compared to the N/S presentation while developers/manufacturers can generate sufficient cash inflow to balance their investments. The size and setup of those incentives will depend on a more in-depth understanding of some key and related aspects such as: the manufacturing partner, the appropriate manufacturing setup and scale, the COGS of MR-MAPs and the likely level of demand. Such a mechanism will likely prove critical to allow for this innovation to succeed and reach un- and under-immunized children that the N/S is currently unable to reach.

G. Conclusion and call to action

With the assumed product characteristics, MR-MAPs can serve as a key tool to address the barriers that are preventing countries from achieving and maintaining high MCV coverage. Further, MR-MAPs could accelerate progress towards regional elimination and eventual global eradication by reaching the hard-to-reach and reducing MOVs that the N/S is currently missing. The iFVVA analyses imply that, in absence of supply constraints, MR-MAPs could reach an additional 80-110 million children and reduce up to 66% of measles cases, up to 73% of measles deaths, and up to 72% of measles DALYs. This estimated reduction in measles burden highlights the public health importance of pursuing the development and delivery of MR-MAPs, which could decrease inequities between and within countries while accelerating the ability to achieve measles and rubella control and elimination goals.

While in most scenarios, MR-MAPs are anticipated to have a higher cost per dose administered, this higher cost allows access to an innovative product that could close immunity gaps by reaching zero dose and under-immunized children. Although the cost per dose administered may be higher, MR-MAPs are shown to be cost effective across all countries, even in HICs and UMICs that would only utilize MR-MAPs in special situations. Further, and not included in the analyses, there could be additional cost savings due to changes in immunization strategies if MR-MAPs accelerated the achievement of measles or rubella control and elimination (e.g., the cessation of SIAs and the reduction of the required number of doses for routine administration).

The analyses of the iFVVA have revealed that the main programmatic questions concern countries' interest and willingness to adopt as well as the speed and size of MR-MAPs uptake, which impact the number of doses required by countries, the future trends in coverage, and the ability to increase routine vaccination coverage among hard-to-reach and to

[4] In absence of detailed information on the manufacturing setup and product design, a simplified assumption has been used for COGS where the cost remains flat irrespective of volume. The assumption is conservative since COGS is always reduced when manufacturing volumes increase.

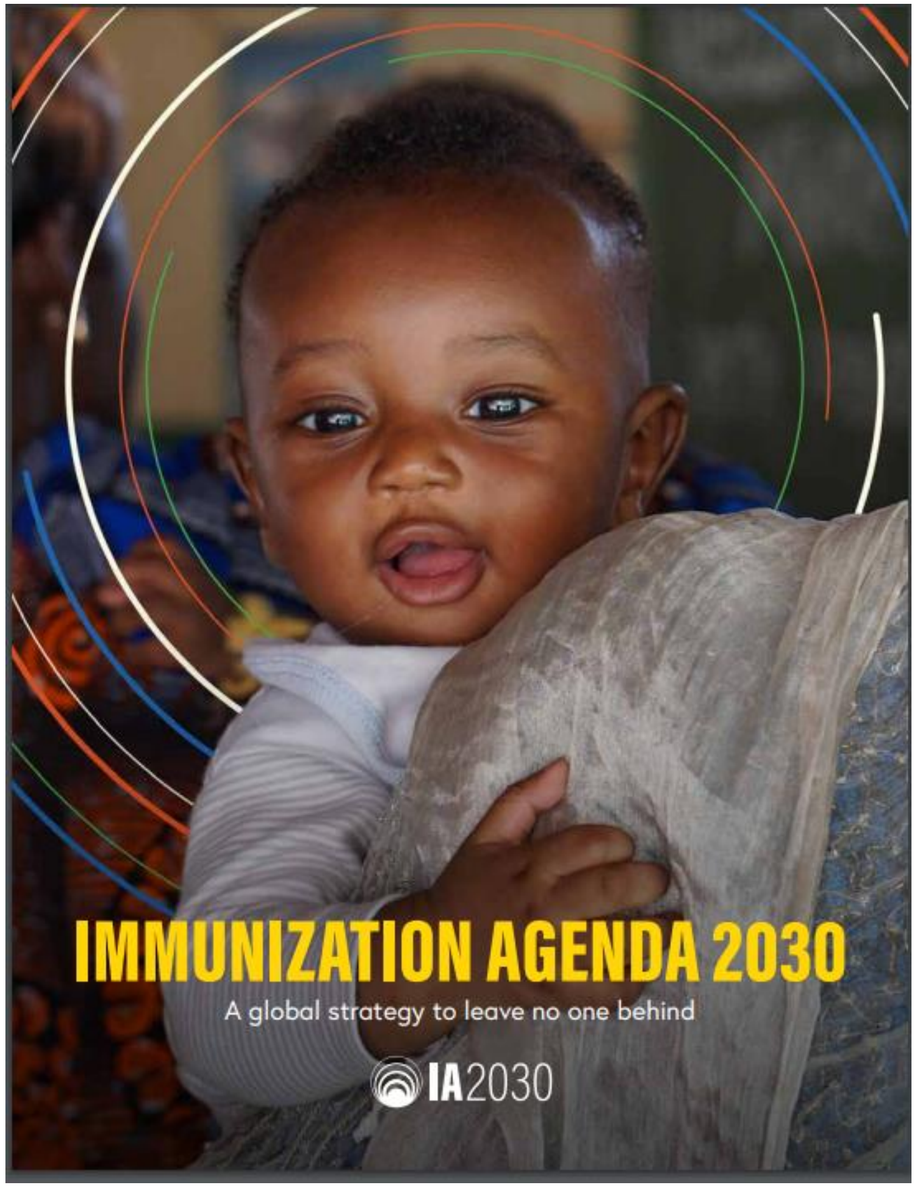
World Health Organization

Session 8

IA 2030 vaccine impact estimates

Immunization Agenda 2030 (IA2030) Vaccine impact estimates

For IVIR-AC recommendations



IA2030 vaccine impact estimates project team

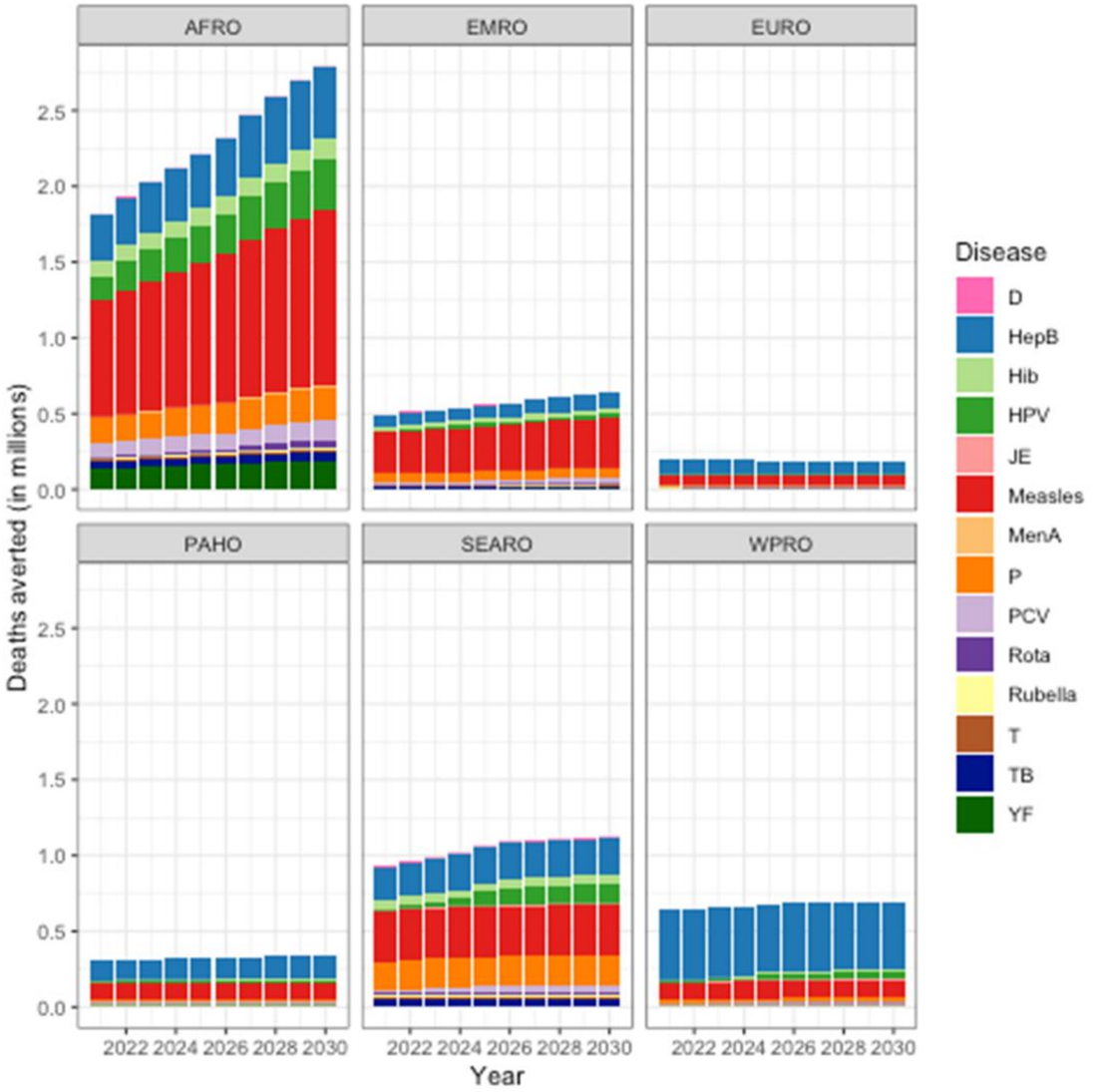
13 September 2022

Agenda

1. Recap of the project & IVIR-AC recommendations
2. Questions for IVIR-AC
    - Uncertainty analysis
    - Annual monitoring and reporting
    - Project updates
3. Discussion

Project objectives

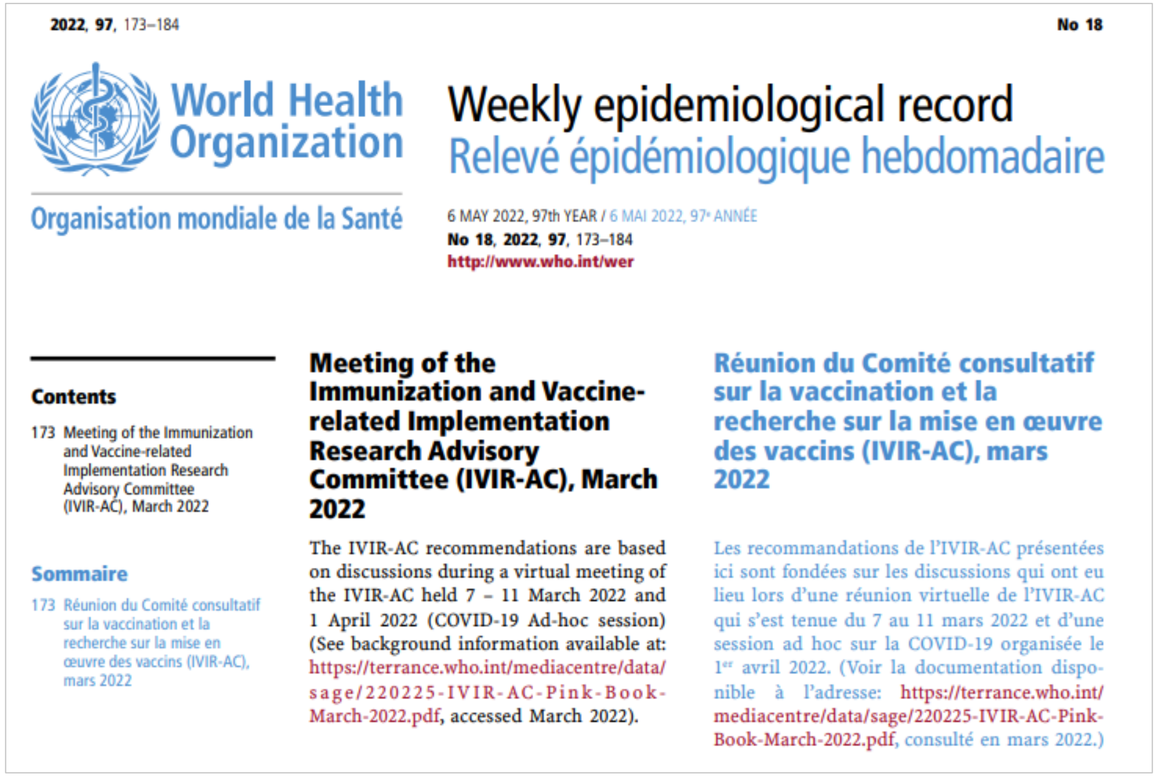
- Objectives:
  - Generate modelled vaccine impact estimates for WHO's 194 Member States from 2021-2030
  - Document the methodology in a transparent manner
  - Inform strategic priorities for the Immunization Agenda 2030 and Triple Billion target for the Thirteenth



Deaths averted by pathogen and by region, 2021-2030

Previous IVIR-AC recommendations for IA2030 vaccine impact estimates

1. September 2020: Weekly Epidemiological Record, 4 December 2020, vol. 95, 49 (pp. 609–628)
2. March 2021: Weekly epidemiological record, 30 April 2021, No 17, 2021, 96, 133–144
3. September 2021: Weekly epidemiological record, 26 November 2021, No 47, 2021, 96, 569–584
4. March 2022: Weekly epidemiological record, 06 May 2022, No 18, 2022, 97, 173–184



2022, 97, 173–184 No 18

World Health Organization

Organisation mondiale de la Santé

Weekly epidemiological record

Relevé épidémiologique hebdomadaire

6 MAY 2022, 97th YEAR / 6 MAI 2022, 97e ANNÉE

No 18, 2022, 97, 173–184

http://www.who.int/wer

Contents

173 Meeting of the Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC), March 2022

Sommaire

173 Réunion du Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC), mars 2022

Meeting of the Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC), March 2022

The IVIR-AC recommendations are based on discussions during a virtual meeting of the IVIR-AC held 7 – 11 March 2022 and 1 April 2022 (COVID-19 Ad-hoc session) (See background information available at: https://terrance.who.int/mediacentre/data/sage/220225-IVIR-AC-Pink-Book-March-2022.pdf, accessed March 2022).

Réunion du Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC), mars 2022

Les recommandations de l'IVIR-AC présentées ici sont fondées sur les discussions qui ont eu lieu lors d'une réunion virtuelle de l'IVIR-AC qui s'est tenue du 7 au 11 mars 2022 et d'une session ad hoc sur la COVID-19 organisée le 1er avril 2022. (Voir la documentation disponible à l'adresse: https://terrance.who.int/mediacentre/data/sage/220225-IVIR-AC-Pink-Book-March-2022.pdf, consulté en mars 2022.)

Summary of IVIR-AC feedback & recommendations (March 2022)

IVIR-AC recommended ways to simplify yet strengthen the proposed methodology, namely:

- Support the uncertainty analysis by liaising with VIMC and the Institute for Health Metrics Evaluation (IHME) to access and utilize their estimates of deaths averted and to avoid recreating such estimates using arbitrary assumptions about parameter distribution and independence.
- Decouple HIC and LMIC vaccine impact assessments in order not to delay the progress of LMICs (in which the burden of VPD is higher) by methodological challenges related to the former.
- Publish (or post a pre-print version of) the literature review and synthesize the review with summary metrics (e.g., countries covered; size of VPD burden addressed; time period).

(continued in the next slide)

Summary of IVIR-AC feedback & recommendations (March 2022)

IVIR-AC is uniquely positioned to provide highly technical modelling feedback to the IA2030 initiative in order to shape, validate and reinforce the initiative's proposed modelling framework. To that end, IVIR-AC recommended the importance of:

- elaborating on and clarifying the intended meaning of "location-specific Latin hypercube sampling";
- generating predictions by sampling multiple draws from the regression model and producing the full distribution, mean, median and 95% uncertainty intervals (UIs) (to consider whether multivariate normal distribution is the most appropriate distribution to use);
- considering fixing the mean of the beta distribution rather than giving extra weight to the mean difference in the objective function;
- gaining an understanding of the magnitude of scaling multipliers in the VIMC calibration;
- providing prediction intervals in background documents;
- leaving out 1 uncertainty type at a time when producing uncertainty intervals (UIs) and,
- providing more details on how Approach 3 ("Incidence reduction in a certain period directly provided by the studies"), Approach 5 ("QALY") and Approach 6 ("DALY") are implemented;
- considering the herd effect of vaccination in Approach 4 ("Only the prevalence of the disease is known").

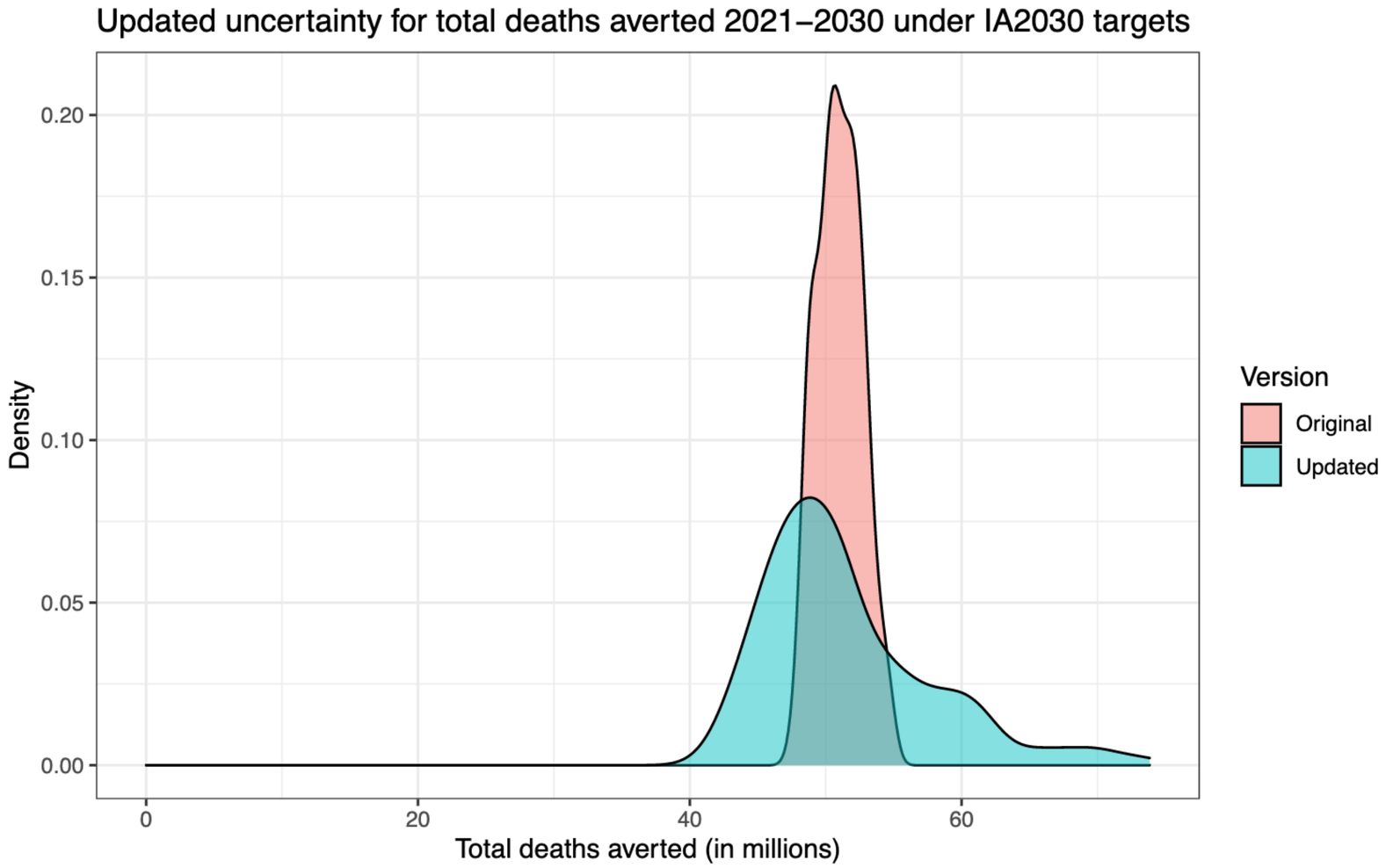
Questions for IVIR-AC

The project team requests IVIR-AC:

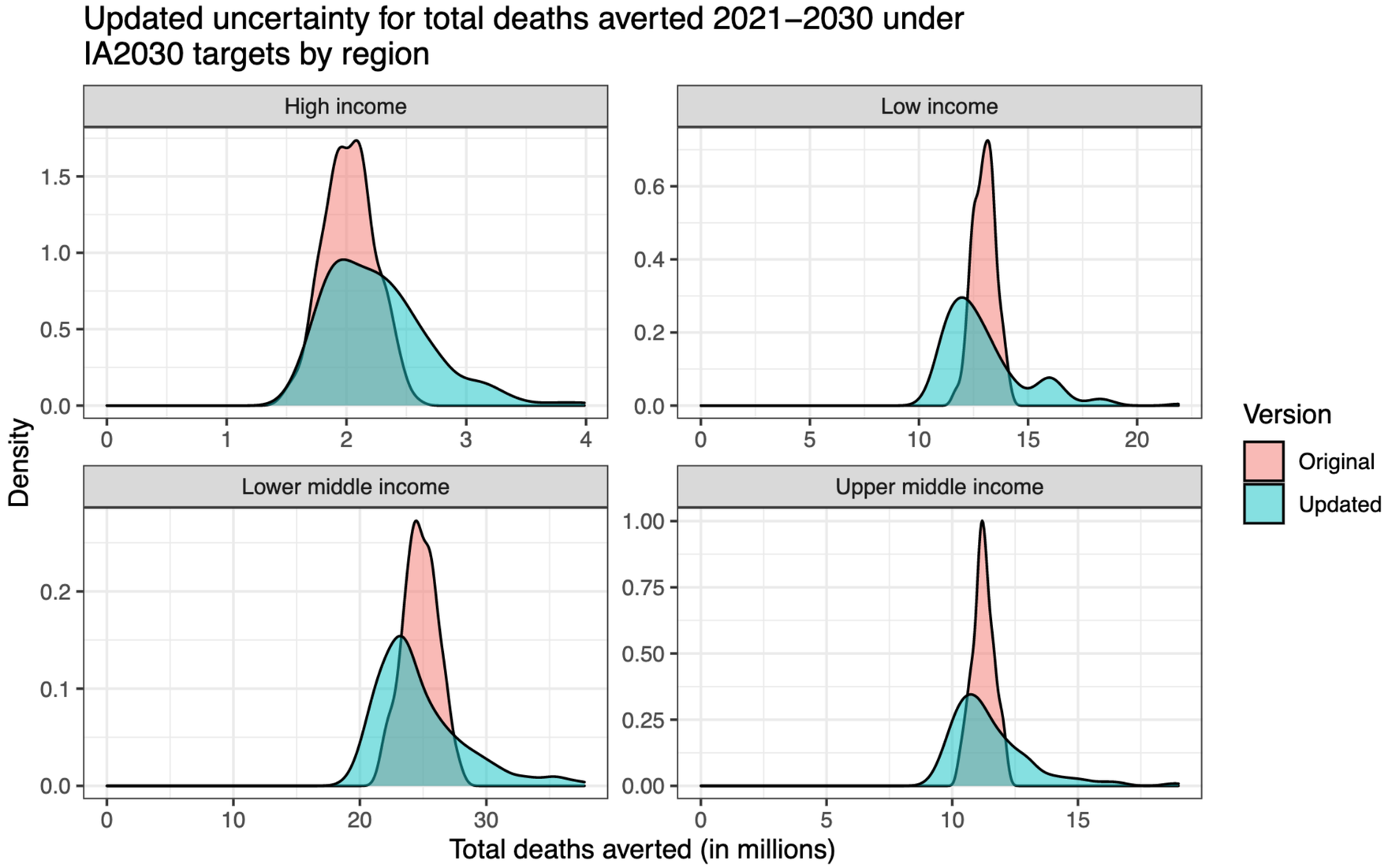
- To review the final results from the uncertainty analysis
- To provide feedback on approaches to tracking annual progress against targets
- To provide feedback on the planned next steps for the project

Uncertainty analysis updates

- Draw level uncertainty analysis was conducted, including propagation of uncertainty from regression coefficients
- Latin hypercube sampling was used to pull draws from randomly sampled distribution
- Vaccine efficacy uncertainty was pinned to the mean of the beta distributions



Uncertainty analysis updates



Correction: HPV estimates in high income countries

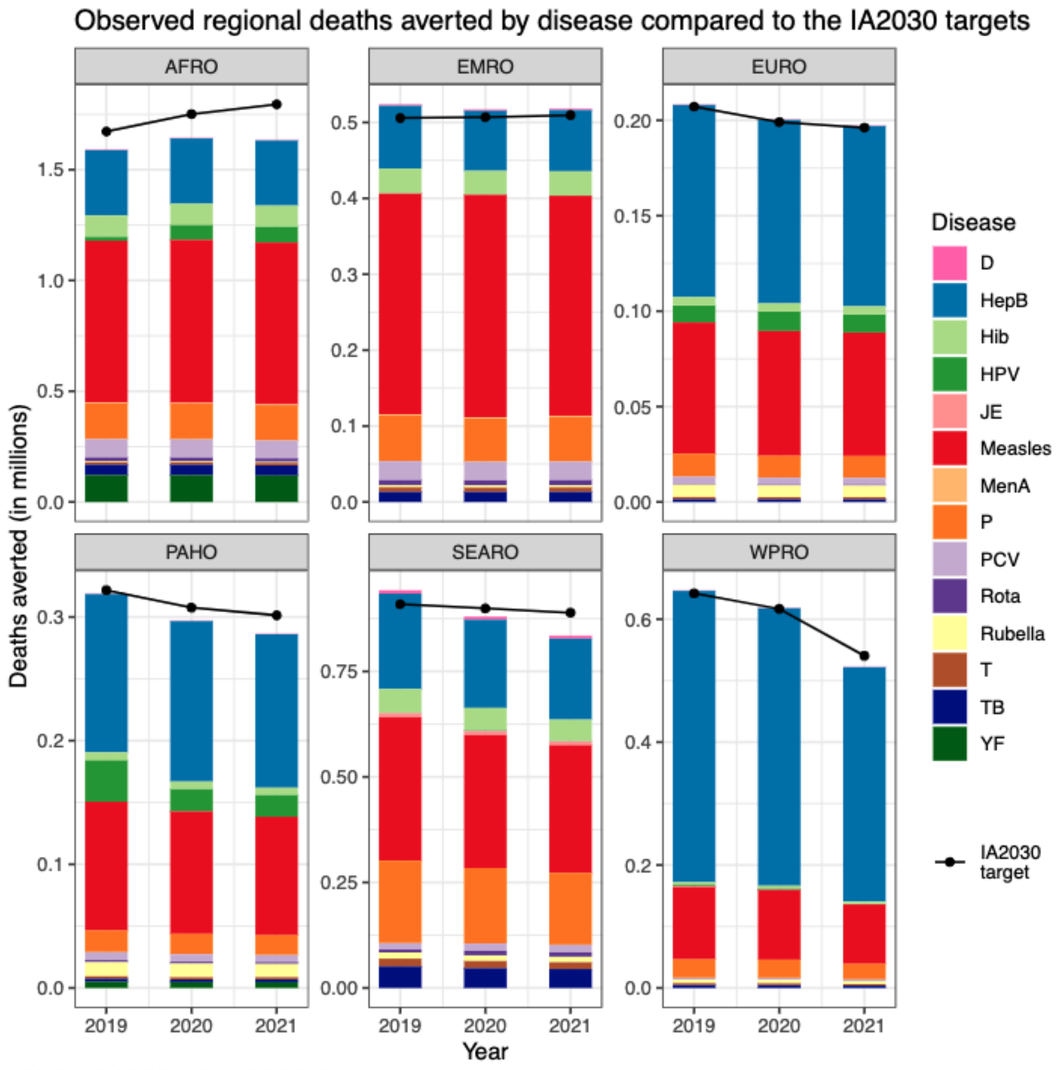
1. While updating, we discovered that HPV estimates in high income countries were absent from our initial estimates. The issue was identified as a labeling problem, where the activity type for non-VIMC locations was input as “campaign” instead of ”routine”. This led to exclusion from the IA2030 reference results, as we included only “routine” vaccination. Further, we concentrated vaccine administration on age 9, avoiding an issue of repeated vaccine administration to ages 10 through 13.
2. The correction shifts the total from 51.0 million deaths averted to 51.5 million deaths averted from 2021-2030
3. Low cervical cancer burden in high income countries results in fewer lives saved
4. HPV fix will be integrated into all future rounds of our estimates

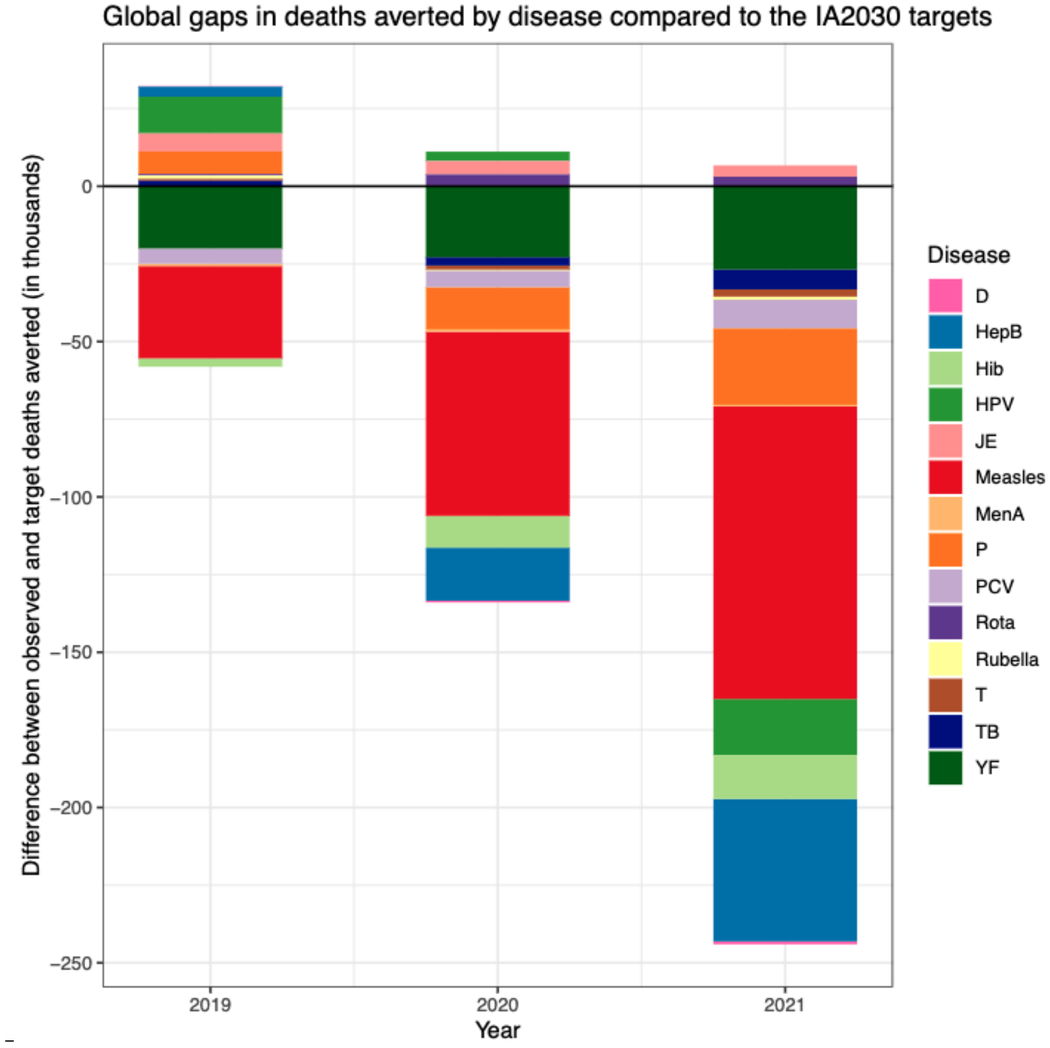
Annual monitoring of Impact Goal 1.1 (IA2030 M&E framework)

In addition to target setting, our team has taken on monitoring of progress and comparing observed coverage rates to aspirational targets. In doing so we:

- Process updated WUENIC vaccine coverage estimates and WPP population estimates
- Translate coverage and population estimates in fully vaccinated persons (FVPs)
- Convert FVPs to deaths averted
- Compare observed deaths averted to target deaths averted

Annual monitoring of Impact Goal 1.1 (IA2030 M&E framework)



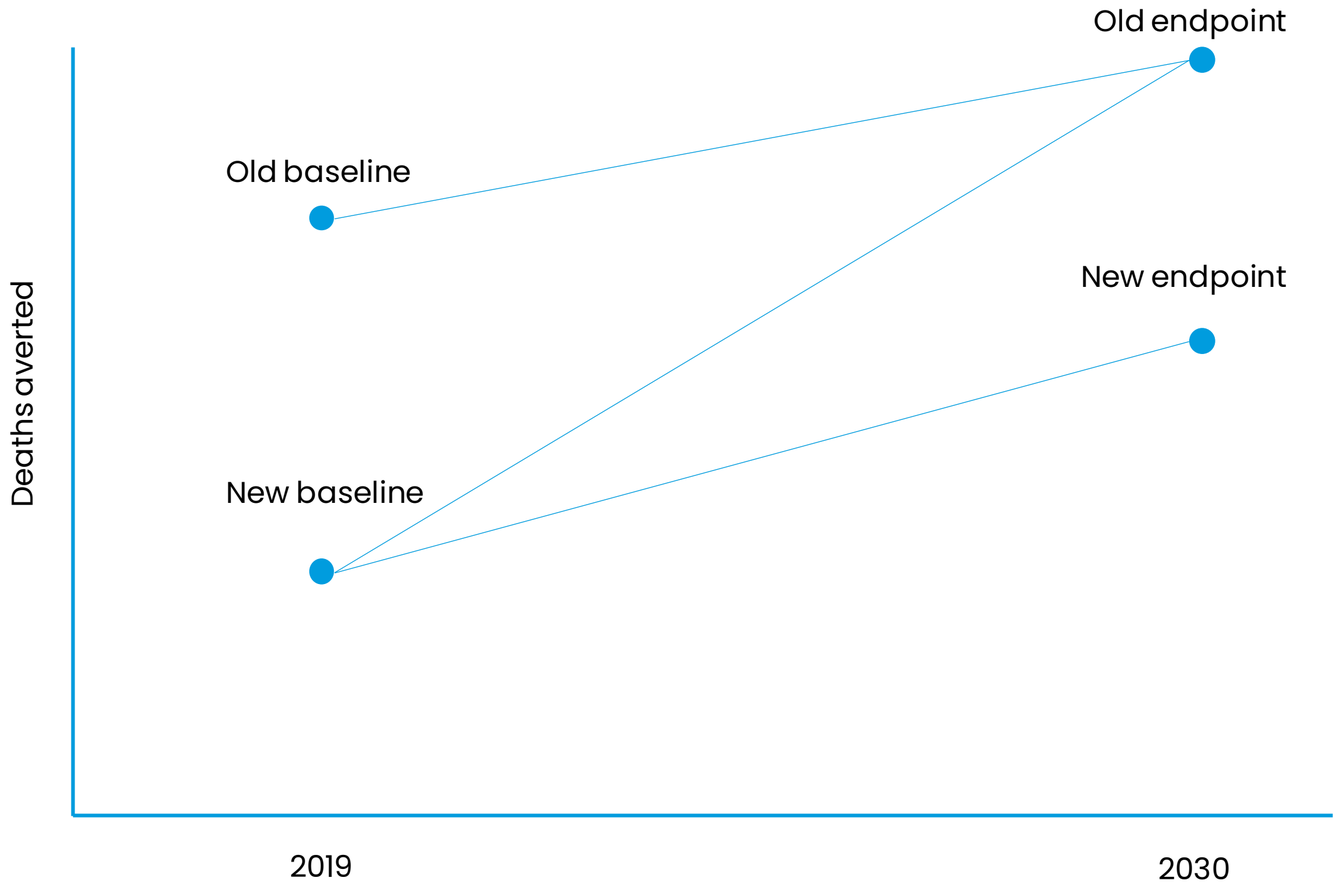


Annual monitoring options

Annual reporting options	Steps	Strengths	Weaknesses
Keep current targets	Leave as is	Retain existing goal, avoiding confusion	Evaluating performance is complicated
Adjust targets with new 2019 baseline	Reset targets with the new WUENIC 2019 baseline	Clear monitoring of progress	Level of ambitiousness of target is changed
Adjust targets with new 2019 baseline and 2030 endpoint	New baseline and calculate DTP1 using zero-dose target update	Clear monitoring of progress and ambitiousness stays the same	Most work intensive

* We are planning to adjust the population to the latest WPP estimates for all options

Annual monitoring options



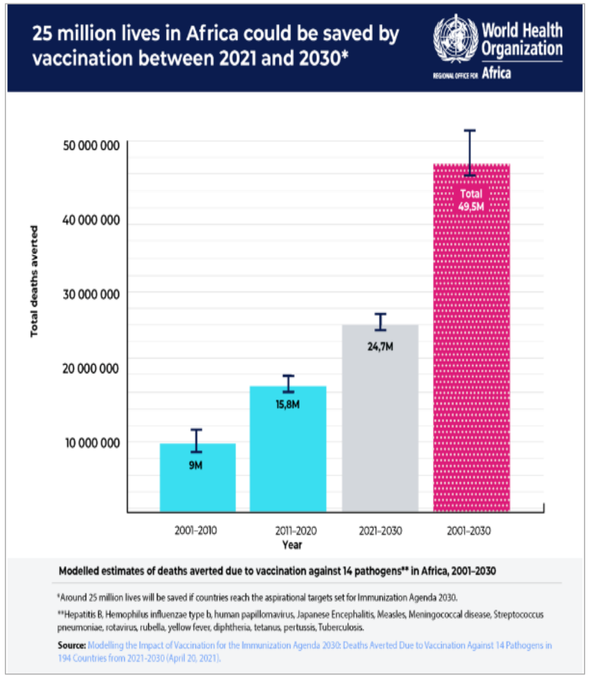
Outputs from the first year (2020-2021)

- The first iteration of estimates were:
  - Submitted to the 74th World Health Assembly as targets for the Impact Goal indicator 1.1 (IG 1.1 "number of future deaths averted through immunization") aspart of IA2030 M&E framework
  - Used for advocacy for the launch of IA2030 during the World Immunization Week 2021
  - Shared as pre-print and submitted to *Vaccine* as part of the IA2030 supplement
  - The IA2030 coverage scenario was used as an input into the IA2030 cost estimates generated by JHU IVAC Economics & Finance team and WHO VOV team

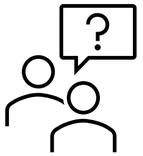
Impact Goal		Indicator	2030 Target
1 Prevent Disease	Save lives	**1.1** Number of future deaths averted through immunization[i]	**50 million future deaths averted globally**
	Control, eliminate & eradicate VPDs	**1.2** Number and % of countries achieving endorsed regional or global VPD control, elimination and eradication targets[ii]	**All countries achieve the endorsed regional or global VPD control, elimination and eradication targets**
	Reduce VPD outbreaks	**1.3** Number of large or disruptive VPD outbreaks[iii]	**All selected VPDs[iii] have a declining trend in the global annual number of large or disruptive outbreaks**

Outputs from the second year (2021-2022)

- The first iteration estimates were:
  - Used for advocacy during the African Vaccination Week 2022 (WHO AFRO)
  - Used as input into the Return on investment estimates for WHO's second Investment Case
- Improvement in models and methods:
  - Updated uncertainty analysis & analysis plan for validation of high-income country estimates based on recommendations from IVIR-AC
  - Updated manuscript for submission to another journal
- Next target pathogens identified
  - Analytical framework for polio, influenza
  - Coordinate with VIMC on Typhoid, Cholera, Malaria, and COVID-19



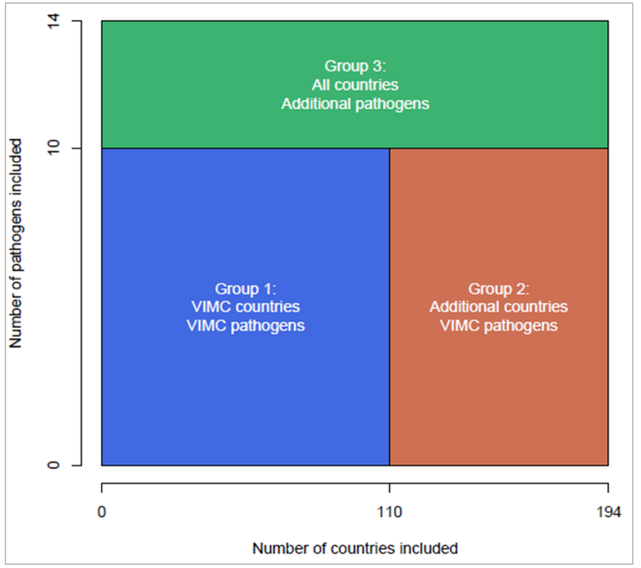
IA2030 vaccine impact estimates –Project objectives for 2022-2023

Use cases	Key objectives	Key outputs
Use case 1: Annual monitoring & reporting	• Establish a protocol and process for annual reporting to SAGE as part of IA2030 M&E process • Incorporate estimates into existing platforms for annual updates	• IA2030 M&E reporting template for IG 1.1 • Annually updated estimates available on 1) the IA2030 scorecard and 2) the WIISE public portal
Use case 2: Mid-point target setting	• Add pathogens and burden measures • Improve models and methods	• Updated estimates of future deaths and DALYs averted for midpoint target updates in 2025*
Additional use cases: IA2030 strategies 	• Identify key questions related to IA2030 strategies that can be answered through IA2030 impact estimates	• Impact analyses tailored to global or regional level needs

*In coordination with Vaccine Impact Modelling Consortium (VIMC)

Collaboration with VIMC

- Close collaboration with Vaccine Impact Modelling Consortium (VIMC) Science Lead as well as Scientific and Technical team:
  - IA2030 vaccine impact estimates incorporate VIMC's impact estimates from their 2019 full model runs for 110 Member States and 10 pathogens (Blue box for Group 1). They were also extrapolated to remaining Member States for 10 pathogens (Red box for Group2).
  - Future target updates in 2025 will leverage VIMC's future models runs including COVID-19 and Malaria



eLife RESEARCH ARTICLE

Lives saved with vaccination for 10 pathogens across 112 countries in a pre-COVID-19 world

Jaspreet Toor[1†], Susy Echeverria-Londono[1†], Xiang Li[1†], Kaja Abbas[2], Emily D Carter[3], Hannah E Clapham[4], Andrew Clark[2], Margaret J de Villiers[1], Kirsten Eilertson[5], Matthew Ferrari[6], Ivane Gamkrelidze[7], Timothy B Hallett[1], Wes R Hinsley[1], Daniel Hogan[8], John H Huber[9], Michael L Jackson[10], Kevin Jean[1,11], Mark Jit[2,12], Andromachi Karachaliou[13], Petra Klepac[2], Alicia Kraay[14], Justin Lessler[3], Xi Li[15], Benjamin A Lopman[14], Tewodaj Mengistu[8], C Jessica E Metcalf[16], Sean M Moore[9], Shevanthi Nayagam[1,17], Timos Papadopoulos[18,19], T Alex Perkins[9], Allison Portnoy[20], Homie Razavi[7], Devin Razavi-Shearer[7], Stephen Resch[20], Colin Sanderson[2], Steven Sweet[20], Yvonne Tam[3], Hira Tanvir[2], Quan Tran Minh[9], Caroline L Trotter[13], Shaun A Truelove[3], Emilia Vynnycky[18], Neff Walker[3], Amy Winter[3], Kim Woodruff[1], Neil M Ferguson[1], Katy AM Gaythorpe[1*]

HIC validation analysis plan

Using vaccine impact estimates in HIC according to the literature, extend estimates in three ways:

- To other high and upper middle economies that were not included in the studies,
- To the IA2030 period which may be many years after some of the studies (differing underlying VPD burden, health system strength),
- To the deaths averted measure where some studies may quantify impact according to cases or DALYS averted.

Next steps will be:

1) Finalize contract for a consultant to support the validation exercise.
2) Complete the literature survey which was started last year.
3) Create a data base of all the results obtained from the literature searches.
4) Document and apply framework for the three estimate extensions as described above.
5) Apply estimates generated to create database of impact estimates in HIC

Thank you

Appendix

Project team

*Changes in the coming year 2022-2023

Function	Name	Affiliation	Location/time zone
Analytics	Austin Carter	Independent consultant for WHO IVB; University of Washington	Portland, USA
Analytics	William Msemburi	WHO Division of Data, Analytics and Delivery for Impact (DDI)	Geneva, Switzerland
VIMC focal point	Katy Gaythorpe	Imperial College London Vaccine Impact Modelling Consortium (VIMC)	London, UK
Project management	So Yoon (Yoonie) Sim	WHO Department of Immunization, Vaccines and Biologicals (IVB)	Geneva, Switzerland
Supervision	Philipp Lambach a.i. Value of Vaccines, Economics and Modelling team lead (Raymond Hutubessy)	WHO Department of Immunization, Vaccines and Biologicals (IVB)	Geneva, Switzerland

- Additional team member: 1 consultant (HIC validation) and 1 consultant (analytics) will join the project team for 2022-2023

- The project team will coordinate closely with WHO IVB's IA2030 focal points:

Alba Maria Ropero, Senior Lead, Immunization Agenda 2030
Erlyn Macarayan, M&E Specialist, Immunization Agenda 2030
Carolyn Inae Kim, Data analyst, Immunization Agenda 2030
Jan Grevendonk, Co-Chair of I2030 M&E WG & Technical Officer, Immunization Information Systems

Stakeholder Committee membership

*New members of the Stakeholder Committee (2022-2023)

	Representative	Organization, consortium or committee	Location/time zone
1	Emily Dansereau	The Bill & Melinda Gates Foundation (BMGF)	Seattle, USA
2	Todi Mengistu*	Gavi, the Vaccine Alliance (Gavi)	Geneva, Switzerland
3	Jon Mosser	Institute for Health Metrics and Evaluation (IHME)	Seattle, USA
4	Walt Orenstein	Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC)	Atlanta, USA
5	Katy Gaythorpe	Vaccine Impact Modeling Consortium (VIMC)	London, UK
6	Ulla Griffiths	United Nations International Children's Emergency Fund (UNICEF)	New York, USA
7	Dimitri Prybylski/Erin Palmisano*	US Centers for Disease Prevention and Control (US CDC)	Atlanta, USA
8	William Msemburi*	WHO Division of Data, Analytics and Delivery for Impact (DDI)	Geneva, Switzerland
9	Marta Gacic-Dobo Unit head a.i., IAI*	WHO Department of Immunization, Vaccines and Biologicals (IVB)	Geneva, Switzerland
10	Philipp Lambach Team Lead a.i., VoV* (Raymond Hutubessy)	WHO Department of Immunization, Vaccines and Biologicals (IVB)	Geneva, Switzerland

Please find the presentations, notes and background materials from the previous meeting in the shared folder.

World Health Organization

Session 9

VIMC

WHO IVB's collaboration with the Vaccine Impact Modelling Consortium

For IVIR-AC meeting

14 September 2022

WHO IVB Value of Vaccines, Economics and Modelling team

Introduction to VIMC (2017-2022)

1. The Vaccine Impact Modelling Consortium (VIMC) comprises 21 modelling groups for 12 diseases (cholera, hepatitis B, Hib, HPV, Japanese encephalitis, measles, meningitis A, pneumococcal disease, rotavirus, rubella, typhoid and yellow fever)
   - focus on consistency, efficiency and quality of vaccine impact modelling analyses
2. VIMC's goals have been to:
   - Provide Gavi and BMGF with vaccine impact estimates for 12 diseases and 112 countries
   - Advance the research agenda in modelling vaccine impact

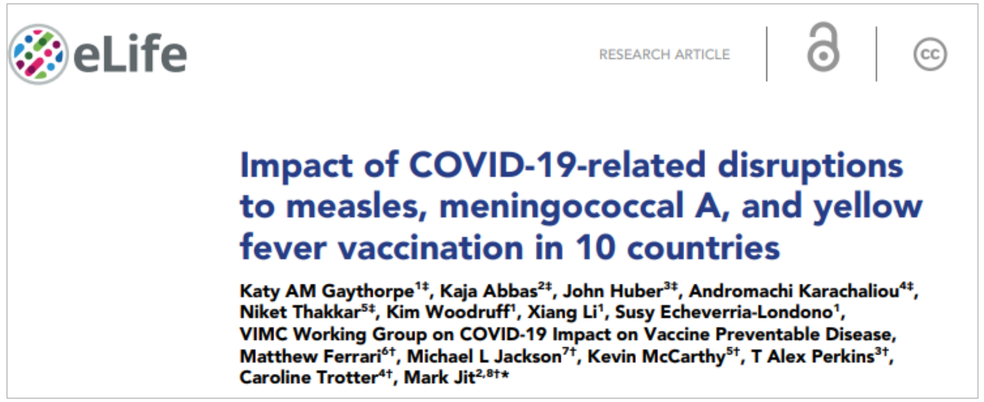
Previous collaboration between WHO IVB & VIMC (2017-2022)

1. **IA2030 vaccine impact estimates** incorporate VIMC's impact estimates from their 2019 model runs for 110 Member States and 10 pathogens

2. With input from WHO disease focal points, VIMC modelling groups estimated **the impact of RI and SIA disruptions for measles, meningococcal A and yellow fever vaccination** during the early phase of the COVID-19 pandemic

3. Individual modelling groups collaborated with WHO disease focal points to address **pathogen-specific policy questions** (e.g. measles mortality estimates, Defeating Meningitis by 2030 global roadmap, etc.)

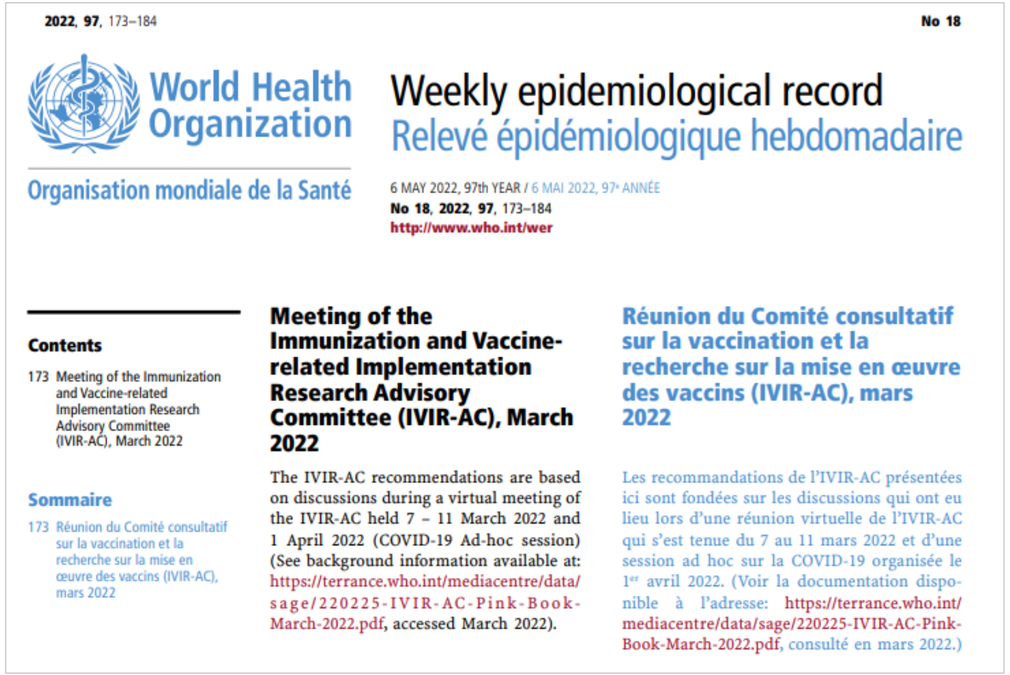
4. **Coordination** through regular calls between WHO IVB & VIMC; the IVB director serving on the Scientific Advisory Board of VIMC; WHO Collaborating Centre for Infectious Disease Modelling agreement



VIMC and IVIR-AC

Standing session for information during previous IVIR-AC meetings:

- March 2021: Weekly epidemiological record, 30 April 2021, No 17, 2021, 96, 133–144
- September 2021: Weekly epidemiological record, 26 November 2021, No 47, 2021, 96, 569–584
- March 2022: Weekly epidemiological record, 06 May 2022, No 18, 2022, 97, 173–184



2022, 97, 173–184 No 18

World Health Organization

Organisation mondiale de la Santé

Weekly epidemiological record

Relevé épidémiologique hebdomadaire

6 MAY 2022, 97th YEAR / 6 MAI 2022, 97e ANNÉE

No 18, 2022, 97, 173–184

http://www.who.int/wer

Contents

173 Meeting of the Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC), March 2022

Sommaire

173 Réunion du Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC), mars 2022

Meeting of the Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC), March 2022

The IVIR-AC recommendations are based on discussions during a virtual meeting of the IVIR-AC held 7 – 11 March 2022 and 1 April 2022 (COVID-19 Ad-hoc session) (See background information available at: https://terrance.who.int/mediacentre/data/sage/220225-IVIR-AC-Pink-Book-March-2022.pdf, accessed March 2022).

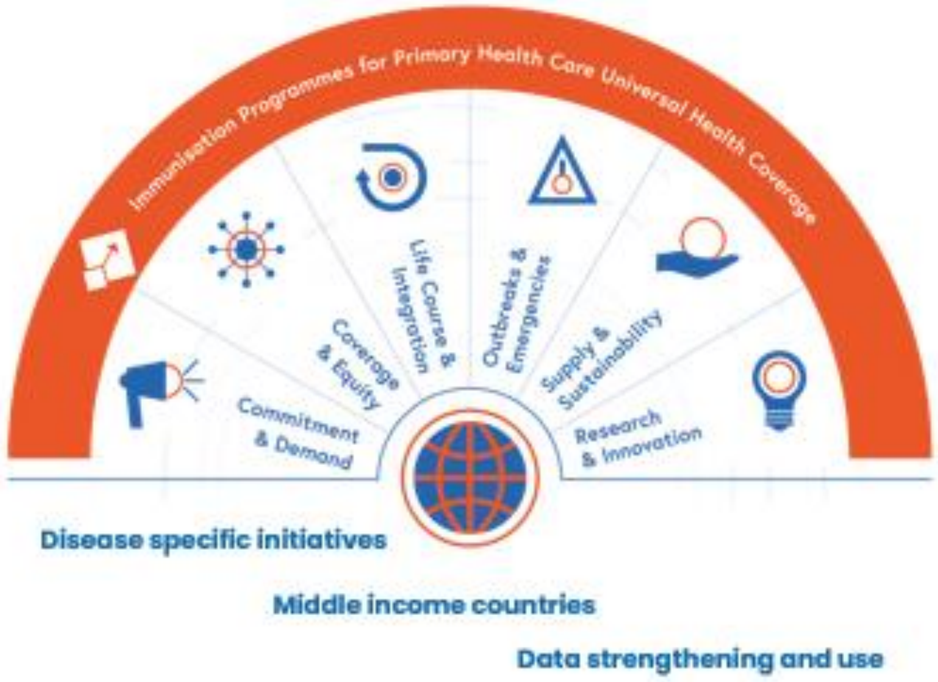
Réunion du Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC), mars 2022

Les recommandations de l'IVIR-AC présentées ici sont fondées sur les discussions qui ont eu lieu lors d'une réunion virtuelle de l'IVIR-AC qui s'est tenue du 7 au 11 mars 2022 et d'une session ad hoc sur la COVID-19 organisée le 1er avril 2022. (Voir la documentation disponible à l'adresse: https://terrance.who.int/mediacentre/data/sage/220225-IVIR-AC-Pink-Book-March-2022.pdf, consulté en mars 2022.)

During the March 2022 meeting, VIMC presented their latest 2021 model runs and ongoing workstreams that examine the effect of subnational heterogeneity on vaccination coverage, the role of demographic uncertainty and investigations on vaccine equity as part of a systematic literature review.

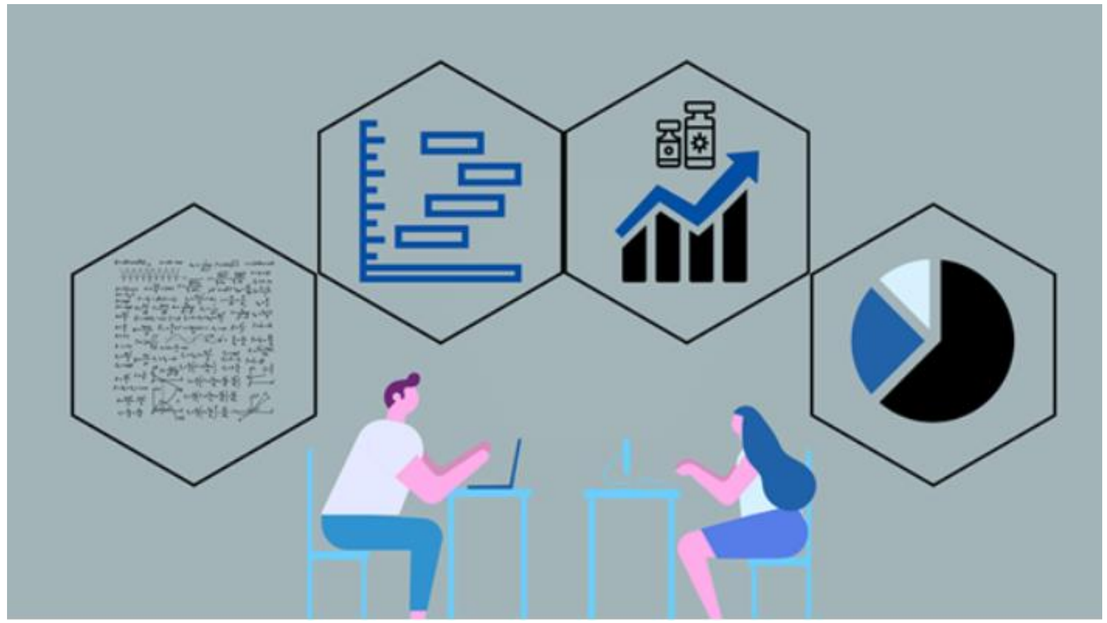
WHO IVB Priorities for modelling for vaccine impact (from 2022 onwards)

IA2030 Strategic Priorities



1. Coordinate the generation of modelled estimates to inform the Immunization Agenda 2030 and other global level strategies
2. Bring together experts to advise on modelling methods and evidence to inform immunization policy at the global level
   - IVIR-AC
   - Support for SAGE Working Group on COVID-19 vaccines - impact modelling subgroup
3. Collaborate with partners to increase capacity for generating and using modelled evidence for policy and programmatic decisions in low- and middle-income countries.

VIMC 2.0 and key areas for collaboration (from 2022 onwards)



- IA2030 vaccine impact estimates will be updated in close coordination with VIMC (their full model runs & inclusion of additional pathogens such as Cholera, Typhoid, COVID-19, Malaria).
- Through VIMC's Stakeholder Group mechanism, WHO IVB will share key questions related to strategic, policy and program decisions that could benefit from VIMC's modelling work.
- We expect more opportunities for collaboration to increase capacity for generating and using modelled evidence in low- and middle-income countries

World Health Organization | IVB

Thank you

Vaccine Impact Modelling Consortium

Updates on VIMC

IVIR-AC meeting September 2022

Dr. Katy Gaythorpe

VACCINE IMPACT MODELLING CONSORTIUM
Imperial College London
Gavi The Vaccine Alliance
BILL & MELINDA GATES foundation
wellcome

This presentation

- Overview of VIMC 2.0
  - Aims
  - Priorities

- Summarise progress on third-wide consortium paper on the implications of immunisation disruptions on burden and vaccine impact

VACCINE IMPACT MODELLING CONSORTIUM

VIMC 2.0

Vision for VIMC by 2027

By the end of the five-year grant in 2027 VIMC expects to be:

- A normative source providing reliable and accessible estimates of vaccine impact across the Gavi portfolio
- Able to address critical modelling-related vaccine policy questions raised by international stakeholders who will be dynamically engaged in our work
- Able to demonstrate translation from VIMC modelling to real-world policy that improves health outcomes
- A diverse international community of vaccine impact modellers, inclusive of modellers in LMICs, that clearly articulates its own mission and adds value as a partner to other vaccine modelling groups and entities
- A significant global provider of training in infectious disease modelling and its application to vaccine-preventable diseases for both modellers and policymakers using modelling to inform their decisions.

VACCINE IMPACT MODELLING CONSORTIUM

Overview

- In VIMC 2.0 we will focus on
  - high-quality vaccine impact estimates across multiple countries and antigens
  - incorporating new vaccines including malaria and COVID
  - policy-relevant questions that require infectious disease modelling
- Vertical (disease specific) research program: led by VIMC modelling groups (including new groups recruited though requests for proposals (RfPs)
- Horizontal work program: involves all VIMC modelling groups, led by VIMC secretariat. 4 major themes

VACCINE IMPACT MODELLING CONSORTIUM

Themes

- (1) **stakeholder engagement**, to:
  - disseminate VIMC outputs
  - identify and refine vaccine impact modelling questions posed by decision-makers
  - help ensure that timely answers to these questions are well communicated and understood
- (2) **coordination** of the modelling response to address vaccine policy-relevant questions
- (3) **ecosystem building** to ensure the consortium is more inclusive of modelling groups in low- and middle-income countries (LMICs)
- (4) **shared learning agenda** to optimize use of available vaccines through efficient schedule and campaign design and to respond to future challenges in vaccine impact modelling

VACCINE IMPACT MODELLING CONSORTIUM

Shared learning agenda

- Initial specific research questions will focus on:
  - Optimising the use of current vaccines
    - Improving campaign efficiency
    - Improving schedule efficiency or scope
    - Optimise stockpiling of vaccines
    - Does vaccine efficiency or effectiveness vary in different groups
    - Are we on track to meet targets?
  - Future challenges for vaccine-preventable disease management
    - Climate change and its implications for vaccine-preventable disease management: co-funded by the Wellcome Trust (see later slide)
    - Conflict and displaced populations
    - Health care improvements
  - The implications of vaccination coverage disruptions (see later slide on the third consortium-wide publication)

But we are actively seeking new priority topics and questions

VACCINE IMPACT MODELLING CONSORTIUM

Policy relevant questions

- We are forming a new stakeholder group and wider VIMC network
  - to advise on the consortium's overall strategic direction
  - to identify, refine, and prioritize policy-relevant questions
  - to advise on the selection of new modelling groups (following RfPs)
  - to assist disseminating VIMC outputs and provide feedback as 'consumers' of vaccine impact estimates

- We are actively seeking policy-relevant priority questions- please do get in touch:
  - vimcquestions@imperial.ac.uk
  - k.gaythorpe@imperial.ac.uk

VACCINE IMPACT MODELLING CONSORTIUM

Climate change and vaccine-preventable diseases

- Aims:
  - Enhancing core VIMC capabilities
  - Capacity-strengthening of modelling in LMICs
  - Better characterisation of the mechanistic relationship between environment/climate and disease transmission
  - Assessing implications of long-term climate change for disease burden, range and routine vaccination
  - Optimising control programmes to respond to seasonal variation in disease burden and the consequences of increasingly frequent extreme climate events

VACCINE IMPACT MODELLING CONSORTIUM

Third consortium-wide publication

Impact of immunisation disruptions

Overview

- Based on the 2021 model runs from all current VIMC groups
  - 12 diseases/vaccines
  - 112 countries
  - Data as of 2020
- Additional analyses to be added based on latest (2022) WUENIC and campaign information
- Aims:
  - Assess the impact of coverage disruptions on burden
  - Highlight groups and cohorts to target for catch-up activities
  - Assess progress towards targets given disruption
  - Examine the field of opportunity for recovering from coverage disruptions

VACCINE IMPACT MODELLING CONSORTIUM

Summary

- As we look towards VIMC 2.0 and the next 5 years, we will expand our network
  - We are seeking collaborators
  - We are seeking policy-relevant priority questions

- The third consortium-wide publication will be submitted Q4 2022

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