World Health Organization

Department of Immunization, Vaccines and Biologicals (IVB)

IVIR-AC – February 2024

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

MICROSOFT TEAMS - VIRTUAL MEETING

WHO HEADQUARTERS, GENEVA, SWITZERLAND

26 February 2024 – 1 March 2024

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)
26 February 2024 – 1 March 2024

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	28
3. **WER summary of last IVIRAC**	38
4. **Background information to the sessions**	
Session 1: Modelling public health impact and cost-effectiveness of the R21/Matrix-M malaria vaccine	52
Session 2: Meta-Analysis of Economic Evaluations of Vaccines	140
Session 3: Global Analysis Estimating the impact of vaccination over 50 years	187
Session 4: Modelling the impact of different dose schedules for RTS,S malaria vaccine	220

World Health Organization

Current IVIR-AC – Advisory Committee Members

Sheetal Silal, Modelling and Simulation Hub, Africa (MASHA), University of Cape Town, Cape Town, **South Africa**
Rakesh Aggarwal, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, **India**
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**
Alexandra Hogan, School of Population Health, University of New South Wales, Sydney, **Australia.**
Sun-Young Kim, Global Health, School of Public Health, Seoul National University, Seoul, **Republic of Korea**
Kathy Leung, School of Public Health, The University of Hong Kong, **Hong Kong SAR, China**

World Health Organization

William Moss, International Vaccine Access Center Johns Hopkins Bloomberg School of Public Health, **USA**
Patrick Munywoki, U.S. Centers for Disease Control and Prevention, Kenya, Nairobi, Kenya
Allison Portnoy, Department of Global Health of the Boston University School of Public Health, Boston, **USA**
Meru Sheel, School of Public Health, the University of Sydney, Sydney, Australia
Xuan-Yi Wang, Research Scientist, Shanghai Medical College, Fudan University, **China**

World Health Organization

IVIR-AC Terms of References

The IVIR-AC 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 Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC)
26 February – 1 March 2024
Virtual Meeting
WHO HQ
Agenda

Day 1: Monday, 26 February 2024 (CET)

Time CET	Session	Purpose of the session, target outcomes and questions for IVIR-AC	Duration
12:00	**Welcome** K O'Brien	Update on global strategies and issues of relevance to WHO	**5 min**
12:05	**Introduction** P Lambach, S Silal, Chair	Welcome, Objectives, Administrative information	**5 min**
12:10	**Modelling public health impact and cost-effectiveness of the R21/Matrix-M malaria vaccine** Background summary. *10 min.* M Hamel Technical Presentation on modelled estimates of impact and cost-effectiveness of R21/Matrix-M (Imperial College). *20 min.* N Schmit Technical Presentation on Description of the proposed modelling of impact and cost-effectiveness of R21/Matrix-M (Telethon Kids Institute (formerly at STPH)). *20 min.* M Penny Discussion. *20 min.* IVIR-AC FPs: **S Flasche**, W Moss, K Leung, P Munywoki SAGE WG FP: Kathy Neuzil, Kim Mulholland, Peter Smith	FOR DECISION To what extent does the Imperial modelling analysis estimate the impact and cost-effectiveness of the R21 vaccine across transmission intensities, seasonal patterns, and settings using different malaria interventions? For any gaps identified, to what extent are these due to a) model structure or b) uncertainties in the data informing model parameters What comments or recommendations does IVIR-AC have on the proposed analysis based on the Telethon Kids Institute model to address questions 1 and 2 Are there suggestions on how parameter estimates can be improved?	**1h10**
13:20	**Wrap-up** S Silal, Chair	Summary of the day's findings and request any follow-up from WHO Secretariat/IVIR-AC FPs for closed session	**5 min**
13:25	**Closed session**	Closed session discussion/finalization of recommendations among IVIR-AC focal points	**35 min**
14:00	**End of day**		

Day 2: Tuesday, 27 February 2024 (CET)

Time CET	Session	Purpose of the session, target outcomes and questions for IVIR-AC	Duration
13:00	**Recap** S Silal, Chair	Recap of the previous day and objectives for the day	**5min**
13:05	**Meta-Analysis of Economic Evaluations of Vaccines** Background summary.*10 min.* K Yeung Technical Presentation on Overview of existing MAEE studies, gaps and challenges *20 min.* N Chaiyakunapruk Technical Presentation Proposal of next steps to guide the advice on how the work of MAEE of vaccines should be continued. *20 min.* A Hogan Discussion. *20 min.* IVIR-AC FPs: **H Farooqui**, R Aggarwal, XY Wang, A Portnoy SAGE WG FP: Gabriel Leung	**FOR DECISION** Review and provide feedback on the identified gaps and challenges of MAEE Review and provide feedback on the proposed research agenda to guide the advice on how the work of MAEE of vaccines should be continued	**1h10**
14:15	**Wrap-up** S Silal, Chair	Summary of the day's findings and request any follow-up from WHO Secretariat/IVIR-AC FPs for a closed session	**10 min**
14:25	**Closed session**	Closed session discussion/finalization of recommendations among IVIR-AC focal points	**35 min**
15:00	**End of day**		

Day 3: Wednesday, 28 February 2024 (CET)

Time CET	Session	Purpose of session, target outcomes and questions for IVIR-AC	Duration
12:00	**Recap** S Silal, Chair	Recap of the previous day and objectives for the day	**5 min**
12:05	**Global Analysis Estimating the impact of vaccination over 50 years** Background summary. *10 min.* Y Sim Technical Presentation on Analysis results on the global impact of vaccination over the last 50 years A Shattock, H Johnson. *20 min.* Discussion. *20 min.* IVIR-AC FPs: A Hogan, SY Kim, M Sheel SAGE WG FP: Folake Olayinka	**FOR INFORMATION** Does the proposed approach to estimating DALYs and the uncertainty thereof sufficiently address IVIR-AC recommendations from the September meeting? Is the proposed approach for SIA data appropriately applied to incorporate impact estimates from non-routine immunization activities? Does IVIR-AC have recommendations for communicating the results for advocacy for the 50 year anniversary of EPI?	**50 min**
12:55	**Wrap-up** S Silal, Chair	Summary of the day's findings and request any follow-up from WHO Secretariat/IVIR-AC FPs for a closed session	**5 min**
13:00	**Closed session**	Closed session discussion/finalization of recommendations among IVIR-AC focal points	**40 min**
13:40	**End of day**		

Day 4: Thursday, 29 February 2024 (CET)

Time CET	Session	Purpose of session, target outcomes and questions for IVIR-AC	Duration
12:00	**Recap** S Silal, Chair	Recap of the previous day and objectives for the day	**5 min**
12:05	**Modelling the impact of different dose schedules for RTS, S malaria vaccine in seasonal settings** Background summary. *10 min.* M Hamel. Technical Presentation on Presentation of modelled public health impact of RTS, S in perennial and seasonal settings. *15 min.* D. Figueroa-Downing (STPH). Technical Presentation on Presentation of modelled public health impact of different dose schedules in seasonal settings. *15 min.* H Thompson (PATH). Discussion. *20 min.* IVIR-AC FPs: S Flasche, W Moss, K Leung, P Munywoki SAGE WG FP: K Neuzil, Ki Mulholland, P Smith	**FOR DECISION** Given the lack of clinical data to inform different dosing intervals, are the current modelling results sufficient to support a specific policy recommendation on the optimal spacing between dose 3 and 4? To what extent do the models (or proposed modelling) address potential differences in vaccine impact across transmission intensities and seasonal settings, accounting for variations in the age distribution of severe disease? Does IVIR-AC have feedback on the approach and results of the sensitivity analysis conducted on the assumed efficacies for the timing of the 4th dose (Telethon Kids Institute model)?	**60 min**
13:05	**Wrap-up**	Summary of the day's findings and request any follow-up from WHO Secretariat/IVIR-AC FPs for a closed session	**10 min**
13:15	**Meeting Closure**	Follow up to meeting and next steps	**5 min**
13:20	**Closed session**	Closed session, discussion/finalization of recommendations among IVIR-AC focal points	**40 min**
14:00	**End of day**		

Day 5: Friday, 1 March 2024 (CET)

Time CET	Session	Purpose of session, target outcomes and questions for IVIR-AC	Duration
13:00	**Closed Session**	Closed session with all IVIR-AC members	**3 h**
16:00	**End of day**		

Meeting of the Advisory Committee on Immunization and Vaccines-Related Implementation Research (IVIR-AC)
Microsoft Teams
Geneva, Switzerland
26 February to 1 March 2024

Draft list of participants

Advisory Committee Members

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

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

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**

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

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

Kathy Leung, University of Hong Kong, Hong Kong, **People's Republic of China**

William Moss, International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, Baltimore**, United States of America**

Patrick Munywoki, Centers for Disease Control and Prevention, Kenya, Nairobi, **Kenya**

Allison Portnoy, Boston University School of Public Health, Boston, **United States of America**

Meru Sheel, University of Sydney, Sydney, **Australia**

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

Xuan-Yi Wang, Shanghai Medical College, Fudan University, Shanghai, **People's Republic of China**

SAGE WG Focal Points

Gabriel Leung, University of Hong Kong, Hong Kong, **People's Republic of China**

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

Kim Mulholland, University of Melbourne, Department of Paediatrics, Australia, Melbourne, **Australia**

Hanna M. Nohynek, National Institute for Health and Welfare THL, Helsinki, **Finland**

Kathy Neuzil, Center for Vaccine Development and Global Health (CVD), Division of Geographic Medicine, University of Maryland School of Medicine, Maryland, **United States of America**

Folake Olayinka, U.S. Agency for International Development (USAID), Washington DC**, United States of America**

Peter Smith, London School of Hygiene and Tropical Medicine, London, **United Kingdom of Great Britain and Northern Ireland**

Participants

Nathorn Chaiyakunapruk, University of Utah, Salt Lake City, **United States of America**

Azra Ghani, Imperial College London, London, **United Kingdom of Great Britain and Northern Ireland**

Helen Johnson, Consultant to WHO, Geneva, **Switzerland**

Jessica Ochalek, University of York, York, **United Kingdom of Great Britain**

Richmond Owusu, University of Ghana, Accra, **Ghana**

Melissa Penny, Swiss Tropical and Public Health Institute, Basel, **Switzerland**

Francis Ruiz, London School of Hygiene & Tropical Medicine, London, **United Kingdom of Great Britain**

Andrew Shattock, Consultant to WHO, Geneva, **Switzerland**

Nora Schmit, Imperial College London, London, **United Kingdom of Great Britain and Northern Ireland**

Hayley Thompson, PATH, Seattle, **United States of America**

Marcia Weaver, The Institute for Health Metrics and Evaluation, Seattle, **United States of America**

Peter Winskill, Imperial College London, London, **United Kingdom of Great Britain and Northern Ireland**

Observers

Sharon Achilles, Bill and Melinda Gates Foundation (BMGF), 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**

Marta Tufet Bayona, Gavi, the Vaccine Alliance, Geneva, **Switzerland**

Joseph Breeze, Taskforce for Global Health, Georgia, **United States of America**

Roy Burnstein, Bill and Melinda Gates Foundation (BMGF), Seattle, **United States of America**

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

Chi-Tai Fang

Maria Christou-Ergo, Sydney School of Public Health, Faculty of Medicine and Health, Sydney, **Australia**

Anne-Marie Copek, Bill and Melinda Gates Foundation (BMGF), Seattle, **United States of America**

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

Daniella Figueroa-Downing, Swiss Tropical and Public Health Institute (TPH), Allschwil, **Switzerland**

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

Tara Jatlaoui, Centers for Disease Control and Prevention, Atlanta, **United States of America**

Mark Jit, London School of Hygiene & Tropical Medicine, London, **United Kingdom of Great Britain**

Katrina Kretsinger, Independent Consultant, **United States of America**

Supriya Kumar, Bill and Melinda Gates Foundation (BMGF), Seattle, **United States of America**

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

Alan Martin, GSK Vaccines, Wavre, **Belgium**

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**

Kinga Meszaros, GSK Vaccines, Wavre, **Belgium**

Bruno Moonen, Bill and Melinda Gates Foundation (BMGF), Seattle, **United States of America**

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

Emily Nickels, Bill and Melinda Gates Foundation (BMGF), Seattle, **United States of America**

Jacquie Narotso Oliwa, KEMRI-Wellcome Trust Research Programme, Nairobi, **Kenya**

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

Simon Procter, London School of Hygiene & Tropical Medicine, London, **United Kingdom of Great Britain**

Arindam Ray, Bill and Melinda Gates Foundation (BMGF), Seattle, **United States of America**

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

Celina Schocken, Bill and Melinda Gates Foundation (BMGF), Seattle, **United States of America**

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

Larry Slutsker, Independent Consultant, **United States of America**

Duncan Steele, Bill and Melinda Gates Foundation (BMGF), Seattle, **United States of America**

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

Niket Thakkar, Bill and Melinda Gates Foundation (BMGF), Seattle, **United States of America**

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

Everett Tremblay (Unify), Bill and Melinda Gates Foundation (BMGF), Seattle, **United States of America**

Caroline Trotter, University of Cambridge, Department of Pathology, Cambridge, **United Kingdom of Great Britain, and Northern Ireland**

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

Sajesh Veettil, London School of Hygiene & Tropical Medicine, London, **United Kingdom of Great Britain**

Tom Ward, GSK Vaccines, Wavre, **Belgium**

Pan-ngum Wirichada, Mathematical and Economic Modelling (MAEMOD), Bangkok, **Thailand**

Yusuf Yusufari, Bill and Melinda Gates Foundation (BMGF), Seattle, **United States of America**

WHO Regional Offices

Tigran Avagyan, World Health Organization, Regional Office for South-East Asia, New Delhi, **India**

Anne E. Jean Baptiste, World Health Organization Regional Office for the Americas, Washington DC, **United States of America**

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

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

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

Niyazi Cakmak, World Health Organization Regional Office for Europe, Copenhagen**, Denmark**
Heeyoun Cho, World Health Organization, Regional Office for the Western Pacific, Manila, **Philippines**

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

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

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

Liudmila Mosina, World Health Organization Regional Office for Europe, Copenhagen**, Denmark**

Desireé Pastor, 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 Office of the Americas, Washington DC, **United States of America**

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

Jennifer N. Sanwogou, World Health Organization Office of the Americas, Washington DC, **United States of America**

Rahul Srivastava, World Health Organization Regional Office for the South-East Asia, New Delhi, **India**

Carlos Torres, World Health Organization Office of the Americas, Washington DC, **United States of America**

María Soledad Urrutia, World Health Organization Office of the Americas, Washington DC, **United States of America**

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

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

Charles Shey Umaru Wiysonge, Regional Office for Africa, Brazzaville**, Republic of the Congo**

Weigong Zhou, World Health Organization, Regional Office for the Western Pacific Region, Manila, **Philippines**

WHO Secretariat

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

Roodly Archer, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Naor Bar-Zeev, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

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

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

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

Cynthia Bergstrom, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

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

Paul Bloem, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

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

Andrew Bosman, Communicable and Noncommunicable Diseases, World Health Organization, **Switzerland**

Tania Cernuschi, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

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

Lucia Helena De Oliveira, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

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

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

Jeremy Farrar, Chief Scientist, World Health Organization, **Switzerland**

Johanna Fihman, Immunization, Vaccines & 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**

Gitte Giersing, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

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

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

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

Mary Hamel, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

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

Louise Henaff, Immunization, Vaccines & 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**

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**

Mitsuki Koh, 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**

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

Lisa Menning, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

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

Vittal Mogasale, Economic Evaluation & Analysis, World Health Organization, **Switzerland**

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

Rafiq Nii Attoh Okine, Communicable and Noncommunicable Diseases**,** World Health Organization, **Switzerland**

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

Tara Lavanya Prasad, Immunization Vaccines and Biologicals, World Health Organization, **Switzerland**

Vaseeharan Sathiyamoorthy, Communicable and non-Communicable Diseases**,** 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**

Nathalie Vande Maele, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Anshu Varma, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

Jenny Walldorf, Immunization, Vaccines & Biologicals, World Health Organization, **Switzerland**

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

Lindsey Wu, Communicable and Noncommunicable Diseases, World Health Organization, **Switzerland**

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

Nasir Yusuf, 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 IVIR-AC

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

19 JANUARY 2024, 99th YEAR / 19 JANVIER 2024, 99e ANNÉE
No 3, **2024**, **99**, 11–22
http://www.who.int/wer

Contents

11 Meeting of the Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC), September 2023

Sommaire

11 Réunion du Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC), septembre 2023

Meeting of the Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC), September 2023

The Immunization and Vaccine-related Related Implementation Research Advisory Committee (IVIR-AC) held its most recent meeting on 11–13 September 2023.[1] The meeting comprised 8, during which IVIR-AC provided technical feedback on various topics including measles vaccination campaigns and elimination, the TAK-003 dengue vaccine, COVID-19 modelling in the WHO African Region, therapeutic vaccination for human papillomavirus virus (HPV) and the translation of modelling into policy.

The IVIR-AC meeting was opened by Dr Kate O'Brien, Director of the WHO Department of Immunization, Vaccines and Biologicals (IVB), who emphasized the importance of vaccine-related research as immunization systems continue to recover from disruptions related to the COVID-19 pandemic. Contributing IVIR-AC members included: Rakesh Aggarwal, Habib Hasan Farooqui, Stefan Flasche, Alexandra Hogan, Sun-Young Kim, Julie Leask, Paula M. Luz, Dafrossa C. Lyimo, William Moss, Walter Orenstein, Virginia Pitzer, Sheetal Silal, Xian-Yi Wang, and Joseph Wu. Committee members did not receive funding for this meeting. On the basis of discussions in open and closed sessions, IVIR-AC members developed recommendations for each topic presented.

Réunion du Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC), septembre 2023

Le Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC) a tenu sa dernière réunion du 11 au 13 septembre 2023.[1] Cette réunion comportait 8 sessions traitant de différents thèmes sur lesquels l'IVIR-AC a émis des avis techniques, notamment: les campagnes de vaccination contre la rougeole et l'élimination de cette maladie, le vaccin TAK-003 contre la dengue, la modélisation de la COVID-19 dans la Région africaine de l'OMS, les vaccins thérapeutiques contre le papillomavirus humain (HPV) et la transposition des résultats de modélisation en politiques.

La réunion de l'IVIR-AC a été ouverte par le Dr Kate O'Brien, Directrice du Département Vaccination, vaccins et produits biologiques (IVB) de l'OMS qui a souligné l'importance que revêt la recherche sur les vaccins à un moment où les systèmes de vaccination continuent de se relever des perturbations occasionnées par la pandémie de COVID-19. Parmi les membres contributeurs de l'IVIR-AC figuraient: Rakesh Aggarwal, Habib Hasan Farooqui, Stefan Flasche, Alexandra Hogan, Sun-Young Kim, Julie Leask, Paula M. Luz, Dafrossa C. Lyimo, William Moss, Walter Orenstein, Virginia Pitzer, Sheetal Silal, Xian-Yi Wang et Joseph Wu. Les membres du Comité n'ont pas reçu de financement pour cette réunion. Sur la base des discussions menées en sessions ouvertes ou à huis clos, les membres de l'IVIR-AC ont formulé des recommandations sur chacun des thèmes présentés.

[1] Meeting of the Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC). Geneva: World Health Organization; 2023 (https://terrance.who.int/internet/data/sage/IVIR-AC_Pink_Book_Sept2023.pdf, accessed September 2023).

[1] Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC). Genève: Organisation mondiale de la santé, 2023 (https://terrance.who.int/internet/data/sage/IVIR-AC_Pink_Book_Sept2023.pdf [document disponible uniquement en langue anglaise], consulté en septembre 2023)..

Vaccine Impact Modelling Consortium

The Vaccine Impact Modelling Consortium (VIMC)[2] is a multinational collaboration of research groups funded by Gavi, the Vaccine Alliance, the Wellcome Trust, and the Bill & Melinda Gates Foundation. The VIMC began its second 5-year grant phase (VIMC 2.0) in September 2022 with a focus on responsive policy-driven mathematical modelling to answer priority research questions. WHO IVB established a new mode of engagement with VIMC to inform global strategies and policies specific to pathogens or immunization programmes overall.

As part of this 5-year grant phase, VIMC has new ways of working that include modeler-led project working groups (PWGs). VIMC presented the process for defining research questions and initiating PWGs within the consortium, while highlighting ongoing and completed workstreams from the first year of VIMC 2.0 and reviewing the workflow of suggested questions to modelled outputs. The VIMC also presented an update on plans and actions for the next round of full model estimates, where each modelling group runs a range of vaccination scenarios and impact is calculated by the central Secretariat. IVIR-AC was asked to provide feedback on the PWG strategy and the process to identify future priority questions for PWGs, as well as to highlight considerations for communicating future VIMC full model estimates in 2024.

Summary of IVIR-AC feedback and recommendations

Overall, IVIR-AC recognized the value of evidence generated by the PWGs and largely agreed with the workflow of the PWG for addressing relevant policy questions. IVIR-AC highlighted the importance of ongoing model validation of each pathogen against historical data for the upcoming full model runs. IVIR-AC recommended the following:

- To gain confidence in the model results among non-modelers, it would be useful to validate the models with historical input data to determine how well they predict what actually occurred with a given pathogen and vaccination strategy.

- For the PWGs:
  - The VIMC should clarify the diversity of stakeholders, including partners and immunization programme managers, and the processes for identifying policy questions for the PWGs that can be addressed or informed by using modelling approaches.

[2] Vaccine Impact Modelling Consortium (https://www.vaccineimpact.org/, accessed September 2023).

Consortium de modélisation de l'impact des vaccins

Le Consortium de modélisation de l'impact des vaccins (VIMC, Vaccine Impact Modelling Consortium)[2] est une collaboration multinationale réunissant plusieurs groupes de recherche, financée par l'Alliance Gavi, le Wellcome Trust et la Fondation Bill & Melinda Gates. La deuxième phase d'activité de 5 ans du VIMC (VIMC 2.0), qui a débuté en septembre 2022, est axée sur des travaux de modélisation mathématique adaptés aux besoins politiques, visant à répondre à des questions de recherche prioritaires. Le Département IVB de l'OMS a instauré de nouvelles modalités de collaboration avec le VIMC en vue d'orienter les stratégies et les politiques mondiales relatives à des agents pathogènes spécifiques ou aux programmes de vaccination en général.

Pour cette nouvelle phase de 5 ans, le VIMC a adopté de nouvelles méthodes de travail, reposant notamment sur la création de groupes de travail axés sur les projets (GTP), dirigés par des modélisateurs. Le VIMC a présenté le processus utilisé pour définir les questions de recherche et mettre en place les GTP au sein du consortium, a décrit les travaux menés lors de la première année de la phase VIMC 2.0, qu'ils soient encore en cours ou déjà achevés, et a passé en revue la séquence des tâches entre la suggestion des questions et la production des résultats de modélisation. Le VIMC a également fait le point sur les actions prévues pour le prochain cycle de production d'estimations complètes de modélisation, au cours duquel chaque groupe de modélisation appliquera divers scénarios de vaccination, l'impact étant ensuite calculé par le secrétariat général. Il a été demandé à l'IVIR-AC de donner son avis sur la stratégie fondée sur les GTP, sur le processus utilisé pour identifier les futures questions prioritaires devant être traitées par les GTP, ainsi que sur les éléments en prendre en compte pour la communication des prochaines estimations complètes de modélisation du VIMC en 2024.

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

Globalement, l'IVIR-AC a estimé que les données produites par les GTP sont utiles et a largement adhéré au processus mis en œuvre par les GTP pour traiter les questions politiques pertinentes. L'IVIR-AC a souligné qu'il est important, pour les prochains cycles de modélisation complète, d'assurer une validation continue des modèles pour chaque agent pathogène en effectuant une comparaison avec les données historiques. Il a formulé les recommandations suivantes:

- Afin de renforcer la confiance des non-modélisateurs à l'égard des résultats de modélisation, il serait utile de valider les modèles en utilisant des données historiques comme données d'entrée pour voir dans quelle mesure les prévisions produites correspondent à la situation effectivement observée pour un agent pathogène et une stratégie de vaccination donnés.
- Pour les GTP:
  - Le VIMC devrait apporter des précisions sur la diversité des parties prenantes, y compris les partenaires et les administrateurs des programmes de vaccination, ainsi que sur les processus mis en œuvre pour identifier les questions politiques pouvant être traitées ou élucidées par les GTP à l'aide de la modélisation.

[2] Vaccine Impact Modelling Consortium (https://www.vaccineimpact.org/, consulté en septembre 2023).

  - There should be regular communication with the secretariat of the Strategic Advisory Group of Experts on Immunization (SAGE), the working group focal points and the Gavi Vaccine Investment Strategy, because those are key sources for identifying short-term questions that the PWGs are equipped to address.
  - The VIMC secretariat should provide flexible funding, beyond the scope of ongoing commitments as part of the funding through VIMC, to members who are asked to participate in multiple PWGs, and governance mechanisms must ensure the independence of the PWGs from stakeholder incentives.
  - The VIMC should conduct a more in-depth review of the progress made by PWGs in answering critical questions, such as: the number of policy questions proposed to the PWG, and by whom; the reasons for decisions to address or not address a specific policy question; the reasons for success and timely completion and failure of the task; and whether the outputs had the desired impact.
  - The VIMC should identify the 2 research groups responsible for modelling each pathogen and the level of preparedness to engage in new projects in view of available resources and ongoing projects. IVIR-AC also recommended clarification procedures for incorporating new pathogens into the VIMC portfolio.

- For the upcoming full model runs, IVIR-AC recommended:
  - developing a communication plan for model dissemination;
  - identifying the synergies and interdependencies with IA2030 and other related work;
  - providing code and parameters for each model for transparency and reproducibility; and
  - indicating the level and major drivers of uncertainties in the vaccine impact estimates for each pathogen.

Immunization Agenda 2030 vaccine impact estimates

The vaccine impact estimates for Immunization Agenda 2030 (IA2030) were first generated in 2021 for the Impact Goal Indicator 1.1 "Number of future deaths averted through immunization" as part of the IA2030 Monitoring & Evaluation framework.[3] The IA2030 vaccine impact estimates project team continues to make progress on improving annual reporting of Impact Goal Indicator 1.1 and expanding the scope of pathogens, immunization activities, and impact measures.

[3] Immunization Agenda 2030: a global strategy to leave no one behind. Geneva: World Health Organization; 2020 (https://www.who.int/teams/immunization-vaccines-and-biologicals/strategies/ia2030, accessed September 2023).

  - Il conviendrait d' avoir une communication régulière avec le secrétariat du Groupe stratégique consultatif d'experts sur la vaccination (SAGE), les chargés de liaison des groupes de travail et les responsables de la stratégie d'investissement dans les vaccins de l'Alliance Gavi, car il s'agit d'interlocuteurs clés pour identifier les questions à court terme que les GTP sont aptes à aborder.
  - Le secrétariat du VIMC devrait octroyer un financement souple, au-delà des engagements financiers déjà pris par le VIMC, aux membres à qui il est demandé de participer à plusieurs GTP; les mécanismes de gouvernance doivent en outre garantir l'indépendance des GTP vis-à-vis des incitations éventuelles des parties prenantes.
  - Le VIMC devrait procéder à un examen plus approfondi des progrès accomplis par les GTP pour répondre à certaines questions fondamentales, telles que: le nombre de questions politiques proposées au GTP et par qui; les raisons pour lesquelles il été décidé de traiter ou non une question politique donnée; les raisons de la réussite, de l'achèvement en temps utile ou de l'échec de la tâche concernée; et dans quelle mesure les résultats ont eu l'impact escompté.
  - Il convient que le VIMC identifie les 2 groupes de recherche chargés de la modélisation de chaque agent pathogène et détermine leur niveau de préparation pour entreprendre de nouveaux projets compte tenu des ressources disponibles et des projets en cours. L'IVIR-AC recommande également une clarification des procédures régissant l'intégration de nouveaux agents pathogènes dans le portefeuille du VIMC.

- Pour les prochains cycles de modélisation complète, l'IVIR-AC a recommandé:
  - d'élaborer un plan de communication pour la diffusion du modèle;
  - d'identifier les synergies et les interdépendances avec le Programme pour la vaccination à l'horizon 2030 (IA2030) et d'autres travaux connexes;
  - de fournir le code et les paramètres de chaque modèle à des fins de transparence et de reproductibilité; et
  - d'indiquer le degré d'incertitude et les principaux facteurs d'incertitude des estimations de l'impact des vaccins pour chaque agent pathogène.

Estimations de l'impact des vaccins dans le cadre du Programme pour la vaccination à l'horizon 2030

Les premières estimations de l'impact des vaccins dans le cadre du Programme de vaccination à l'horizon 2030 (IA2030) ont été générées en 2021 et portaient sur l'indicateur d'objectif d'impact 1.1, tel qu'énoncé dans le cadre de suivi et d'évaluation de l'IA2030, c'est-à-dire le «nombre de décès futurs évités grâce à la vaccination».[3] L'équipe de projet chargée de l'estimation de l'impact des vaccins pour l'IA2030 a continué d'œuvrer à une meilleure notification annuelle des données relatives à l'indicateur d'objectif d'impact 1.1 et à étendre ses travaux à un champ

[3] Programme pour la vaccination à l'horizon 2030: Une stratégie mondiale pour ne laisser personne de côté. Genève, Organisation mondiale de la Santé, 2020 (https://www.who.int/fr/publications/m/item/immunization-agenda-2030-a-global-strategy-to-leave-no-one-behind, consulté en septembre 2023).

Since the project's inception in 2020, 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 processes. Following earlier recommendations, IVIR-AC reviewed the final results of an uncertainty analysis and provided feedback on approaches to annual monitoring and reporting, especially with regard to communication strategies.

The project team for the IA2030 vaccine impact estimates presented an update on annual progress tracking for Impact Goal 1.1, scientific communication, and target metrics assessed, including the incorporation of disability-adjusted life years (DALYs), the use of coverage data from supplementary immunization activities (SIAs), and the addition of polio impact estimates. IVIR-AC was asked to provide feedback on the team's ongoing efforts to update the target estimates by 2025, specifically on communicating progress towards Impact Goal 1.1, estimating DALYs, and the suitability of an open-source R package.

Summary of IVIR-AC feedback and recommendations

In addition to acknowledging the response to previous recommendations and revised methods, IVIR-AC recommended clarifying the terminology used by, and the online dissemination strategy of the project code base, including the following:

- Some of the terms used, such as "future deaths" or "observed deaths averted", could be liable to misinterpretation. IVIR-AC suggested clearly defining various terms and using them consistently.
- Regarding the inclusion of DALYs in target metrics, IVIR-AC found the proposed approach sound, and encouraged systematic identification of key drivers of heterogeneity in case fatality and basing the stratification of estimates on identified drivers.
- IVIR-AC noted that the uncertainty in estimates of both deaths and case fatality ratios need to be propagated in the estimates of DALYs.
- IVIR-AC commended the open-source sharing of project code, recommends additional documentation and communication on use of the code, and advises considering the merit of developing a supplementary online tool or dashboard to allow user-friendly data exploration.

Modelling of timeliness versus coverage of measles supplementary immunization activities

WHO partners have increasingly focused on achieving high quality campaign implementation in recent years, but the criteria used to define "quality" have prioritized high coverage at the expense of timeliness (i.e., the need

plus large d'agents pathogènes, d'activités de vaccination et de mesures d'impact. Depuis le lancement du projet en 2020, l'IVIR-AC a procédé à des examens indépendants des modèles, des cadres analytiques et des méthodes pour veiller à la meilleure utilisation possible des estimations dans la planification et l'élaboration des politiques à l'échelle mondiale et régionale. Conformément à des recommandations antérieures, l'IVIR-AC a examiné les résultats finaux d'une analyse d'incertitude et avait donné son avis sur les approches adoptées en matière de suivi et d'établissement de rapports annuels, en particulier en ce qui concerne les stratégies de communication.

L'équipe de projet chargée de l'estimation de l'impact des vaccins pour l'IA2030 a présenté une mise à jour sur le suivi annuel des progrès pour l'indicateur d'objectif d'impact 1.1, la communication scientifique et les paramètres cibles évalués, notamment la prise en compte des années de vie ajustées sur l'incapacité (DALY), l'utilisation des données de couverture des activités de vaccination supplémentaire (AVS) et l'ajout d'estimations de l'impact de la vaccination antipoliomyélitique. Il a été demandé à l'IVIR-AC de donner son avis sur les efforts actuellement déployés par l'équipe pour mettre à jour les estimations cibles d'ici 2025, en particulier en ce qui concerne la communication des progrès pour l'indicateur d'objectif d'impact 1.1, l'estimation des DALY et la pertinence d'un progiciel R open source.

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

L'IVIR-AC a pris acte de la suite donnée aux recommandations précédentes et des méthodes révisées. Il a également préconisé de clarifier la terminologie utilisée et la stratégie de diffusion en ligne du code de base du projet, notamment en ce qui concerne les points suivants:

- Certains des termes employés, tels que «décès futurs» ou «décès évités observés», pourraient être mal interprétés. L'IVIR-AC a suggéré de définir clairement les différents termes et de les utiliser de manière cohérente.
- S'agissant de l'inclusion des DALY dans les paramètres cibles, l'IVIR-AC a estimé que l'approche proposée etait solide et a préconisé d'identifier de manière systématique les principaux facteurs d'hétérogénéité des taux de létalité et de stratifier les estimations en fonction des facteurs ainsi identifiés.
- L'IVIR-AC a noté que l'incertitude des estimations des taux de mortalité et de létalité devait être répercutée dans les estimations des DALY.
- L'IVIR-AC s' est félicitée du partage en open source du code du projet, a recommandé d'intensifier les efforts de documentation et de communication concernant l'utilisation du code et a conseillé de mener une réflexion pour déterminer s'il serait judicieux d'élaborer un nouvel outil ou tableau de bord en ligne permettant une exploration conviviale des données par les utilisateurs.

Modélisation visant à comparer la rapidité de mise en œuvre et la couverture des activités de vaccination supplémentaire contre la rougeole

Depuis quelques années, les partenaires de l'OMS mettent plus que jamais l'accent sur la nécessité de mettre en œuvre des campagnes de qualité. Cependant, les critères employés pour définir la «qualité» portent en priorité sur le taux de couverture

to conduct a campaign prior to anticipated measles outbreaks). Technical advice has been consistently against delays of SIAs based on expertise and experience, yet there are concerns that accrued delays have seen outbreaks starting before campaigns were implemented.

The Institute for Disease Modeling (IDM) presented results from an analysis of the relationship between timeliness and coverage in preventing measles outbreaks and determining campaign quality. The IDM's findings suggested that timeliness should be considered in planning SIAs and that this could have implications for policy and the criteria used for making decisions about campaigns. IVIR-AC was asked to provide feedback on the robustness of the methods to justify generalized conclusions regarding the balance of timeliness and coverage in determining SIA quality and utility in programmatic decision making.

Summary of IVIR-AC feedback and recommendations

IVIR-AC agreed that the methods presented by IDM are appropriate for illustrating that high-quality SIAs are a function of both timeliness and coverage. However, further contextualisation is required before the modelling methods and results can be applied to specific settings. The committee noted that it is critical to achieve high coverage campaigns while allowing for adequate planning horizons. Nevertheless, if an outbreak is imminent, nominal reductions by coverage in SIAs deployed prior to the outbreak could prevent more infections compared to delaying the campaign. IVIR-AC recommended following:

- While the model results are valuable as a general exercise, they are not appropriate for guiding the timing of SIAs in specific settings. For specific settings, it is necessary to account for immunity gaps on national and subnational scales, as well as uncertainty in the size and timing of outbreaks geographically.

- It is difficult to know when measles outbreaks will occur, and longer planning horizons may be needed for SIAs. To allow the modelling results to be interpreted in light of different planning horizons, the results should also be presented in terms of the number of months that the SIA is implemented before the outbreak (e.g. -3, -1, 0, 2 months), rather than in terms of the delay from the planning time.
- Model results should be presented for multiple longer time horizons, rather than for only 1 year, because low-coverage campaigns may delay

atteint, plutôt que sur la rapidité de mise en œuvre (c'est-à-dire le fait de mener une campagne avant qu'une flambée épidémique prévisible de rougeole ne se produise). Sur la base des connaissances existantes et de l'expérience acquise, les experts techniques ont toujours conseillé d'éviter tout retard dans la mise en œuvre des AVS. On a pourtant constaté des retards accumulés qui pourraient être à l'origine de flambées épidémiques survenues avant la conduite des campagnes.

L'Institute for Disease Modeling (IDM) a présenté les résultats d'une analyse de la relation entre ces deux paramètres (rapidité de mise en œuvre des campagnes et couverture vaccinale) dans la prévention des flambées épidémiques de rougeole et la détermination de la qualité des campagnes. Les résultats de l' IDM suggèrent que la rapidité de mise en œuvre devrait être prise en compte dans la planification des AVS et que cela pourrait avoir une incidence sur les politiques adoptées et sur les critères utilisés pour prendre des décisions relatives aux campagnes. Il a été demandé à l'IVIR-AC de donner son avis sur la solidité des méthodes employées, d'indiquer si elles permettent à son avis de tirer des conclusions généralisables concernant l'équilibre entre la rapidité de mise en œuvre et la couverture vaccinale dans la détermination de la qualité des AVS, et de se prononcer sur l'utilité de cette information dans la prise de décision programmatique.

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

L'IVIR-AC a convenu de la pertinence des méthodes présentées par l'IDM pour démontrer que la qualité des AVS est fonction à la fois de la rapidité de la mise en œuvre et de la couverture vaccinale. Toutefois, des efforts supplémentaires de contextualisation sont nécessaires avant que les méthodes de modélisation et les résultats puissent être appliqués à des contextes spécifiques. Le Comité a noté qu'il était essentiel de parvenir à une couverture élevée des campagnes tout en prévoyant des horizons de planification suffisants. Néanmoins, si une épidémie est imminente, le déploiement d'une AVS avant la survenue de l'épidémie, avec une baisse modique de la couverture, pourrait permettre de prévenir davantage d'infections que si la campagne était retardée. L'IVIR-AC a formulé les recommandations suivantes:

- Bien que les résultats de modélisation soient utiles à titre général, ils ne sont pas adaptés pour déterminer à quel moment il convient de mener les AVS dans des contextes spécifiques. Dans ces derniers, il faut en effet tenir compte des lacunes immunitaires à l'échelle nationale et infranationale, ainsi que des incertitudes relatives à l'ampleur et à la chronologie des flambées épidémiques dans la zone géographique concernée.
- Il est difficile de savoir quand les flambées de rougeole sont susceptibles de se produire, et des horizons de planification plus longs peuvent être nécessaires pour les AVS. Pour que les résultats de la modélisation puissent être interprétés à la lumière des différents horizons de planification, ils devraient également être présentés en indiquant le nombre de mois avant la flambée où l'AVS a été mise en œuvre (p. ex., -3, -1, 0, 2 mois), plutôt qu' en terme de délai écoulé depuis la date de planification.
- Les résultats de modélisation devraient être présentés pour des horizons multiples et plus longs, plutôt que pour 1 an seulement, car les campagnes à faible couverture peuvent

measles outbreaks only slightly. At a minimum, a 2-year time horizon should be used to represent settings where SIAs are planned for every 2 years.

- For future work, it is important to understand the barriers to routine immunization coverage and the extent to which these are overcome through SIAs and other strategies and technologies (e.g., micro-array patches and rapid diagnostic tests) before modelling the impact of SIAs.
- The conservative assumption that initial SIA doses are administered to persons who have been routinely vaccinated somewhat limits the extent of parameter space that can be explored. A scenario in which SIA doses are targeted at persons who did not receive the primary vaccine series should also be modelled.
- The development of new tools is needed to identify immunity gaps and to better predict when outbreaks might occur. It is also important to understand the extent to which seroprevalence studies and other data are representative of the target population for SIAs (i.e., unvaccinated persons) when assessing the value of such data for informing the timing of SIAs.

Modelling on measles/rubella elimination in South-East Asia

Measles and rubella elimination targets are critical for strategically allocating the necessary resources and rallying political will at a regional level. At a global level, targets are important for strategy implementation. Following the feasibility assessment presented to SAGE in 2019, the setting of a global goal has been delayed pending 2 key factors: further progress on reaching regional goals, and the development of definitions for scenarios from which a final push towards eradication would be feasible. Furthermore, measles and rubella vaccination programme targets and timelines for achieving elimination were disrupted due to the COVID-19 pandemic, leading to the need for an increased focus on strategic planning which would require setting evidence-based goals.

Combining modelling and operational experience can be effective for developing objective, evidence-based reviews of timelines and goals. A VIMC project working group presented an overview of scenario modelling work previously performed in relation to WHO's South-East Asia Region and described the experience of using these modelling outputs to structure a discussion with immunization programme staff about resetting their elimination goal. The team discussed lessons and challenges from this experience of integrating scenario modelling into goal setting and suggested how a similar modelling exercise could be conducted in other regions. IVIR-AC was asked to provide feedback on how the methods can be strengthened and comment on the utility and generalizability of the methods for adaptation in other regions.

ne retarder que légèrement les flambées épidémiques de rougeole. Cet horizon sera fixé au minimum à 2 ans pour tenir compte des contextes où les AVS sont prévues tous les 2 ans.

- Pour les travaux futurs, il est important, avant de modéliser l'impact des AVS, d'identifier les obstacles à la couverture de la vaccination systématique et de comprendre dans quelle mesure les AVS et d'autres stratégies et technologies (p. ex., timbres à micro-aiguilles et tests de diagnostic rapide) permettent de les surmonter.
- L'hypothèse conservatrice selon laquelle les doses initiales des AVS sont administrées à des personnes ayant déjà bénéficié de la vaccination systématique limite quelque peu le champ des paramètres à explorer. Il convient de modéliser également un scénario dans lequel les doses des AVS sont administrées de manière ciblée aux personnes qui n'ont pas reçu la série de primovaccination.
- De nouveaux outils devront être mis au point afin d'identifier les lacunes immunitaires et de mieux prédire quand les flambées sont susceptibles de se produire. Il est également important de comprendre dans quelle mesure les données issues des études de séroprévalence et d'autres sources sont représentatives de la population cible des AVS (c.-à-d. les personnes non vaccinées) lorsque l'on évalue l'intérêt que présentent ces données pour décider du moment opportun pour mener les AVS.

Modélisation de l'élimination de la rougeole et de la rubéole en Asie du Sud-Est

La définition de cibles d'élimination de la rougeole et de la rubéole est essentielle pour permettre une allocation stratégique des ressources requises et mobiliser la volonté politique au niveau régional. À l'échelle mondiale, la définition des cibles est importante pour la mise en œuvre d'une stratégie. À la suite de l'étude de faisabilité présentée au SAGE en 2019, la fixation d'un objectif mondial a été retardée dans l'attente de 2 éléments clés, à savoir: de nouveaux progrès dans la réalisation des objectifs régionaux, et la définition de scénarios dans lesquels une dernière ligne droite vers l'éradication serait envisageable. De plus, les cibles du programme de vaccination contre la rougeole et la rubéole et les échéances fixées pour parvenir à l'élimination ont été perturbées par la pandémie de COVID-19, ce qui impose d'accorder une attention accrue à la planification stratégique, avec des objectifs définis sur la base de données probantes.

La combinaison de la modélisation et de l'expérience opérationnelle peut être un moyen efficace d'examiner les objectifs et les échéances de manière objective et sur la base de données probantes. Un groupe de travail du VIMC a présenté des travaux de modélisation de scénarios effectués précédemment pour la Région de l'Asie du Sud-Est de l'OMS et a décrit comment ces résultats de modélisation ont permis de structurer la discussion engagée avec le personnel des programmes de vaccination au sujet de la révision de leur objectif d'élimination. L'équipe a abordé les difficultés rencontrées et les leçons tirées de cette expérience qui visait à intégrer la modélisation des scénarios dans le processus de fixation des objectifs et a suggéré qu'un exercice de modélisation similaire puisse être mené dans les autres Régions. Il a été demandé à l'IVIR-AC de donner son avis sur les améliorations qui pourraient être apportées aux méthodes présentées et de se prononcer sur leur utilité et sur la possibilité de les généraliser aux autres Régions.

Summary of IVIR-AC feedback and recommendations

IVIR-AC agreed with the overall concept of, and approach to, using multiple models and agreed feasible vaccination scenarios to understand which scenarios would be most effective for achieving elimination in specific countries; this can be extremely useful for developing realistic elimination goals. Further consideration should be given to how to adapt the models to be suitable to other settings. Additional recommendations included the following:

- IVIR-AC recommended updating the vaccination scenarios while considering the impact of the COVID-19 pandemic and potential immunity gaps in adolescents and adults.
- When considering applying this framework to other regions, it would be crucial to understand what elements of model design and parameterization can be readily adapted to the other regions and what elements would remain unchanged, while ensuring that model scenarios are realistic and country-specific.
  - IVIR-AC recommended providing more details on each of the vaccination scenarios, especially with regard to the age groups targeted by SIAs, since the 5 vaccine scenarios used for countries in the South-East Asia Region might not be the most appropriate scenarios for other regions.
- Issues of operational feasibility often pose a great challenge to the elimination of measles and rubella. Vaccine refusal due to inappropriate deployment of SIAs, failure of service delivery to fill immunity gaps, and insensitive surveillance are all extremely critical. Modellers should consider incorporating additional model parameters to account for the sensitivity of surveillance systems in strengthening the transferability of models.

Translating vaccine impact modelling into immunization strategy, policy and programme decisions

Modelling has played an increasingly important role in informing immunization strategy, policy and programme decisions, though many countries have not yet systematically incorporated modelled evidence into their immunization policy and programme decision-making. To support the appropriate use of modelling evidence in countries, the WHO Secretariat and IVIR-AC have established a subgroup that will oversee the development of guidance on translating vaccine impact modelling into strategy, policy and programme decisions for immunization. This guidance will be tailored to the needs of national immunization technical advisory groups (NITAGs) and immunization decision-makers in the form of a document, training modules or other required formats by 2025.

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

L'IVIR-AC a approuvé le concept global et l'approche consistant à utiliser plusieurs modèles et des scénarios de vaccination convenus et réalisables afin d'identifier ceux qui seraient les plus efficaces pour atteindre l'élimination dans des pays spécifiques, ce qui peut être d'un apport très précieux pour définir des objectifs d'élimination réalistes. Il conviendrait de réfléchir plus avant à la manière d'adapter les modèles à d'autres contextes. Les autres recommandations formulées sont les suivantes:

- L'IVIR-AC a recommandé d'actualiser les scénarios de vaccination en tenant compte de l'impact de la pandémie de COVID-19 et des lacunes immunitaires potentielles chez les adolescents et les adultes.
- Pour l'application de ce cadre à d'autres Régions, il est primordial de comprendre quels éléments de la conception et du paramétrage du modèle peuvent être facilement adaptés aux autres Régions et quels éléments resteront inchangés, tout en veillant à utiliser des scénarios de modélisation qui soient réalistes et propres à chaque pays.
  - L'IVIR-AC a recommandé de fournir des informations plus détaillées sur chacun des scénarios de vaccination, en particulier sur les tranches d'âge ciblées par les AVS, car les 5 scénarios de vaccination retenus pour les pays de la Région de l'Asie du Sud-Est ne sont pas nécessairement bien adaptés pour les autres Régions.
- Les questions de faisabilité opérationnelle constituent souvent un défi majeur pour l'élimination de la rougeole et de la rubéole. Certaines de ces questions revêtent une importance cruciale, notamment: le refus de la vaccination, résultant d'un déploiement inadéquat des AVS; une prestation de services qui ne parvient pas à combler les lacunes immunitaires; et un manque de sensibilité de la surveillance. Afin d'améliorer la transférabilité des modèles, les modélisateurs devraient envisager d'incorporer des paramètres supplémentaires pour tenir compte de la sensibilité des systèmes de surveillance.

Transposer les résultats de la modélisation de l'impact des vaccins en décisions stratégiques, politiques et programmatiques en matière de vaccination

La modélisation est de plus en plus souvent utilisée pour orienter les décisions stratégiques, politiques et programmatiques relatives à la vaccination, même si dans de nombreux pays, les données issues de la modélisation ne sont pas encore intégrées de manière systématique dans la prise de décisions politiques et programmatiques sur la vaccination. Afin de favoriser l'utilisation pertinente des données de modélisation dans les pays, le Secrétariat de l'OMS et l'IVIR-AC ont créé un sous-groupe qui sera chargé de superviser l'élaboration d'orientations sur la transposition des résultats de la modélisation de l'impact des vaccins en décisions stratégiques, politiques et programmatiques en matière de vaccination. Ces orientations, qui seront adaptées aux besoins des groupes consultatifs techniques nationaux sur la vaccination et des décideurs dans le domaine de la vaccination, seront disponibles d'ici 2025 sous la forme d'un document, de modules de formation ou d'autres supports nécessaires.

The working group chair presented an overview of the rationale, activities and progress to date, as well as planned activities and timeline. A working group member reported on plans for a qualitative study interviewing users of modelled evidence, which aims to inform the content and effective delivery of the guidance. IVIR-AC was requested to review the presentation, provide feedback, and seek clarification on content, specifically on the ability of the planned activities to achieve the aims of the subgroup and on the plans for the qualitative needs-assessment study.

Summary of IVIR-AC feedback and recommendations

In view of the support of this subgroup and following review of the presentation, IVIR-AC recommended that the guidance documents should be in line with, and should complement, existing WHO resources for policymakers, and should specifically aim to elucidate model complexity, capabilities and limitations. Additional recommendations included:

- To reformulate the definition of modelling to be specific to the role of modelling in immunization, it should be distinguished from other types of modelling (e.g. economic, statistical).
- To increase the relevance of the guidance, its content should discuss problem formulation, data contextualization, factors affecting generalizability and uncertainty of modelling results, and should acknowledge limitations and assumptions.
- To demystify model complexity, the guidance should provide simple definitions with explanations of common modelling concepts, including highlighting the importance of knowledge exchange.
- To illustrate the guidance delivered, examples may be employed, in addition to historical use cases.
- To reduce the risk of inappropriate use of modelled evidence, the guidance should be clear on limitations, including model structure, inherent uncertainties in the modelling results due to erroneous models or assumptions, biological systems that are not fully understood, and a need for reliable local data for parameters that may influence model results.

Benefit-risk assessment – dengue vaccine

As the incidence of dengue continues to increase with most of the burden in the Americas, South-East Asia and Western Pacific Regions[4–6] this disease has become a global concern. Takeda's tetravalent dengue vaccine

Le président du groupe de travail a présenté la raison d'être de ce groupe, les activités et les progrès réalisés à ce jour, ainsi que les activités prévues et le calendrier correspondant. Un membre du groupe de travail a décrit un projet d'étude qualitative qui consistera à interroger les utilisateurs de données de modélisation afin de recueillir des éléments utiles à l'élaboration du contenu des documents d'orientation et à leur bonne diffusion. Il a été demandé à l'IVIR-AC d'examiner l'exposé qui leur était présenté, d'émettre des commentaires et de demander des éclaircissements si nécessaire, en particulier en ce qui concerne l'adéquation des activités prévues pour atteindre les objectifs du sous-groupe et le projet relatif à l'étude qualitative d'évaluation des besoins.

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

En raison de son soutien au sous-groupe et après avoir examiné l'exposé qui lui était présenté, l'IVIR-AC a recommandé de veiller à ce que les documents d'orientation soient compatibles et complémentaires avec les ressources existantes de l'OMS destinées aux décideurs politiques et qu'ils s'attachent expressément à élucider la complexité, les capacités et les limites des modèles. Les autres recommandations formulées sont les suivantes:

- Reformuler la définition de la modélisation pour la faire porter spécifiquement sur le rôle de la modélisation dans le domaine de la vaccination, en la distinguant des autres types de modélisation (p. ex., économique, statistique).
- Pour être plus pertinentes, les orientations devraient aborder les questions relatives à la formulation des problèmes, à la contextualisation des données et aux facteurs influant sur la généralisation et l'incertitude des résultats de la modélisation, et devraient faire état des limites et des hypothèses de la modélisation.
- Pour démystifier la complexité de la modélisation, il convient que les orientations fournissent des définitions simples assorties d'explications sur les principaux concepts de la modélisation, en soulignant notamment l'importance de l'échange de connaissances.
- Pour illustrer les conseils formulés, des exemples pourront être fournis, outre la description de cas d'utilisation passés.
- Pour réduire le risque d'une utilisation inappropriée des données modélisées, les orientations doivent indiquer clairement les limites de la modélisation, y compris celles qui sont liées à la structure des modèles, aux incertitudes inhérentes aux résultats de modélisation en raison d'hypothèses ou de modèles erronés, à une compréhension incomplète de certains systèmes biologiques et à la nécessité de disposer de données locales fiables pour les paramètres qui pourraient influencer sur les résultats de modélisation.

Évaluation du rapport bénéfice-risque du vaccin contre la dengue

La dengue, dont l'incidence ne cesse d'augmenter, est devenue une source de préoccupation dans le monde entier, les Régions les plus touchées étant celles des Amériques, de l'Asie du Sud-Est et du Pacifique occidental.[4–6] Le vaccin tétravalent de Takeda

[4] Bhatt S et al. The global distribution and burden of dengue. Nature 2013; 496(7446): 504–507.

[5] Dengue and severe dengue. Geneva: World Health Organization; 2022 (https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue, accessed September 2023).

[6] World Health Organization. Dengue. Geneva: World Health Organization; 2021 (https://www.afro.who.int/health-topics/dengue, accessed September 2023).

[4] Bhatt S et al. The global distribution and burden of dengue. Nature 2013; 496(7446): 504–507.

[5] Dengue et dengue sévère. Genève, Organisation mondiale de la Santé, 2022 (https://www.who.int/fr/news-room/fact-sheets/detail/dengue-and-severe-dengue, consulté en septembre 2023).

[6] Dengue. Genève: Organisation mondiale de la Santé, 2021 (https://www.afro.who.int/health-topics/dengue, consulté en septembre 2023).

(TAK-003) is based on a live-attenuated dengue serotype 2 virus (DENV2) backbone which is designed to provide protection against all 4 dengue serotypes. Published efficacy results around DENV3 and DENV4 endpoints are limited, and overall attack rates were lower in years 4 and 5.[7] TAK-003 has recently successfully completed Phase III clinical trials,[7] has been licensed in Indonesia,[8] and has received approval for use from the European Medicines Agency.[9] To support recommendations at the SAGE meeting on 25 September 2023, IVIR-AC reviewed work of 2 modelling teams from the University of Notre Dame, Indiana, and Imperial College London. The results that were presented reflected independent assessments of the individual- and population-level risk-benefit of the introduction of TAK-003, including considerations of pre-vaccination serological screening and cost-effectiveness. IVIR-AC was asked to assist in assessing the presented evidence and to provide feedback on the appropriateness of the modelling approaches and assumptions as well as the robustness of the results.

Summary of IVIR-AC feedback and recommendations

IVIR-AC concluded that the modelling results from both groups were in general consistent in suggesting an overall positive population-level impact of TAK-003, which was greater in setting with higher transmission. The models suggested that under certain circumstances, seronegative vaccinees could have an increased risk for DENV3 and/or DENV4 disease. In light of limited evidence, further studies are needed to better understand the nature of the vaccine protection against all serotypes. Additional recommendations included the following:

- Despite differences in their approach to interpreting trial results, both models are appropriate for evaluating the potential impact of TAK-003 if communicated alongside their respective assumptions.
- While pre-vaccination screening to identify previous infection could minimize the risk of enhanced disease at the individual level, its use is predicted to reduce considerably the population-level benefit by precluding protection of dengue naïve individuals against DENV1 and DENV2 and complicating vaccine delivery.
- Concern was raised that potential serotype replacement with DENV3 and/or DENV4 could lower

[7] ClinicalTrials.com. Efficacy, safety and immunogenicity of Takeda's tetravalent dengue vaccine (TDV) in healthy children (TIDES) (https://clinicaltrials.gov/ct2/show/NCT02747927, accessed September 2023).

[8] Takeda's QDENGA® (dengue tetravalent vaccine [live, attenuated]) approved in Indonesia for use regardless of prior dengue exposure (https://www.takeda.com/newsroom/newsreleases/2022/takedas-qdenga-dengue-tetravalent-vaccine-live-attenuated-approved-in-indonesia-for-use-regardless-of-prior-dengue-exposure, accessed September 2023).

[9] Takeda receives positive CHMP opinion recommending approval of dengue vaccine candidate in EU and dengue-endemic countries (https://www.takeda.com/newsroom/newsreleases/2022/Positive-CHMP-Opinion-Recommending-Approval-of-Dengue-vaccine/, accessed September 2023).

contre la dengue (TAK-003), dont le squelette de base est un virus vivant atténué de la dengue de sérotype 2 (DENV2), est conçu pour conférer une protection croisée contre les quatre sérotypes du virus de la dengue. On ne dispose que de peu de résultats publiés concernant l'efficacité du vaccin au regard des critères d'évaluation pour DENV3 et DENV4, et il a été constaté que les taux d'attaque globaux étaient plus faibles au cours des années 4 et 5.[7] Les essais cliniques de phase III du TAK-003 se sont récemment achevés de manière concluante[7] et le vaccin a été homologué en Indonésie[8] et son utilisation a été approuvée par l'Agence européenne des médicaments.[9] Afin d'étayer les recommandations formulées par le SAGE lors de sa réunion du 25 septembre 2023, l'IVIR-AC a examiné les travaux de 2 équipes de modélisation de l'University of Notre Dame, Indiana, et de l'Imperial College London. Les résultats présentés portaient sur des évaluations indépendantes du rapport bénéfice-risque de l'introduction du TAK-003 au niveau individuel et à l'échelle de la population, y compris des considérations relatives au dépistage sérologique prévaccinal et au rapport coût-efficacité. Il a été demandé à l'IVIR-AC de donner son avis sur les données présentées, la pertinence des méthodes et des hypothèses de modélisation, ainsi que la robustesse des résultats.

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

L'IVIR-AC a conclu que les résultats de modélisation des 2 groupes étaient en généralt cohérents et indiquaient un impact global positif du TAK-003 à l'échelle de la population, particulièrement dans les zones de forte transmission. Les modèles laissent penser que dans certaines circonstances, les personnes séronégatives qui sont vaccinées pourraient présenter un risque accru de maladie due à DENV3 et/ou DENV4. Compte tenu des données limitées disponibles, des études supplémentaires doivent être menées pour mieux comprendre la nature de la protection conférée par le vaccin contre tous les sérotypes. Les autres recommandations formulées sont les suivantes:

- Bien qu'ils utilisent des approches différentes pour interpréter les résultats des essais, les 2 modèles sont appropriés pour évaluer l'impact potentiel du TAK-003 dans la mesure où leurs hypothèses respectives sont également communiquées.
- Le dépistage prévaccinal, qui vise à détecter une infection antérieure éventuelle, peut réduire le risque de forme plus grave de la maladie au niveau individuel; cependant, les prévisions indiquent que cette approche pourrait fortement limiter les bénéfices de la vaccination à l'échelle de la population en empêchant les personnes naïves vis-à-vis de la dengue d'être protégées contre le DENV1 et le DENV2 et en rendant l'administration du vaccin plus complexe.
- Des inquiétudes ont été exprimées quant à la possibilité qu'avec le temps, un remplacement éventuel des sérotypes

[7] ClinicalTrials.com. Efficacy, safety and immunogenicity of Takeda's tetravalent dengue vaccine (TDV) in healthy children (TIDES) (https://clinicaltrials.gov/ct2/show/NCT02747927, consulté en septembre 2023).

[8] Takeda's QDENGA® (dengue tetravalent vaccine [live, attenuated]) approved in Indonesia for use regardless of prior dengue exposure (https://www.takeda.com/newsroom/newsreleases/2022/takedas-qdenga-dengue-tetravalent-vaccine-live-attenuated-approved-in-indonesia-for-use-regardless-of-prior-dengue-expo-sure, consulté en septembre 2023).

[9] Takeda receives positive CHMP opinion recommending approval of dengue vaccine candidate in EU and dengue-endemic countries (https://www.takeda.com/newsroom/newsreleases/2022/Positive-CHMP-Opinion-Recommending-Approval-of-Dengue-vaccine/, consulté en septembre 2023).

vaccine impact and potentially increase the risk of DENV3 and DENV 4 disease among dengue naïve vaccinees over time. IVIR-AC recommended systematic examination of whether the models predict increased circulation of DENV3 and/or DENV4 following vaccination.

- Both models suggested that the population-level impact of TAK-003 would be greater if vaccination prevents infection and not just disease. However, serotype replacement may be more likely if vaccine protection is primarily against infection rather than againt disease. Further studies are needed to better understand the nature of vaccine protection against all serotypes and the impact of TAK-003 vaccine on transmission.

Mathematical modelling of the COVID-19 pandemic according to different vaccination scenarios in Burkina Faso and Cameroon

Since the emergence of SARS-CoV-2, mathematical modelling has served as an important tool to support decision-making. While many high-income countries benefited from mathematical model projections to guide public health measures, these models remain mostly inaccessible to decision-makers in low- and middle-income countries (LMICs). In response, WHO's Regional Office for Africa and the mathematical modelling research group of the Centre de Recherche du CHU de Québec (Université Laval, Canada) started a project in 2022 with the overall aim of building COVID-19 modelling capacity in French-speaking and English-speaking African countries. Specific aims of this project include:

- to identify 2–4 interested countries, with available data and capacity to participate;
- to establish a collaboration with country-specific researchers and decision makers in order to identify the data and modelling needs and aims;
- to develop and calibrate an open-source dynamic mathematical model of COVID-19 transmission, in close consultation with countries through regular meetings and an in-person workshop;
- to examine the potential evolution of the COVID-19 pandemic according to the different vaccination scenarios;
- to hold a close-out simulation workshop to present the modelling methods and interface and to review different steps of model simulation using applied case-based scenarios; and
- to publish at least one manuscript with participating countries.

Following meetings organized by WHO, 2 countries were chosen to participate, namely Burkina Faso and Cameroon. WHO's Regional Office for Africa presented an overview of the general concept and overall project objectives, and the Laval University team presented the specific aims of the project, the methods used for initial aims and planned for future aims, and associated chal-

par DENV3 et/ou DENV4 puisse réduire l'impact du vaccin et augmenter le risque de maladie due à DENV3 et DENV4 chez les personnes naïves vaccinées. L'IVIR-AC a recommandé de vérifier de manière systématique si les modèles prédisent une intensification de la circulation de DENV3 et/ou de DENV4 après la vaccination.

- Les 2 modèles semblent indiquer que le TAK-003 aurait un impact plus important à l'échelle de la population si la vaccination prévenait l'infection, et pas seulement la maladie. Cependant, si la protection vaccinale est principalement dirigée contre l'infection, plutôt que contre la maladie, cela pourrait se traduire par une probabilité accrue de remplacement des sérotypes. Des études supplémentaires sont nécessaires pour mieux comprendre la nature de la protection conférée contre tous les sérotypes et l'impact du vaccin TAK-003 sur la transmission.

Modélisation mathématique de la pandémie de COVID-19 selon différents scénarios de vaccination au Burkina Faso et au Cameroun

Depuis l'émergence du SARS-CoV-2, la modélisation mathématique joue un rôle particulièrement important en tant qu'outil d'aide à la prise de décision. De nombreux pays à revenu élevé ont ainsi bénéficié de l'utilisation des modèles mathématiques, s'appuyant sur leurs projections pour décider des mesures de santé publique à mettre en place. Cependant, ces modèles restent pour la plupart inaccessibles aux décideurs des pays à revenu faible ou intermédiaire. C'est pourquoi en 2022, le Bureau régional de l'OMS pour l'Afrique et le groupe de recherche en modélisation mathématique du Centre de recherche du CHU de Québec (Université Laval, Canada) ont lancé un projet ayant pour objectif général de renforcer les capacités de modélisation de la COVID-19 dans certains pays francophones et anglophones d'Afrique. Les buts spécifiques de ce projet sont les suivants:

- Identifier 2 à 4 pays intéressés, pour lesquels on dispose des données nécessaires et qui ont la capacité de participer au projet;
- Etablir une collaboration avec des chercheurs et des décideurs de chaque pays afin d'identifier les besoins et les objectifs en matière de données et de modélisation;
- Développer et calibrer un modèle mathématique dynamique open source de la transmission de la COVID-19, en étroite consultation avec les pays dans le cadre de réunions régulières et d'un atelier en présentiel;
- Examiner l'évolution potentielle de la pandémie de COVID-19 en fonction des différents scénarios de vaccination;
- Organiser un atelier de simulation de clôture pour présenter l'interface et les méthodes de modélisation et passer en revue les différentes étapes de la simulation à l'aide de scénarios fondés sur des cas pratiques; et
- Publier au moins un manuscrit avec les pays participants.

À l'issue de réunions organisées par l'OMS, 2 pays ont été choisis pour ce projet: le Burkina Faso et le Cameroun. Des membres du Bureau régional de l'OMS pour l'Afrique ont présenté le principe et les objectifs généraux du projet, et l'équipe de l'Université Laval a décrit les buts spécifiques du projet, les méthodes employées pour la première phase et les celles prévues pour les prochaines étapes, ainsi que les difficultés associées. Il a été

lenges. IVIR-AC was asked to provide feedback on the project methods and the proposed modes of engagement with country collaborators, researchers, and decision makers for the close-out simulation workshop.

Summary of IVIR-AC feedback and recommendations

IVIR-AC recommended that as other health priorities take precedence over COVID-19, common modelling interests beyond COVID-19 should be explored at the close-out meeting in order to sustain or further develop capacity that was built and to ensure continuity of engagement in modelling. Additional recommendations included:

- The close-out meeting should incorporate an opportunity to reflect on the process and outcomes of the project, and to evaluate the extent to which modelling capacity, or the ability to interpret and communicate outputs from models, has been enhanced.
- The scope of potential model outputs should be clearly defined in terms of the types of questions the model is able to answer and those beyond its scope.
- Model documentation should be prioritized. Tools such as user guides with screenshots, a database of parameter and data sources, video demonstrations, and options for version control and in-house model updates could be implemented.

- To support use of the user-friendly modelling tool, users should be provided with clearly defined questions to model beyond the close-out meeting.

Therapeutic HPV vaccine impact modelling

Development of a therapeutic human papillomavirus (HPV) vaccine may provide an important addition to current methods for preventing and treating cervical cancer, especially among women in LMICs, who often lack access to screening and treatment. Therapeutic HPV vaccines, which are designed to clear or treat existing HPV infections or HPV-associated cervical lesions (rather than to prevent infection), are currently in early clinical development and might offer an additional tool to address the gaps in current cervical cancer programmes. A WHO-convened group of experts identified 2 overarching contexts with public health needs for therapeutic HPV vaccines, namely:

- in settings where it is difficult to scale up cervical cancer screening and treatment, reaching women who have been infected and who are unlikely to have received preventative HPV vaccines would reduce the overall proportion of women who develop cervical precancers; and

- in settings where some screening and treatment has been implemented (which, however, is costly,

demandé à l'IVIR-AC de donner son avis sur les méthodes adoptées pour ce projet et sur les modes de collaboration proposés avec les partenaires, les chercheurs et les décideurs de chaque pays pour l'atelier de simulation de clôture.

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

Étant donné que d'autres priorités sanitaires commencent à prendre le pas sur la COVID-19, l'IVIR-AC a recommandé d'explorer, lors de la réunion de clôture, l'intérêt commun que revêt la modélisation au-delà de la COVID-19, ce qui permettrait de préserver ou de développer plus avant les capacités qui ont été mises en place et d'inscrire les activités de modélisation dans la durée. Les autres recommandations formulées sont les suivantes:

- La réunion de clôture devrait être l'occasion de réfléchir au processus suivi et aux résultats obtenus et d'évaluer dans quelle mesure la capacité de modélisation, ou la capacité d'interpréter et de communiquer les résultats des modèles, a été renforcée.

- Il convient de définir clairement la portée des résultats de modélisation potentiels, c'est-à-dire les questions auxquelles le modèle est en mesure de répondre et celles qui sortent de son champ d'application.
- La priorité doit être accordée aux activités de documentation de la modélisation. Certains outils pourraient être déployés, tels que des guides d'utilisation contenant des captures d'écran, une base de paramètres et de sources de données, des démonstrations vidéo et des options pour le contrôle des versions et la mise à jour interne des modèles.
- Pour promouvoir l'utilisation de l'outil de modélisation, il convient de fournir aux utilisateurs des questions clairement définies à modéliser après la réunion de clôture.

Modélisation de l'impact des vaccins thérapeutiques contre le HPV

La mise au point de vaccins thérapeutiques contre le HPV pourrait apporter un complément important aux méthodes actuelles de prévention et de traitement du cancer du col de l'utérus, en particulier pour les femmes des pays à revenu faible ou intermédiaire, qui n'ont souvent qu'un accès insuffisant aux services de dépistage et de traitement. Des vaccins thérapeutiques contre le HPV, destinés à éliminer ou traiter les infections à HPV existantes ou les lésions cervicales associées (plutôt qu'à prévenir l'infection), sont actuellement en phase préliminaire de développement clinique et pourraient offrir un moyen supplémentaire de combler les lacunes actuelles des programmes de lutte contre le cancer du col de l'utérus. Un groupe d'experts convoqué par l'OMS a identifié 2 contextes majeurs dans lesquels les vaccins thérapeutiques contre le HPV pourraient être d'un apport crucial pour la santé publique, soit:

- Dans les contextes où il est difficile de généraliser l'accès au dépistage et au traitement du cancer du col de l'utérus, cette intervention auprès de femmes qui ont été infectées et qui n'ont probablement pas reçu de vaccins préventifs contre le HPV permettrait de réduire la proportion globale de femmes qui développent des lésions précancéreuses du col de l'utérus, et
- Dans les contextes où il existe un certain accès aux services de dépistage et de traitement (mais où ils sont coûteux,

complex or has large loss-to-follow-up), providing an alternative, simpler treatment following a positive test for HPV infection would increase the overall proportion of women with precancers who are effectively treated.

Draft preferred product characteristics (PPCs) for therapeutic HPV vaccines have since been developed and posted for public comment,[10] thus addressing the following 2 therapeutic vaccine approaches:

- Vaccines that clear oncogenic HPV infection are to be used in adult women through population-based vaccine delivery without a preceding HPV screening test.
- Vaccines that cause regression of high-grade cervical precancers to be used mainly as an alternative or adjunct to existing cervical precancer treatments following a positive HPV screening test.

A team from the Daffodil Centre at the University of Sydney, Australia, presented results from an analysis of therapeutic HPV vaccine impact on cervical cancer incidence and mortality in LMICs across various use cases and preferred vaccine characteristics. IVIR-AC reviewed information provided during the session. Given the timelines of emerging information, a full evaluation was not possible. IVIR-AC provided the following notes on the basis of discussion during the meeting:

- IVIR-AC discussed the need to consider the acceptability, feasibility, ethical and regulatory implications of mass therapeutic vaccination in the absence of screening.
- IVIR-AC affirmed the need for a clear communication strategy to differentiate between preventative and therapeutic vaccines.

- IVIR-AC acknowledged modelling of the therapeutic vaccine against a baseline of no further scale-up towards the WHO 90-70-90 targets,[11] and discussed the need for comparison to realistic scale-up levels in addition to considering the future value of the therapeutic vaccine after the achievement of the WHO 90-70-90 targets. ■

complexes ou se soldent par un taux élevé de patientes perdues de vue), le fait de proposer un traitement de substitution plus simple aux femmes ayant obtenu un résultat de test positif pour l'infection à HPV permettrait d'augmenter la proportion globale de femmes atteintes de lésions précancéreuses qui bénéficient d'un traitement efficace.

Un projet de document définissant les caractéristiques préférentiels due produit à privilégier pour les vaccins thérapeutiques contre le HPV a depuis été rédigé et soumis à l'avis du public.[10] Il porte sur des vaccins reposant sur les 2 approches thérapeutiques suivantes:

- des vaccins qui éliminent l'infection à HPV oncogène doivent être administrés aux femmes adultes dans le cadre des services de vaccination en population, sans test préalable de dépistage du HPV;
- des vaccins qui entraînent une régression des lésions précancéreuses de haut grade du col de l'utérus doivent être utilisés principalement en tant qu'alternative ou complément aux traitements existants des lésions précancéreuses du col chez les femmes ayant obtenu un résultat positif au test de dépistage du HPV.

Une équipe du Daffodil Centre de l'Université de Sydney, Australie a présenté les résultats d'une analyse de l'impact des vaccins anti-HPV thérapeutiques sur l'incidence et la mortalité du cancer du col de l'utérus dans les pays à revenu faible ou intermédiaire, selon divers scénarios d'utilisation et différentes caractéristiques à privilégier des vaccins. L'IVIR-AC a examiné les informations présentées lors de la session; compte tenu de la chronologie des informations émergentes, une évaluation complète n'a toutefois pas été possible. L'IVIR-AC a formulé les commentaires suivants sur la base des discussions menées au cours de la réunion:

- L'IVIR-AC a discuté de la nécessité d'examiner l'acceptabilité, la faisabilité et les implications éthiques et réglementaires d'une vaccination thérapeutique de masse en l'absence de dépistage.
- L'IVIR-AC a souligné qu'il est essentiel de mettre en place une stratégie de communication claire qui fasse bien la distinction entre les vaccins préventifs et les vaccins thérapeutiques.
- L'IVIR-AC a pris acte du fait que la modélisation des vaccins thérapeutiques se base sur un scénario de référence dans lequel il n'y a pas d'intensification des interventions en vue d'atteindre les cibles 90-70-90 fixées par l'OMS[11] et a discuté de la nécessité d'établir une comparaison avec des scénarios d'intensification des interventions à des niveaux réalistes, ainsi que d'examiner la valeur future des vaccins thérapeutiques après la réalisation des cibles 90-70-90. ■

[10] WHO preferred product characteristics for therapeutic HPV vaccines. Geneva: World Health Organization; 2023 (https://cdn.who.int/media/docs/default-source/reproductive-health/cervical-cancer/who-ppc-therapeutic-hpv-vaccines-public-comment.pdf?sfvrsn=dccee58_3, accessed September 2023).

[11] Global strategy to accelerate the elimination of cervical cancer as a public health problem. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/9789240014107, accessed September 2023).

[10] WHO preferred product characteristics for therapeutic HPV vaccines. Genève: Organisation mondiale de la Santé, 2023 (https://cdn.who.int/media/docs/default-source/reproductive-health/cervical-cancer/who-ppc-therapeutic-hpv-vaccines-public-comment.pdf?sfvrsn=dccee58_3, consulté en septembre 2023).

[11] Stratégie mondiale en vue d'accélérer l'élimination du cancer du col de l'utérus en tant que problème de santé publique. Genève, Organisation mondiale de la Santé, 2020 (https://www.who.int/fr/publications/i/item/9789240014107, consulté en septembre 2023).

World Health Organization

Background information to the sessions

World Health Organization

Session 1

Modelling public health impact and cost-effectiveness of the R21/Matrix-M malaria vaccine

Modeling public health impact and cost effectiveness of the R21/Matrix-M malaria vaccine

Mary J Hamel, MD

Senior Technical Officer and Team Lead for Malaria Vaccines,
Product and Delivery Research Unit, IVB, WHO

World Health Organization

Credit: WHO/F.Combrink

Agenda

• Background	Dr. Mary Hamel, WHO
• Technical presentation of modelled estimates of impact and cost-effectiveness of R21/Matrix M	Dr. Nora Schmit, Imperial College
• Description of proposed modeling of impact and cost-effectiveness of R21/Matrix-M	Dr. Melissa Penny, Telethon Kids Institute
• Q & A and Discussion (SAGE/MPAG WG members present)	

World Health Organization

Oct 2023, WHO update to recommendation for malaria vaccines

WHO recommends the programmatic use of malaria vaccines for the prevention of *P. falciparum* malaria in children living in malaria endemic areas, prioritizing areas of moderate and high transmission

- The malaria vaccine should be provided in a schedule of 4 doses in children from around 5 months of age[1] for the reduction of malaria disease and burden
- A 5th dose, given one year after dose 4, may be considered in areas where there is a significant malaria risk remaining in children a year after receiving dose 4
- Countries may consider providing the vaccine using an age-based, seasonal, or a hybrid of these approaches in areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks
- Countries should prioritize vaccination in areas of moderate and high transmission, but may also consider providing the vaccine in low transmission settings
- Vaccine introduction should be considered in the context of comprehensive national malaria control plans

This recommendation now includes <u>two</u> malaria vaccines:

- **RTS,S/AS01**
- **R21/Matrix-M**

[1] Vaccination programmes may choose to give the first dose at a later or earlier age, based on operational consideration. Studies with RTS,S/AS01 indicated lower efficacy if first dose was given around 6 weeks of age. However, it seems unlikely that efficacy would be substantially reduced if some children received the first dose at 4 rather than 5 months, and providing vaccination at an age younger than 5 months may increase coverage or impact

World Health Organization

R21/ Matrix-M vaccine WHO recommendation: Phase 3 clinical trial findings

Ongoing Phase 3 trial design includes two delivery approaches, with a 3-dose primary series followed by 4th dose given 12 months after dose 3:

1. **Seasonal administration (n=2,400), ages 5-36 months at first vaccination, 2 sites:**
   - Bougouni, Mali and Nanoro, Burkina Faso (highly seasonal transmission, SMC)
   - Strategic delivery so period of highest efficacy aligned with the period of highest malaria transmission
2. **Age-based ("standard") administration (n=2,400), ages 5-36 months at first vaccination, 3 sites:**
   - Dande, Burkina Faso (moderate transmission, highly seasonal, SMC)
   - Kilifi, Kenya and Bagamoyo, Tanzania (low and moderate, no SMC)

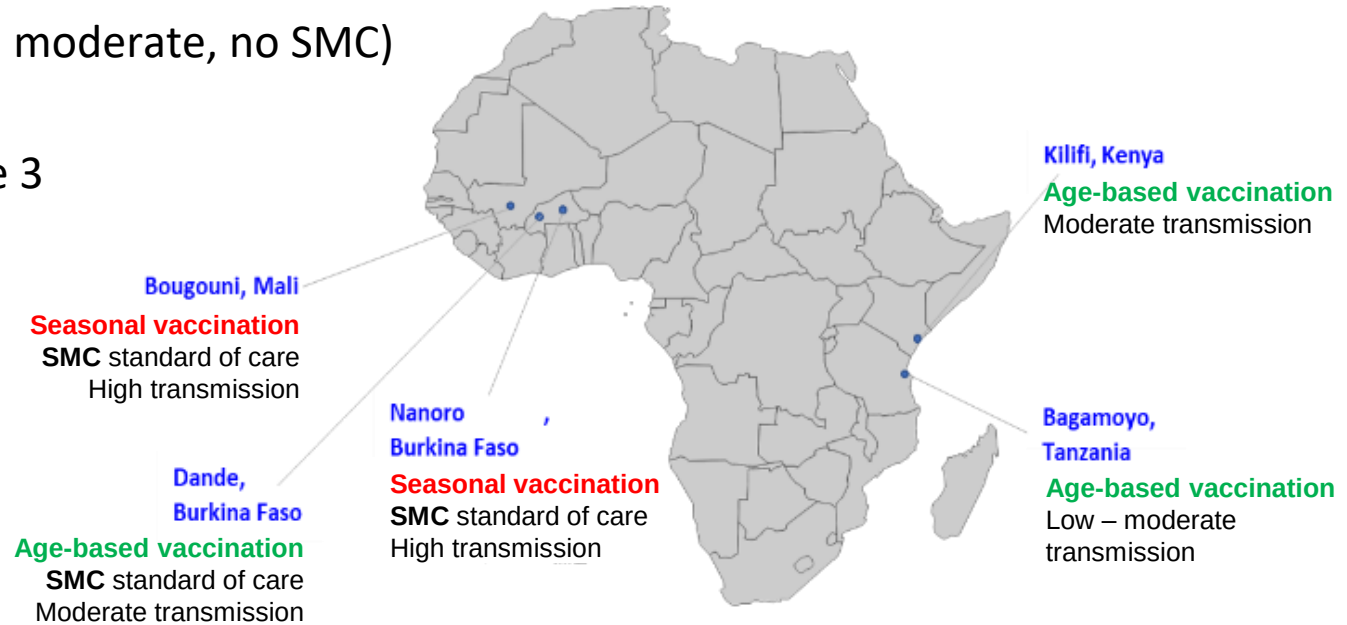
Primary endpoint: 12 months post dose-3

Data available through 18-months follow-up post dose 3

Seasonal malaria chemoprevention (SMC) by MoH as standard of care in areas of highly seasonal malaria in West Africa

Insecticide-treated net (ITN) at the start of the trial

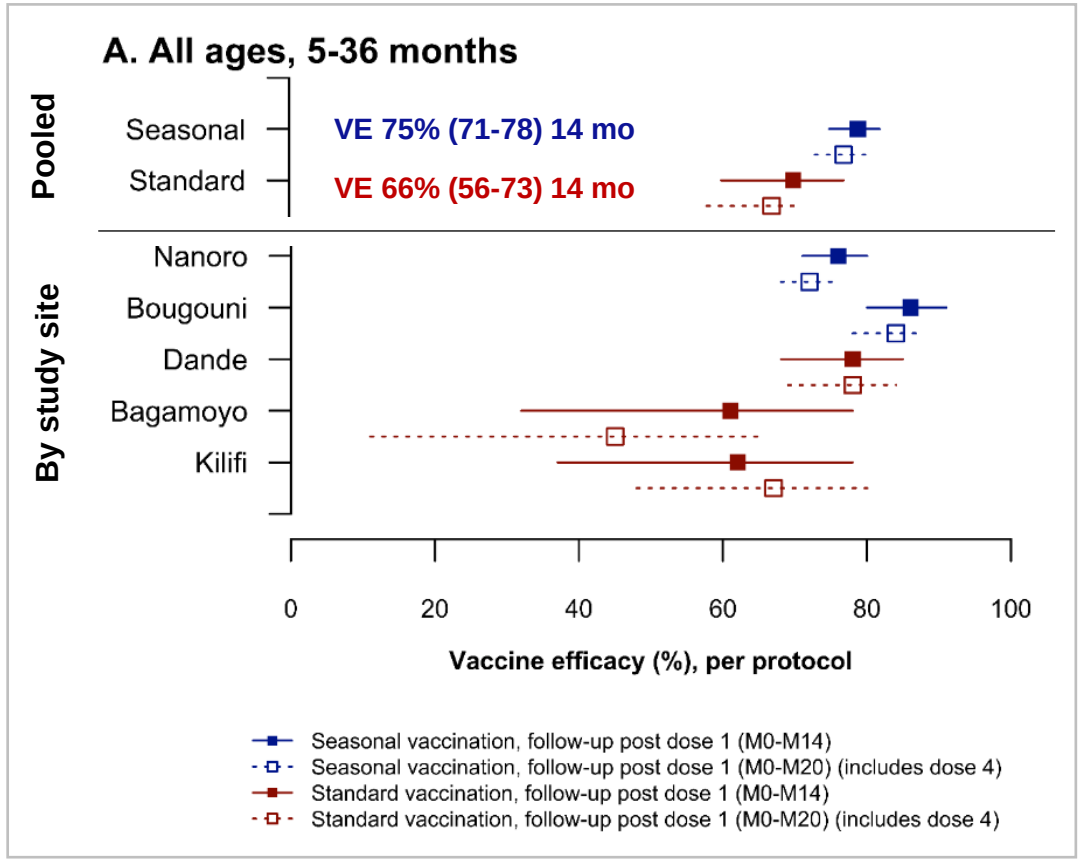
No assessment of vaccine efficacy or duration of protection in areas of high perennial transmission



World Health Organization

Vaccine efficacy against all episodes of clinical malaria, *per protocol*

Seasonal sites, 14- and 20-month follow-up post dose 1 (blue); age-based (standard) sites, 14-month follow-up post dose 1 (red)



- VE similar during 12 months after primary series and during 18 months after primary series with a 4th dose
- VE lower in East African sites where given as age-based administration without SMC **(VE = 56% (95%CI 38,69) during 12 months follow-up post dose 3)**
- VE similar according to the number of rounds of SMC received, but limitations to data*

*study not designed to measure SMC effect, SMC provided through MOH with varying coverage, ascertainment of SMC through home health cards, no written documentation of SMC given on health card interpreted as zero SMC received

VE for modified intention to treat (mITT) population did not differ statistically from per protocol (PP)

Mathematical modeling and R21/Matrix-M (R21) malaria vaccine

- **High impact:** Mathematical modelling conducted by Imperial College estimates high public health impact of the R21 vaccine in a wide range of malaria transmission settings, including low transmission settings
- **Cost effectiveness:** At prices of US$ 2 – US$ 4 per dose, modelling estimates that the cost-effectiveness of the R21 vaccine would be comparable with other recommended malaria interventions and other childhood vaccines
- **SAGE and MPAG asked for additional modelling -** in the lower transmission Phase 3 trial sites (Kenya and Tanzania – where SMC was not provided), the model estimates for VE were outside the upper 95% confidence bound of the observed trial data, reflecting potential uncertainty in both the trial and model estimates in these settings
- The Phase 2 trial was conducted in areas of highly seasonal malaria transmission in the context of ITNs and SMC, and the modeling seems to best fit Phase 3 trial data sites with the same context
- SAGE and MPAG therefore requested that modelling of impact and cost-effectiveness be conducted using inputs from the Phase 3 trial data rather than Phase 2 trial data, and that additional independent cost-effectiveness analyses be conducted to complement that already completed

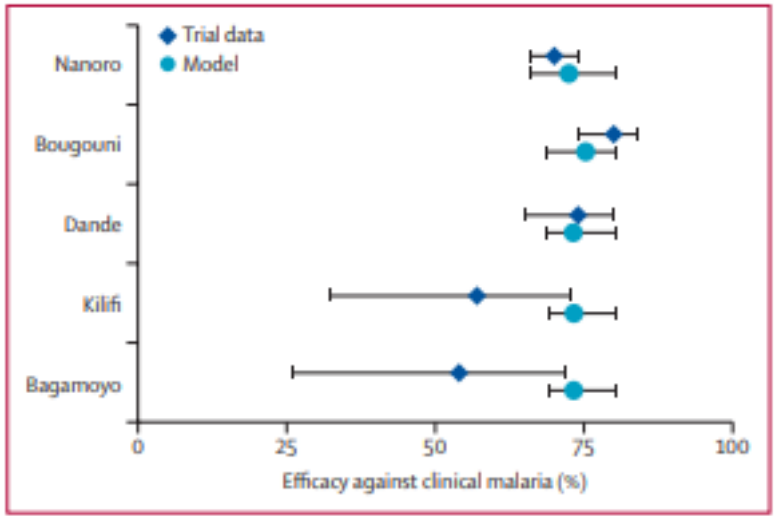
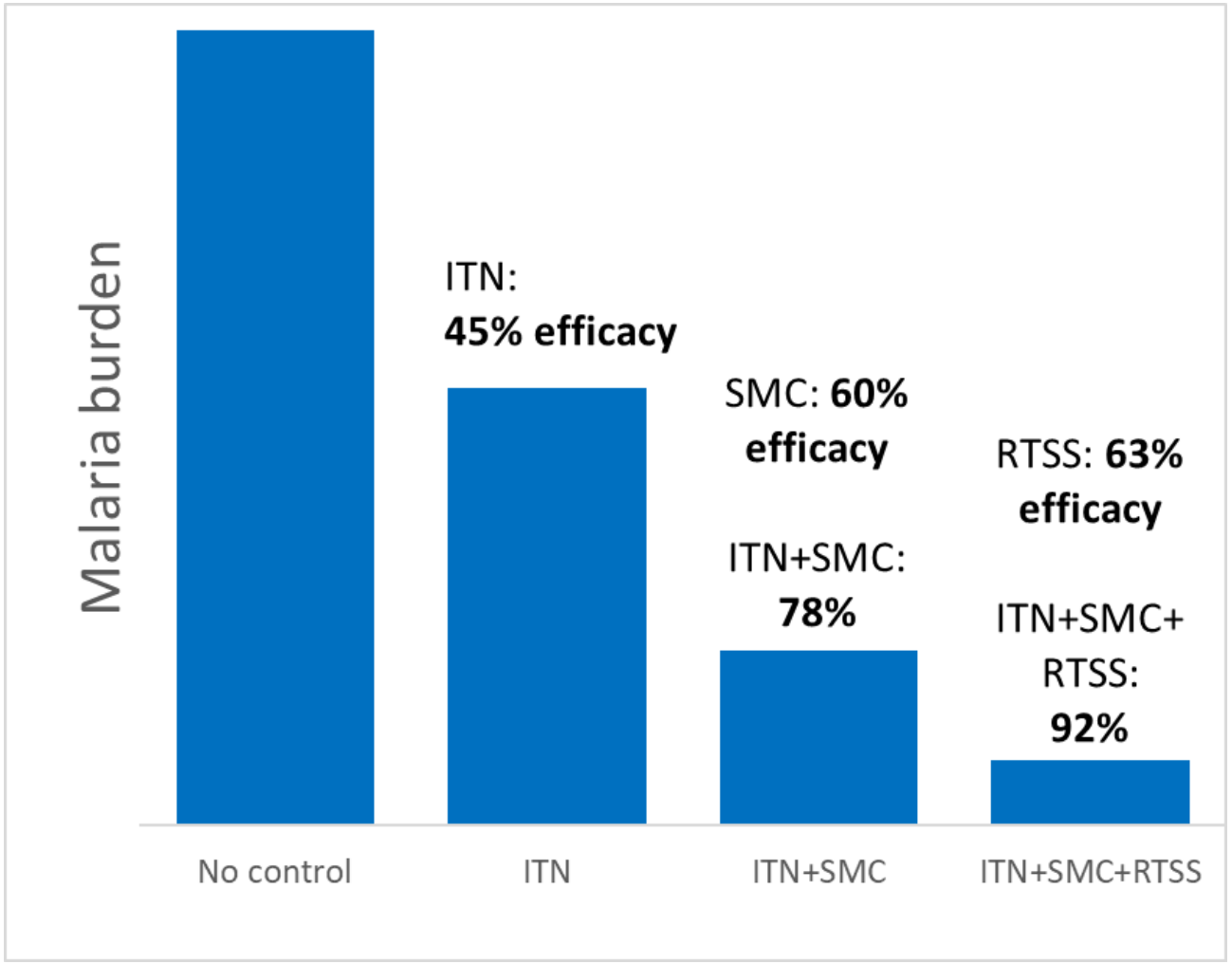


***Figure 2:* Model validation against phase 3 data**
Median model estimates with 95% credible intervals for the fitted model (light blue points and error bars) are shown in relation to trial estimates of vaccine efficacy against multiple episodes of clinical malaria (modified per-protocol analysis) with 95% CIs (dark blue diamonds and error bars). In Nanoro and Bougouni, participants received the seasonal regimen and had a follow-up of 18 months. In Dande, Kilifi, and Bagamoyo, participants received the standard regimen and had a follow-up of 12 months. Nanoro, Bougouni, and Dande are west African sites. Bagamoyo and Kilifi are located in east Africa. The model projections are made over the same time periods as each of the trial sites.

World Health Organization

Highest impact achieved when malaria interventions strategically used together

Reaching high impact in areas of highly seasonal transmission



Prof Paul Milligan, LSHTM

Insecticide Treated Net (ITN) efficacy: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000363.pub3/full

Seasonal Malaria Chemoprevention (SMC) efficacy: **85% per month**, case control studies in 5 countries, https://journals.plos.org/plosmedicine/article/authors?id=10.1371/journal.pmed.1003727 (SMC for 5 months covering 70% of annual burden)

RTS,S/AS01 efficacy of seasonal vaccination **39% efficacious over 3 years** https://www.nejm.org/doi/full/10.1056/NEJMoa2026330

World Health Organization

Questions to IVIR-AC

1. To what extent does the **Imperial modelling** analysis estimate the impact and cost-effectiveness of the R21 vaccine **across transmission intensities, seasonal patterns, and settings using different malaria interventions (e.g., seasonal malaria chemoprevention**)?
    a) Is the impact in low transmission settings overestimated?
2. For any gaps identified in question 1, to what extent are these due to:
    a) Model structure or
    b) Uncertainties in the data informing model parameters (e.g., vaccine antibody dynamics, vaccine efficacy, duration of protection)
3. Regarding the presentation from **Telethon Kids Institute (TKI),** what comments or recommendations does IVIR-AC have on the proposed analysis based on the **TKI** model to address questions 1 and 2?
4. Are there suggestions on how parameter estimates can be improved?
    a) For example, can currently available Phase 3 data better inform the models (currently limited to 18 months follow-up)?
    b) Which uncertainties in the estimates would still remain?

World Health Organization

Thank you

World Health Organization

Credit: WHO/Neil Thomas.

R21/Matrix-M public health impact and cost-effectiveness modelling

Nora Schmit, Hillary Topazian,
Pete Winskill & Azra Ghani

MRC Centre for Global Infectious Disease Analysis

School of Public Health, Imperial College London

Acknowledgements

MRC Centre for Global Infectious Disease Analysis

Imperial College London

Hillary Topazian

Pete Winskill

Azra Ghani, Giovanni Charles, Kelly McCain
Katie Ewer, Mehreen Datoo, Duncan Bellamy, Lisa Stockdale, & Adrian Hill from the Jenner Institute
All trial organizers and participants.

Overview

MRC Centre for Global Infectious Disease Analysis

Imperial College London

- To estimate the impact and cost effectiveness of the R21/Matrix-M malaria vaccine

- The approach is the same as that used for the 2015 RTS,S modelling exercise and for the 2021 RTS,S update. Impact and cost-effectiveness summarised over:
  - A 15 year time horizon
  - Non-seasonal and seasonal settings
  - A range of transmission levels (*Pf*Pr_{2-10}: 3%-65%),
    - Assumes the impact of other interventions are accounted for
    - Assumes the impact and cost-effectiveness estimates for R21 are additional to the impact of other widely deployed control measures
  - Different implementations: age-based, seasonal or hybrid vaccination

Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models

Melissa A Penny, Robert Verity*, Caitlin A Bever*, Christophe Sauboin*, Katya Galactionova, Stefan Flasche, Michael T White, Edward A Wenger, Nicolas Van de Velde, Peter Pemberton-Ross, Jamie T Griffin, Thomas A Smith, Philip A Eckhoff, Farzana Muhib, Mark Jit, Azra C Ghani*

- Costs evaluated at $2, $3 and $4 per vaccine dose + consumables and delivery costs

- Summary measures are not directly comparable with previous analyses
  - Summaries have been updated to better represent the current levels of transmission across sub-Saharan Africa
  - Estimates represent median values at 20% *Pf*Pr_{2-10} and intervals median values at 3% and 65% *Pf*Pr_{2-10} for a four-dose schedule.

Overview of approach

MRC Centre for Global Infectious Disease Analysis

Imperial College London

Fit

Fit the model to phase II data. Estimate antibody dynamics (pattern of waning) over time and the relationship between antibody titre and vaccine efficacy*

Validate

Validate the fitted model by comparing the model predicted efficacy against observed efficacy across phase III sites

Predict

Use the validated model to predict vaccine impact and cost-effectiveness summaries across a wide range of settings†

With some updates and adaptations, after:

* *White, M T et al. "Immunogenicity of the RTS,S/AS01 Malaria Vaccine and Implications for Duration of Vaccine Efficacy: Secondary Analysis of Data from a Phase 3 Randomised Controlled Trial." The Lancet Infectious Diseases 3099, no. 15 (2015): 1450–58.*

† *Penny, Melissa A, Robert Verity, Caitlin A Bever, Christophe Sauboin et al. "Public Health Impact and Cost-Effectiveness of the RTS,S/AS01 Malaria Vaccine: A Systematic Comparison of Predictions from Four Mathematical Models." The Lancet 6736, no. 15 (2015).*

Model fit to phase II data

Fit

MRC Centre for Global Infectious Disease Analysis

Imperial College London

- Model fitted to individual-level phase II trial immunogenicity and event data from Nanoro, Burkina Faso

- 1. Estimate antibody dynamics (pattern of waning) over time
  - Proportion of the antibody response that is short/long-lived
  - Half-life of the short-lived and long-lived component

- 2. Estimate relationship between antibody titres ($CS(t)$) and vaccine efficacy against clinical malaria ($V(t)$)

$$V(t) = V_{max}\left(1 - \frac{1}{1 + \left(\frac{CS(t)}{\beta}\right)^{\alpha}}\right)$$

  - Posterior parameters from antibody model fit (1) are used as input to efficacy model.
  - Clinical hazard over time is simulated accounting for age- and exposure-dependent acquisition of anti-blood-stage immunity and local transmission and participant characteristics in the trial.
  - Parameters V_{max}, α and β are estimated by fitting to the individual-level timing of episodes of symptomatic malaria with survival analysis methods in a Bayesian Markov chain Monte Carlo (MCMC) framework

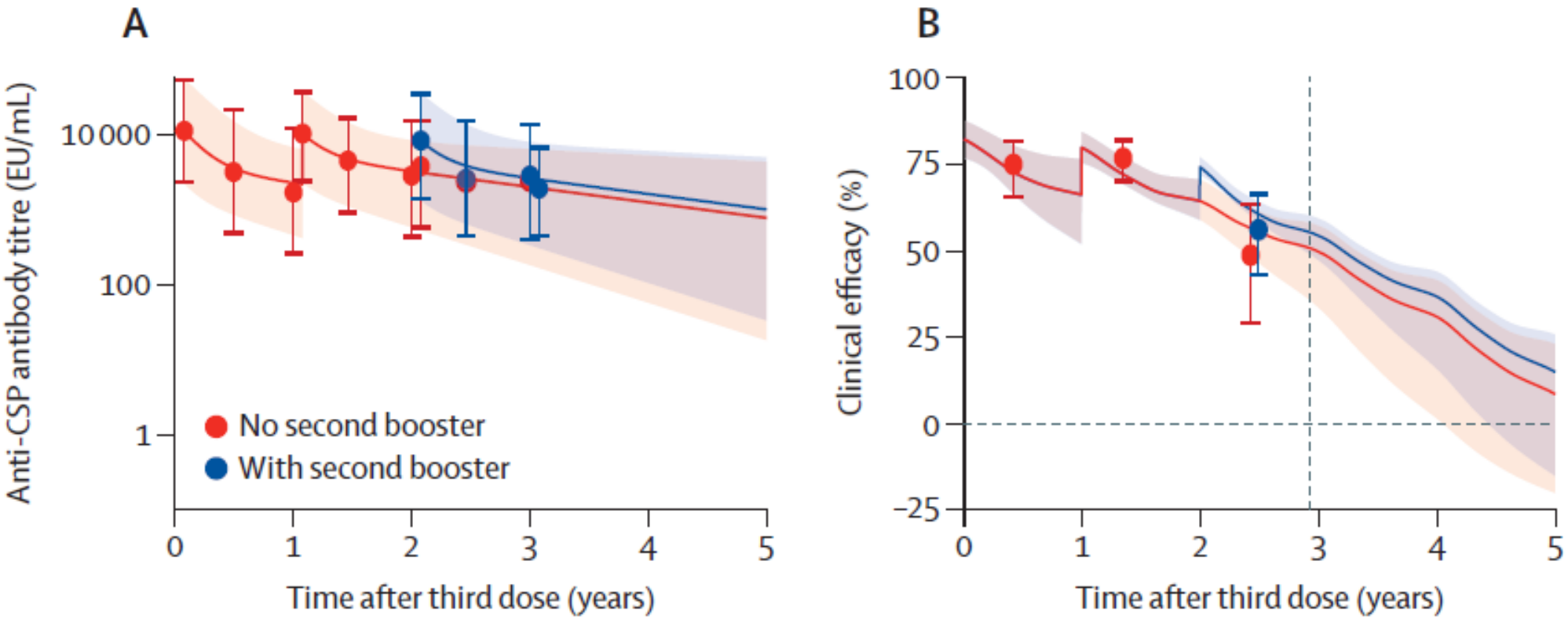
Model fit to phase II data

Fit

MRC Centre for Global Infectious Disease Analysis

Imperial College London

The fitted model was able to capture observed antibody dynamics following vaccination (left) and efficacy against clinical malaria (right).



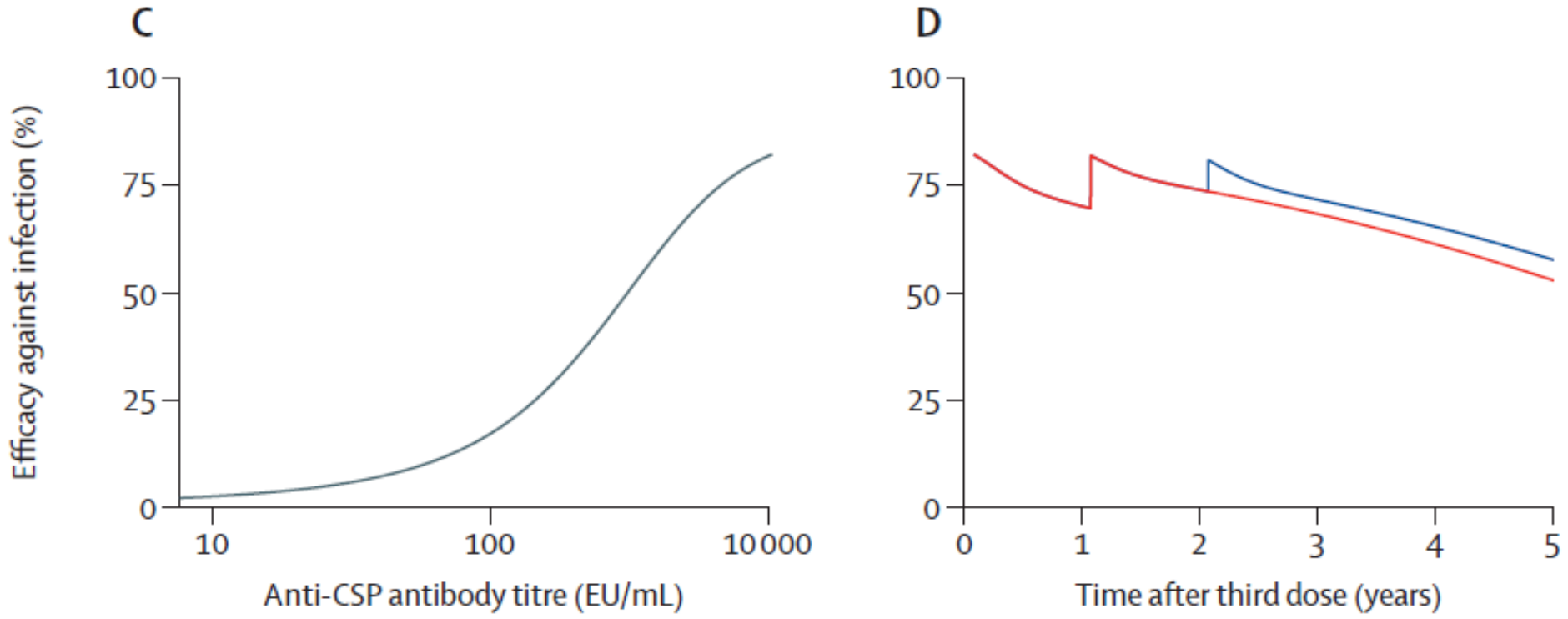
Model fit to phase II data

Fit

MRC Centre for Global Infectious Disease Analysis

Imperial College London

We are also able to estimate the relationship between anti-CSP antibody titres and protection against infection (left) and the efficacy against infection over time following vaccination (right).



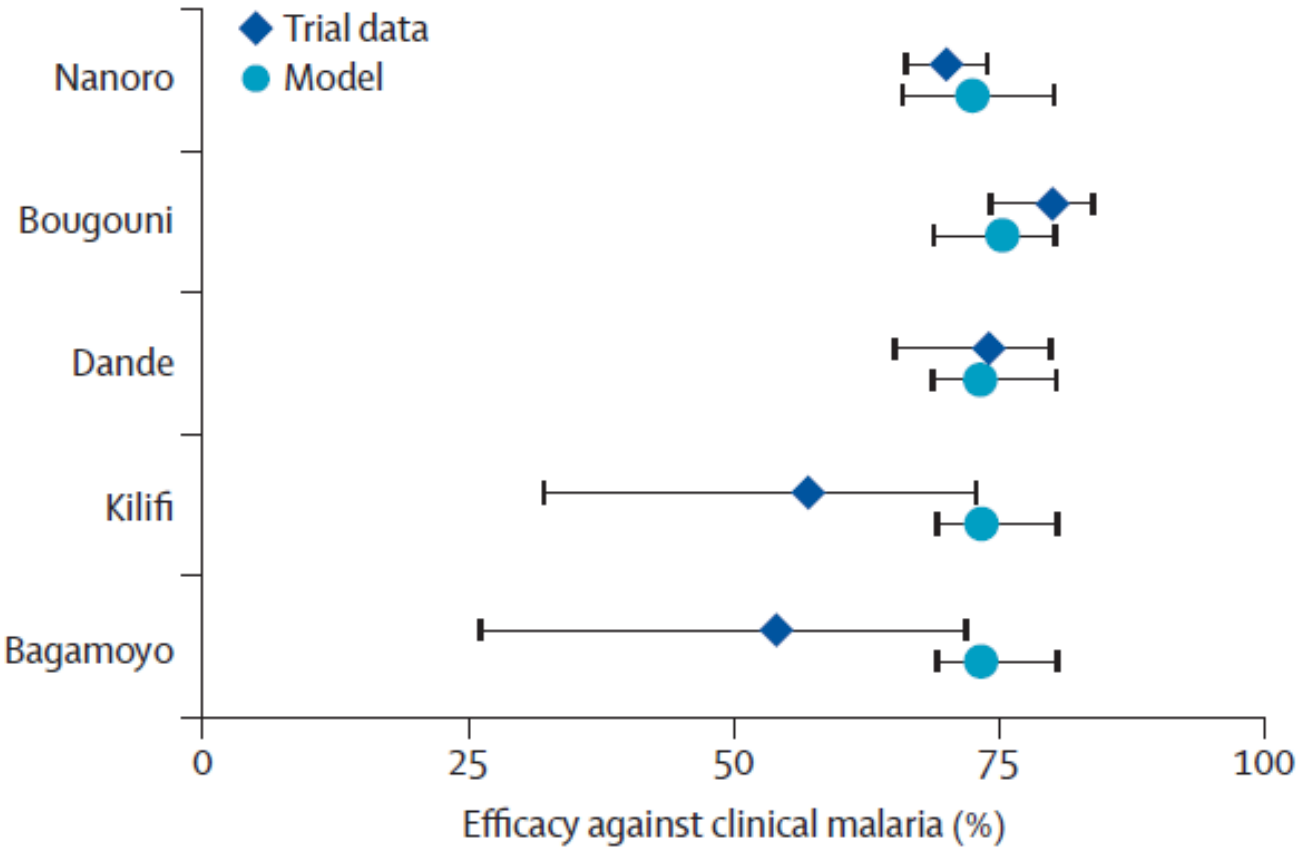
Validation against phase III data

Validate

MRC Centre for Global Infectious Disease Analysis

Imperial College London

Model validated against phase III trial efficacy estimates by site



- Confidence intervals for modelled estimates overlap with those for trial estimates for all sites.
- For the period of follow-up to date the model predicts relatively small differences in efficacy across sites.
- Point estimates of efficacy are closer to observed efficacy in the three higher transmission sites (Nanoro, Bougouni and Dande) than in the lower transmission, non-seasonal sites in East Africa (Bagamoyo and Kilifi) where trial efficacy was lower and more uncertain.

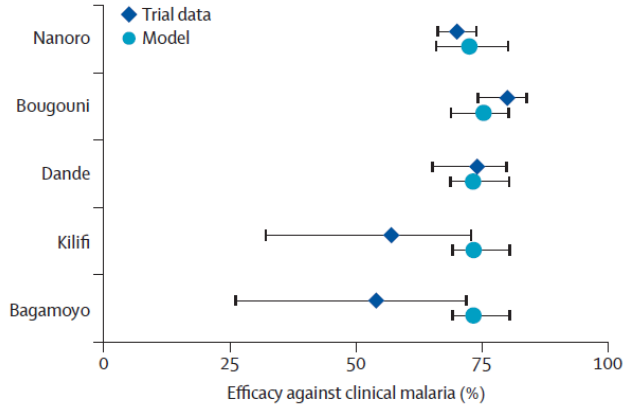
Low-transmission settings

Validate

MRC Centre for Global Infectious Disease Analysis

Imperial College London

- There is uncertainty about whether the model accurately captures vaccine impact in low-transmission settings.
- Evidence to explain differences in the lower- vs. higher-transmission sites is insufficient.



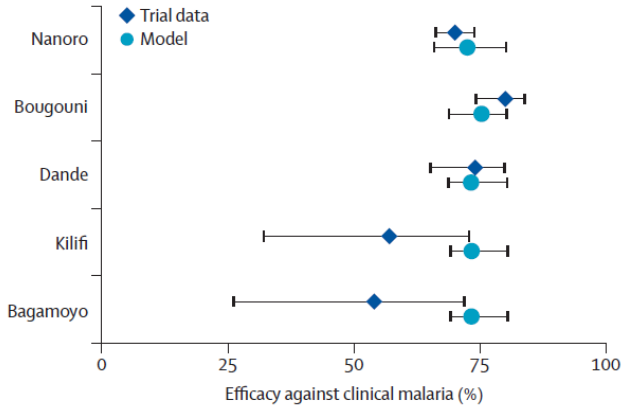
Low-transmission settings

Validate

MRC Centre for Global Infectious Disease Analysis

Imperial College London

- Potential factors:
  - Efficacy estimates in the low transmission sites (Kilifi and Bagamoyo) are noisier due to smaller event numbers. The trial was designed to provide adequate power for a **combined** analysis of data from the two lower-transmission East African sites.*
  - Seasonal malaria chemoprevention (SMC) is implemented in Nanoro, Bougouni and Dande but not in Kilifi and Bagamoyo. Potential differences in vaccine efficacy due to SMC were not accounted for in model fitting.
  - R21 trials were not designed to answer the question of SMC and R21 synergy as was seen for RTS,S.** However, differences in vaccine efficacy between those receiving 0 SMC rounds vs. those receiving 3-4 rounds in seasonal sites was only ~5% over 20 months (non-significant).†
- The inverse pattern was observed for RTS,S - higher efficacy in areas of lower compared to higher transmission.††
- Further research is required once longer-term follow-up data becomes available.



** Datoo, M. S., et al. Safety and efficacy of malaria vaccine candidate R21/Matrix-M in African children: a multicentre, double-blind, randomised, phase 3 trial. The Lancet, 2024.*

*** Chandramohan, D., et al. Seasonal malaria vaccination with or without seasonal malaria chemoprevention. New England Journal of Medicine, 385(11), 2021.*

† *SAGE Yellow Book, September 2023.*

†† *RTS,S Clinical Trials Partnership. Efficacy and safety of RTS, S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. The Lancet, 386(9988), 2015.*

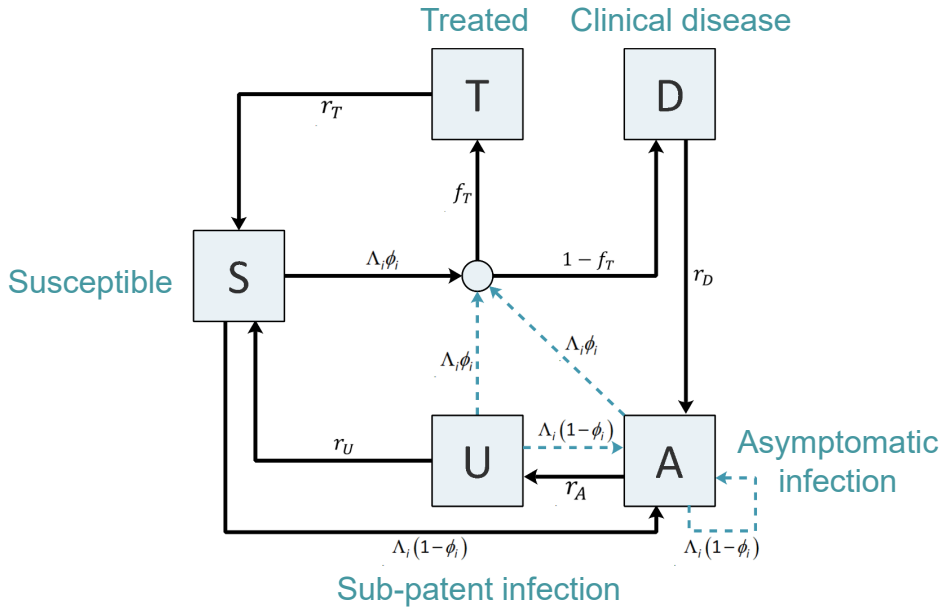
Predicting impact

Predict

MRC Centre for Global Infectious Disease Analysis

Imperial College London

- Mathematical transmission model has been extensively peer-reviewed *
  - Age-structured individual-based model of *P. falciparum* transmission
  - Consists of human component including immunity acquisition and heterogeneity in biting exposure, and mosquito component including life cycle
  - Was calibrated to parasite prevalence and clinical incidence data from various settings in sub-Saharan Africa



** Griffin, J. T. et al. Reducing Plasmodium falciparum malaria transmission in Africa: a model-based evaluation of intervention strategies. PLoS medicine, 7(8), 2010.*

** Griffin, J. T., et al. Potential for reduction of burden and local elimination of malaria by reducing Plasmodium falciparum malaria transmission: a mathematical modelling study. The Lancet Infectious Diseases, 16(4), 2016.*

** Penny, M. A. et al. Public Health Impact and Cost-Effectiveness of the RTS,S/AS01 Malaria Vaccine: A Systematic Comparison of Predictions from Four Mathematical Models."The Lancet 6736, no. 15, 2015.*

** Hogan, A. B. et al. Estimated impact of RTS, S/AS01 malaria vaccine allocation strategies in sub-Saharan Africa: a modelling study. PLoS Medicine, 17(11), 2020.*

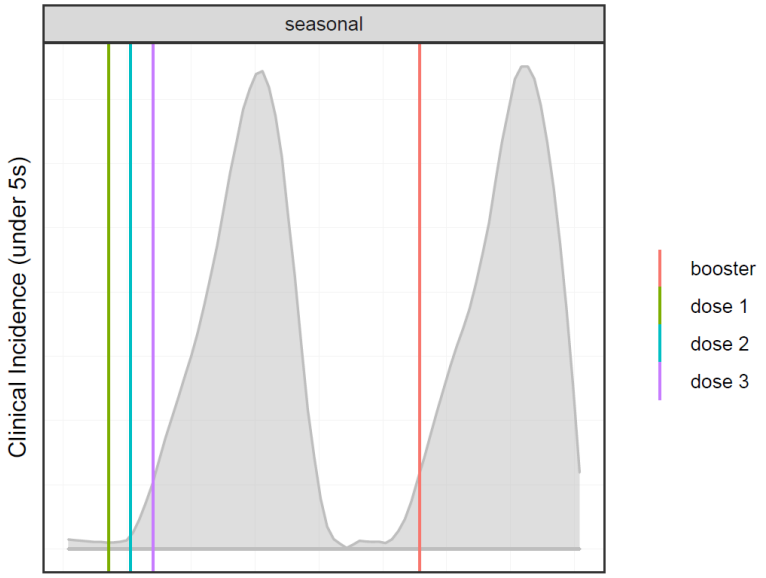
Vaccine implementation

Predict

MRC Centre for Global Infectious Disease Analysis

Imperial College London

	First 3 doses	First booster dose
Age-based	6, 7 and 8 months of age	12 months post dose 3 (at 20 months of age)
Seasonal	5.5, 4.5 and 3.5 months before the seasonal peak in clinical incidence for children aged 5-17 months	12 months post dose 3
Hybrid	6, 7 and 8 months of age (age-based)	3.5 months before the seasonal peak in clinical incidence and 6 months post dose 3 at the earliest



Cost-effectiveness analysis

Predict

MRC Centre for Global Infectious Disease Analysis

Imperial College London

- Costs estimated from secondary data sources using a national government perspective
  - Costs evaluated at $2, $3 and $4 per vaccine dose
  - Delivery costs (per dose): $1.48 age-based, $3.75 seasonal and $2.36 hybrid*
  - Assuming other overheads (e.g. consumables) were the same as for the 2021 RTS,S analysis
  - Cost of treating clinical and severe cases includes rapid diagnostic test, drug and out-/in-patient treatment costs

- Incremental cost per case and per DALY averted calculated in comparison to the same baseline scenario with no vaccination
  - Impact and cost of other interventions assumed to remain constant and equal between the baseline and R21 vaccine introduction scenario

** Malaria Vaccine Implementation Programme (MVIP) Programme Advisory Group. Full Evidence Report on the RTS,S/AS01 Malaria Vaccine. Geneva: World Health Organization, 2021*

** Diawara, H. et al. Cost of introducing and delivering malaria vaccine (RTS,S/AS01 E) in areas of seasonal malaria transmission, Mali and Burkina Faso. BMJ Glob Health 8, 2023.*

Estimated public health impact.

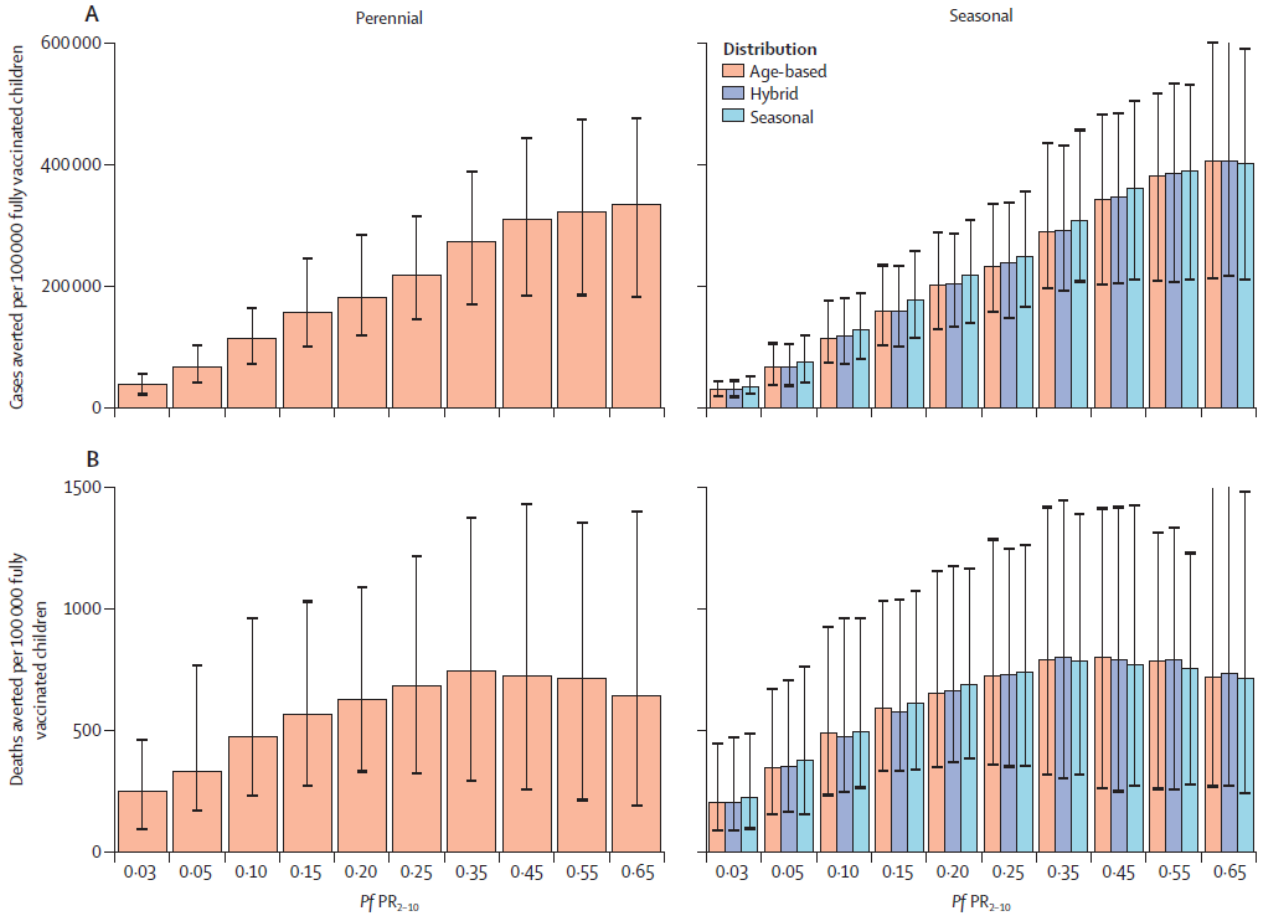
Predict

MRC Centre for Global Infectious Disease Analysis

Imperial College London

Incorporate the fitted, validated vaccine model in the transmission model to predict impact in non-seasonal and seasonal settings with different levels of transmission, over a 15-year time horizon.

- Modelling predictions indicate a significant public health impact across a wide range of settings, including down to *Pf*Pr$_{2\text{-}10}$ of 3%.
- The predicted differences in impact between delivery modes in the seasonal setting are very small.
- The model validation is currently more uncertain in lower transmission sites.



A fully vaccinated child = a child who has received all three doses of the primary series

Estimated public health impact.

Predict

MRC Centre for Global Infectious Disease Analysis

Imperial College London

Incorporate the fitted, validated vaccine model in the transmission model to predict impact in non-seasonal and seasonal settings with different levels of transmission, over a 15-year time horizon.

Seasonal setting	**Perennial**	**Seasonal**		
Implementation method	**Age-based**	**Age-based**	**Seasonal**	**Hybrid**
Proportion of clinical cases averted in children younger than 5 years	40·2% [44·3, 30·0]	40·1% [45·2, 28·9]	42·4% [48·3, 29·1]	40·4% [45·4, 29·0]
Proportion of malaria deaths averted in children younger than 5 years	33·6% [43·0, 21·4]	33·8% [43·8, 20·2]	34·4% [46·4, 19·0]	33·0% [43·8, 20·3]
Clinical cases averted per 100,000 fully vaccinated children	181 825 [38 815, 333 491]	202 017 [29 868, 405 702]	218 472 [34 680, 401 635]	203 134 [30 557, 405 220]
Malaria deaths averted per 100,000 fully vaccinated children	629 [250, 646]	653 [204, 723]	690 [225, 715]	664 [207, 734]

Estimates represent median values at 20% *Pf*Pr_{2-10} and intervals median values at 3% and 65% *Pf*Pr_{2-10} for a four-dose schedule.

Estimated cost effectiveness

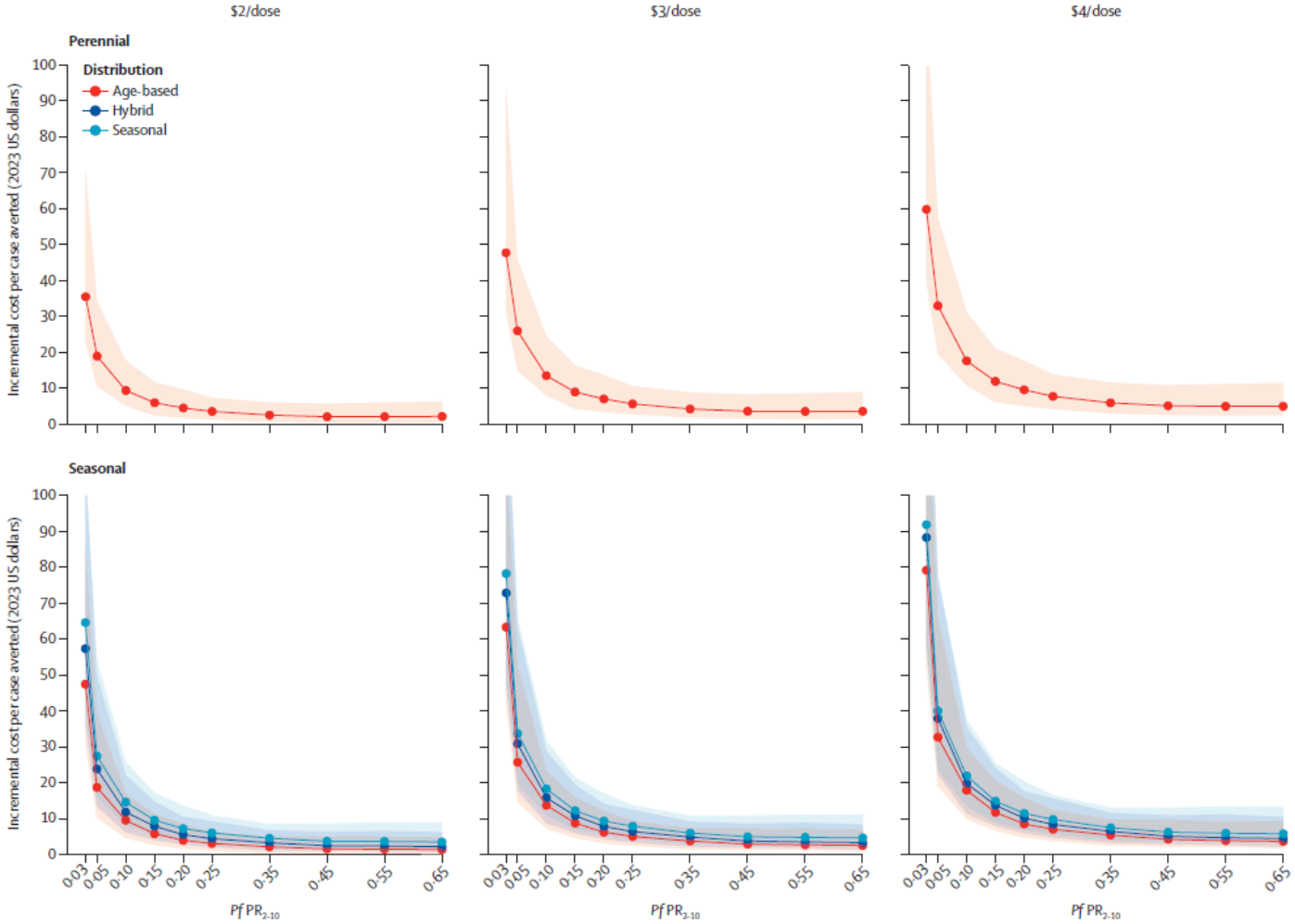
Predict

MRC Centre for Global Infectious Disease Analysis

Imperial College London

Use the fitted, validated model to predict cost effectiveness in non-seasonal and seasonal settings over a range of transmission levels.

- All vaccine introduction scenarios incurred higher costs and positive health impacts compared to the baseline of no vaccination.
- The cost per case averted increases at lower transmission levels.
- Shifted cost-effectiveness curve important to consider regarding any lower transmission threshold for implementation.



Estimated cost effectiveness

Predict

MRC Centre for Global Infectious Disease Analysis

Imperial College London

Use the fitted, validated model to predict cost effectiveness in non-seasonal and seasonal settings over a range of transmission levels.

Seasonal setting	Perennial	Seasonal		
Implementation method	**Age-based**	**Age-based**	**Seasonal**	**Hybrid**
Cost per clinical case averted (USD)				
$2 per dose	$5 [35, 2]	$4 [47, 1]	$7 [65, 3]	$6 [57, 2]
$3 per dose	$7 [48, 4]	$6 [63, 3]	$9 [78, 5]	$8 [73, 3]
$4 per dose	$10 [60, 5]	$9 [79, 4]	$12 [92, 6]	$10 [88, 5]
Cost per DALY averted (USD)				
$2 per dose	$22 [103, 18]	$19 [129, 12]	$37 [183, 34]	$26 [161, 18]
$3 per dose	$34 [139, 29]	$30 [172, 22]	$48 [221, 45]	$38 [204, 29]
$4 per dose	$47 [174, 42]	$42 [214, 33]	$59 [260, 55]	$50 [247, 38]

Estimates represent median values at 20% *Pf*Pr_{2-10} and intervals median values at 3% and 65% *Pf*Pr_{2-10} for a four-dose schedule.

Cost-effectiveness estimates are comparable with other malaria interventions and other childhood vaccines.

Summary

MRC Centre for Global Infectious Disease Analysis
Imperial College London

- Modelling predictions indicate a significant public health impact across a wide range of settings, including lower transmission areas.

- Cost-effectiveness estimates are comparable with other malaria interventions and other childhood vaccines and are additional to the impact of other widely deployed control measures.

- Future work will refine model estimates, including using additional follow up data.

Telethon Kids/Swiss TPH analysis plan: R21 analysis and predictions of public health impact and cost-effectiveness

WHO IVIR-AC meeting 26-29th Feb 2024

Melissa Penny, Daniela Figueroa-Downing, Lydia Braunack-Mayer, Thiery Masserey, Josephine Malinga, Andrew Shattock

Contact: melissa.penny@uwa.edu.au melissa.penny@telethonkids.org.au

Outline

BACKGROUND (Model OpenMalaria, RTS,S/AS01 modelling, &= R21 Modelling)

SUMMARY OF PUBLIC DATA / DATA REQUEST

MODEL CALIBRATION (Analysis plan: approach & data)

PUBLIC HEALTH IMPACT ESTIMATION (Analysis plan)

COST-EFFECTIVENESS ANALYSIS (Analysis plan)

QUESTIONS + NEXT STEPS

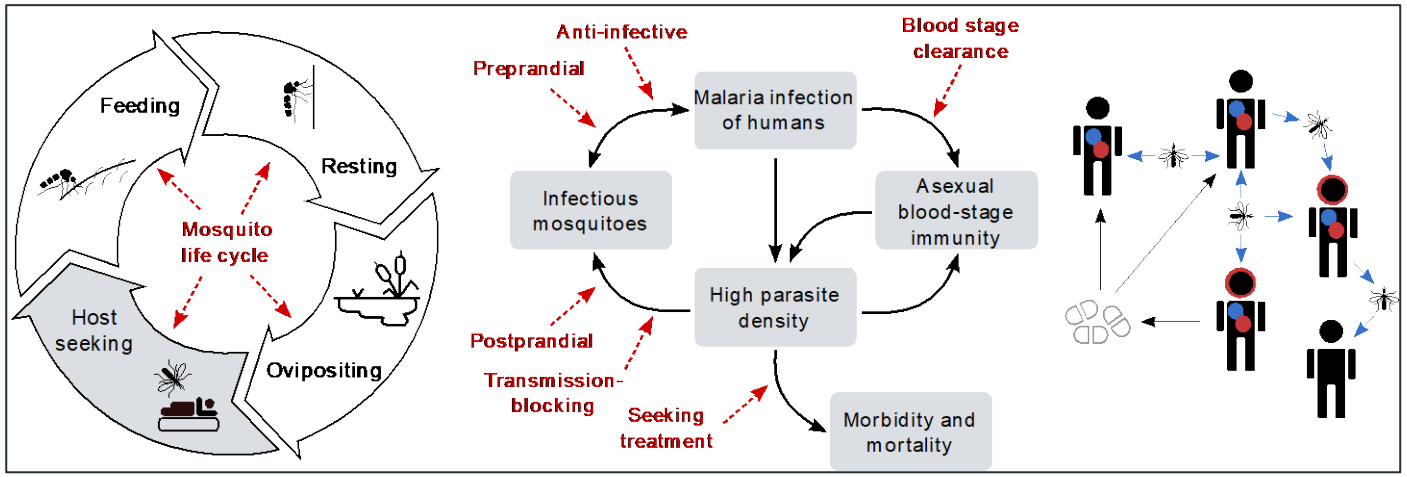
Background

Background: OpenMalaria & vaccine modelling

Telethon Kids and Swiss TPH malaria model: OpenMalaria

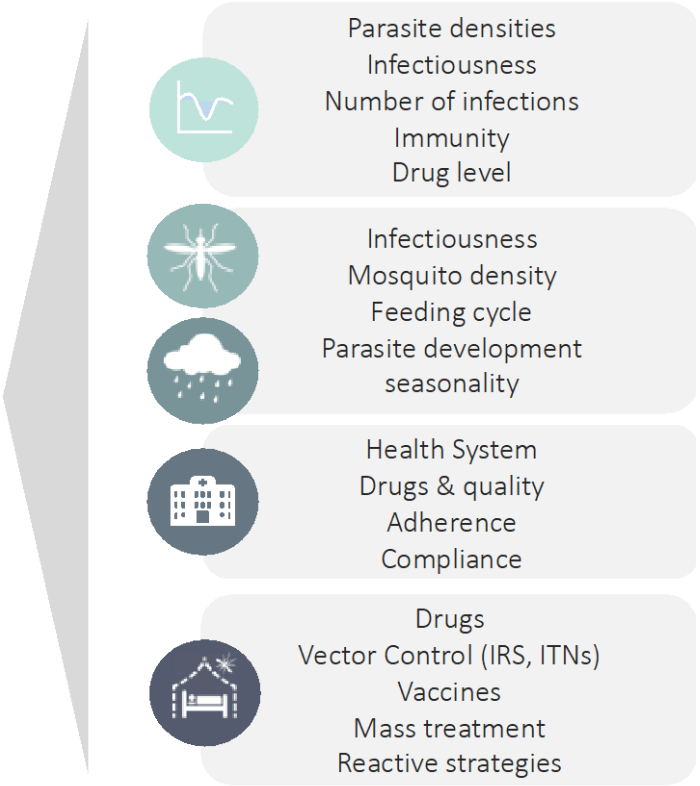
OpenMalaria is **an individual-based, stochastic model of malaria transmission and disease progression** that includes dynamics of mosquito infectiousness, human host infection, blood-stage parasite densities, incidence of severe malaria, hospitalization, and mortality.
The model has been previously reviewed with IVIR-AC in 2013-2015 (part of our modelling work on RTS,S)

OpenMalaria: Individual-based stochastic simulator of malaria epidemiology and control (*Plasmodium falciparum*)
https://github.com/SwissTPH/openmalaria/wiki



Within-host + intervention dynamics *within* population models

OpenSource C++: developed and in use since 2006
(many applications, validated, updated calibrations, used by many groups)



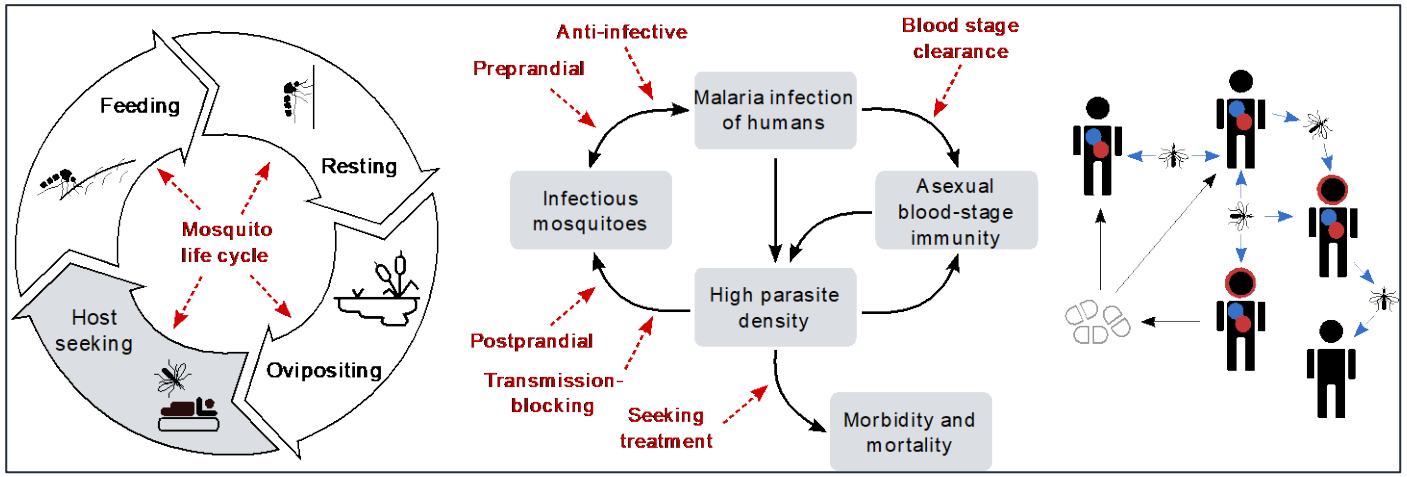
Source: Theresa Reiker et al

Background: OpenMalaria & vaccine modelling

Telethon Kids and Swiss TPH malaria model: OpenMalaria

OpenMalaria is **an individual-based, stochastic model of malaria transmission and disease progression** that includes dynamics of mosquito infectiousness, human host infection, blood-stage parasite densities, incidence of severe malaria, hospitalization, and mortality.
The model has been previously reviewed with IVIR-AC in 2013-2015 (part of our modelling work on RTS,S)

OpenMalaria: Individual-based stochastic simulator of malaria epidemiology and control (*Plasmodium falciparum*)
https://github.com/SwissTPH/openmalaria/wiki



Within-host + intervention dynamics *within* population models

OpenSource C++: developed and in use since 2006
(many applications, validated, updated calibrations, used by many groups)

Source: Theresa Reiker et al

Highlight: model functionality

- **Mechanistic acquisition of immunity**

For **RTS,S vaccine**:

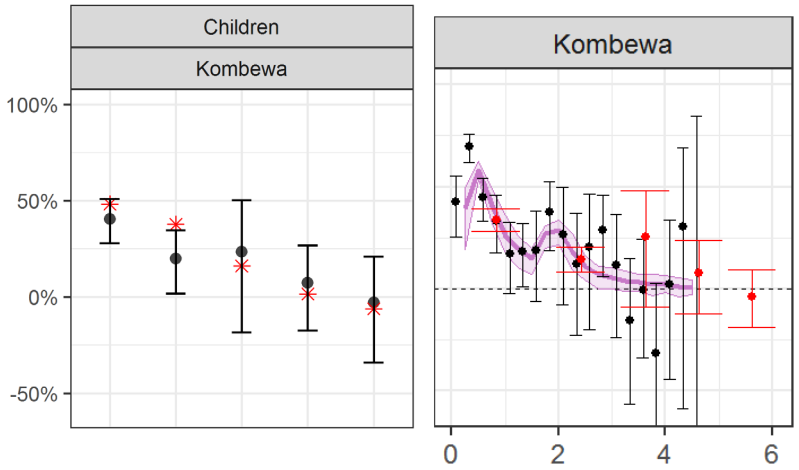
- Model was **calibrated to (a) historical characteristics of trial sites** and; **(b) trial implementation characteristics**
- To **match clinical endpoints** of the trial
- OpenMalaria models RTS,S or R21 as it functions: **prevention of sporozoites and therefore infection**

Background: Model comparisons & validation

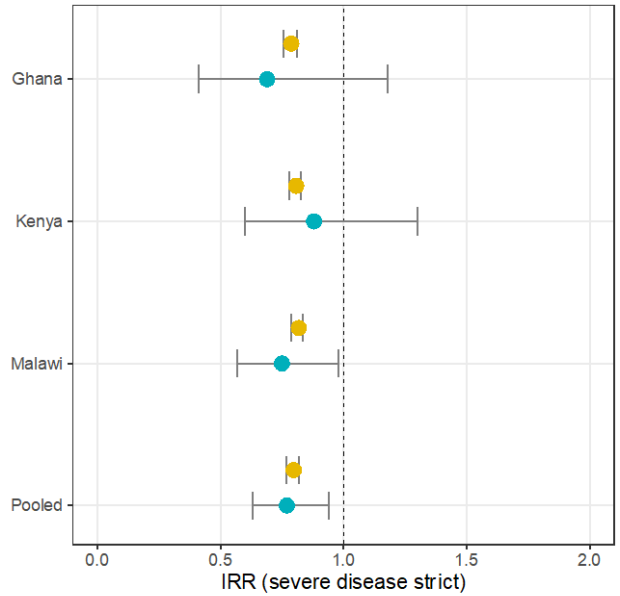
RTS,S modelling and validation

Our model was also employed for model comparisons of impact and economic analyses for RTS,S, carried out in 2013, 2015, 2018, and 2021, under the close collaboration and coordination with PATH and the WHO.

Extensive model validation has been conducted against the 7 year follow-up of RTS,S, and the 24 month MVIP severe disease IRR



Model validataion 7 year follow-up pf the Phase 3 RTS,S Clinical trial



2023 MVIP comparison to OpenMalaria
Model-based IRRs for severe malaria were found to be **consistent** with IRRs from final MVIP results at 46 months:

Source: reports to WHO 2018, and 2023

Background: Model comparisons

Vaccine model comparison and RTS,S predictions of public health impact and cost-effectiveness

Our model was also employed for model comparisons of impact and economic analyses for RTS,S, carried out in 2013, 2015, 2018, and 2021, under the close collaboration and coordination with PATH and the WHO.

Clinical Trial Data

Detailed Phase 3 vaccine results

Models

models informed by **trial data** and **historical data** on malaria dynamics

Swiss TPH

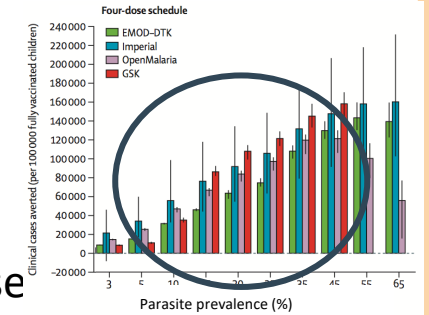
INSTITUTE FOR DISEASE MODELING
INTELLECTUAL VENTURES

gsk GlaxoSmithKline Vaccines

Imperial College London

Simulations: Future Use Case

- Effectiveness: future public health impact
- Beyond trial settings
- Impact on mortality
- Economic analysis
- Target settings for use



Penny, Verity, Bever et al. **Lancet** 2016, **387:**367

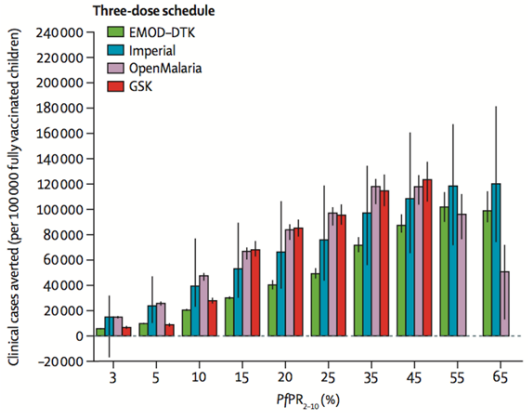
Background: Model comparisons

Vaccine model comparison and RTS,S predictions of public health impact and cost-effectiveness

Our model was also employed for model comparisons of impact and economic analyses for RTS,S, carried out in 2013, 2015, 2018, and 2021, under the close collaboration and coordination with PATH and the WHO.

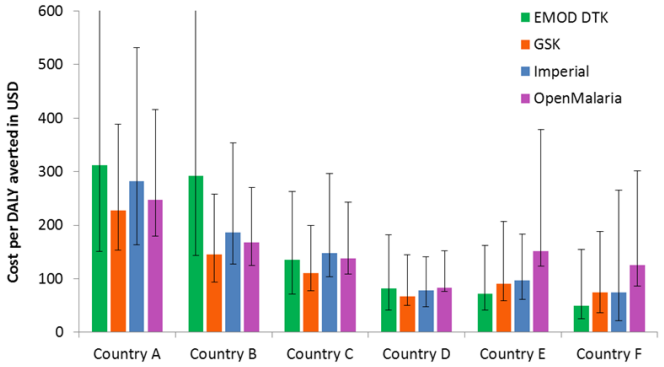
Summary of RTS,S modelling in 2013 - 2015 (Penny *et al.* (2016) and MPAG-SAGE reports)

Step 3



Generic settings

Step 4



Country specific

All covered in background documents

Source: reports to WHO 2015

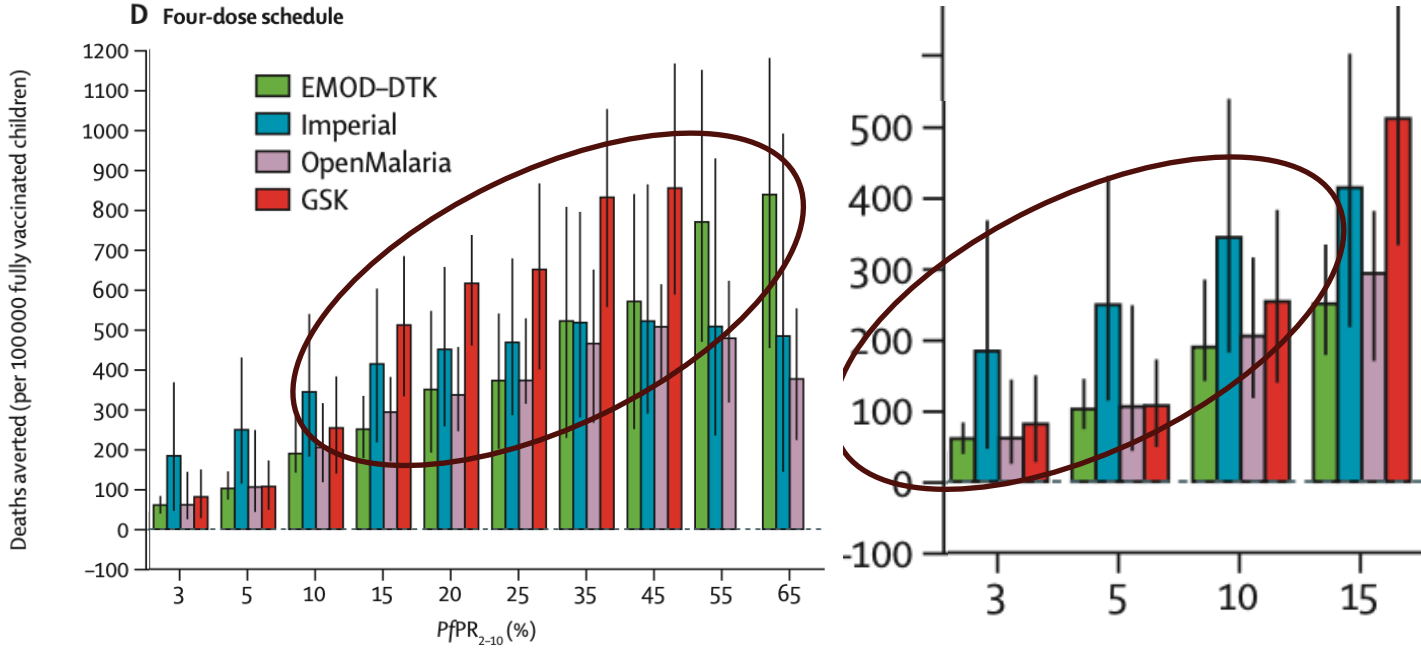
Background: Model comparisons

Vaccine model comparison and RTS,S predictions of public health impact and cost-effectiveness

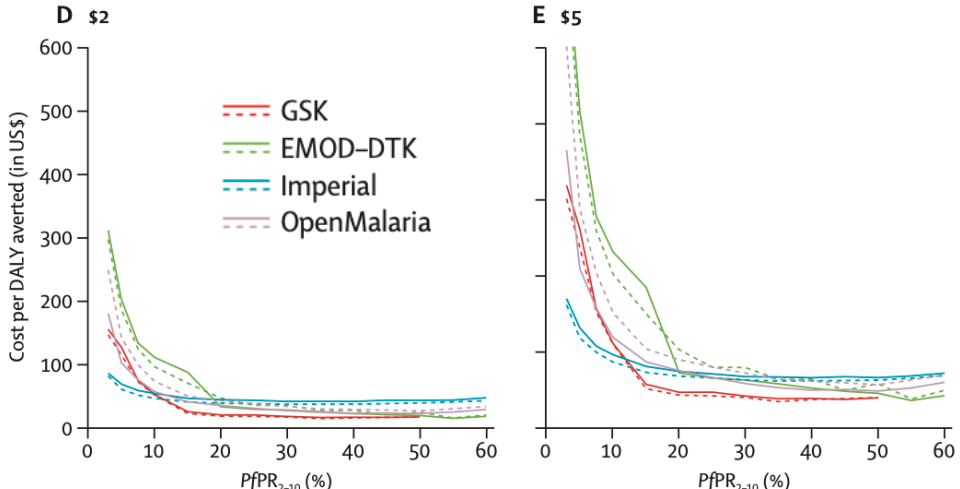
- There are some differences between the predictions of the 4 models, especially at *low transmission settings*. Thus, we should determine if this difference are also observed for R21.
- Each established malaria transmission model has different structural assumptions and is validated to different historical data *(see background material, Supplement of Penny 2016)*

Multiple models were needed to inform projections of vaccine impact beyond clinical trial data

PHI



ICERs



Source: Penny *et al* .2016

Background: Summary of analysis plan

At request of WHO and IVIR-AC we have developed an analysis plan to complement the impact and cost-effectiveness estimates already provided to WHO from Imperial college

To date, only one modelling group (Imperial) has calibrated a vaccine efficacy model to R21 and made predictions of the vaccine's expected public health impact in settings beyond clinical trial sites

Given difference in models and approaches to understand vaccine efficacy: multiple modelling groups are needed to make robust predictions of R21 expected impact and cost-effectiveness (as normally completed with other vaccines/diseases) → also applies for the Vaccine Impact Modelling Consortium (VIMC)

Public data are aggregated data (less than 24 months follow-up for Phase 3):

- Phase 1/2b results (Nanoro): September 2022
- Phase 3 results: SAGE September 2023, trial results February 2024

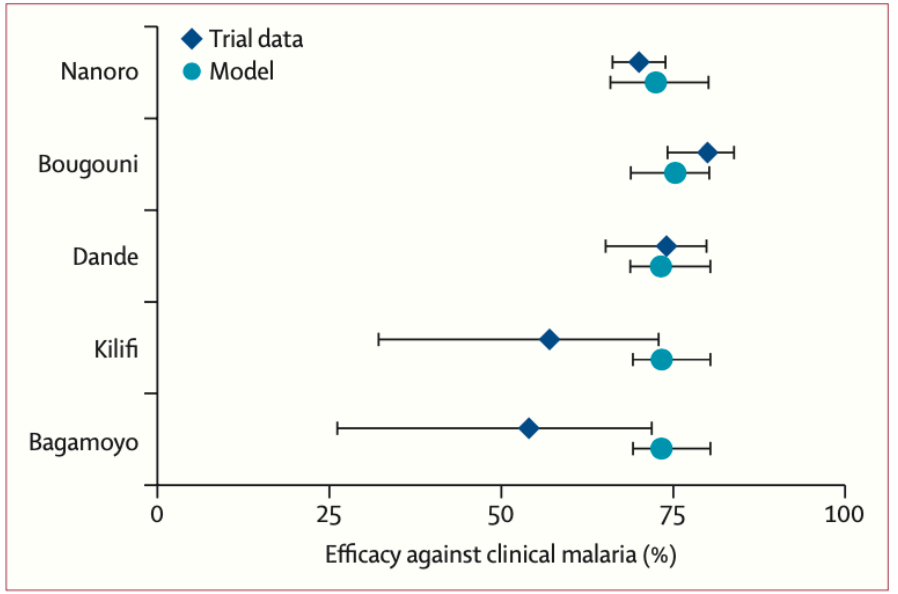


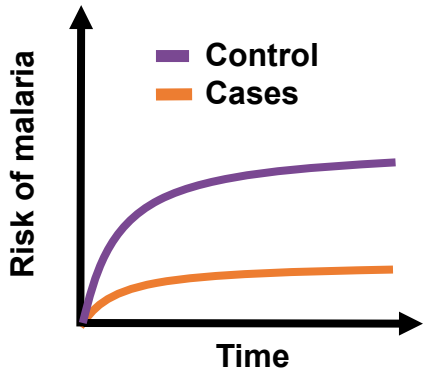
***Figure 2*: Model validation against phase 3 data**

Schmit *et al.* Lancet ID (2024)

Background: Summary of analysis plan

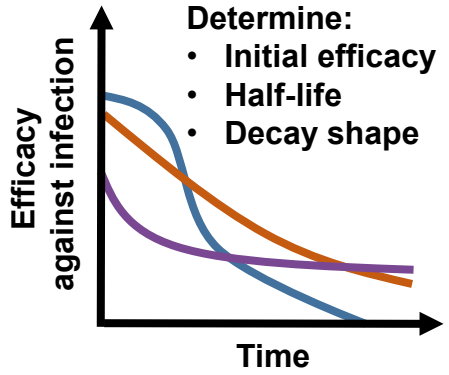
At request of WHO and IVIR-AC we have developed an analysis plan to complement the impact and cost-effectiveness estimates already provided to WHO from Imperial college

Review clinical data



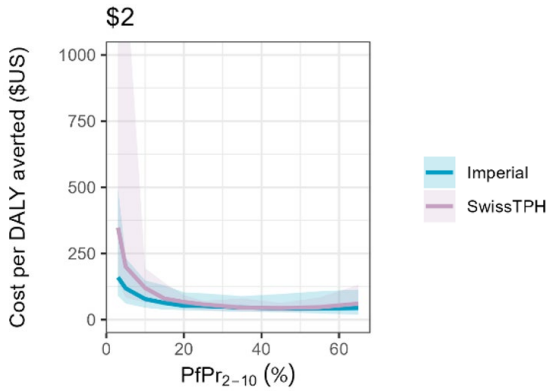
Phase 3 data

Vaccine Model calibration



Informed by trial data and historical data

Predicted health impact and cost effectiveness



Calculate events averted, ICERs, and DALYs using the model

Plan A: Using 3-monthly aggregate data ***(preferred)***
Plan Backup: Using 12 month and 18 month summary data

SUMMARY OF R21: Request / public data

R21 Data availability to inform models

Trial summary

R21/Matrix-M Phase 3 Trial Design (VAC078): Seasonal administration in areas of highly seasonal transmission

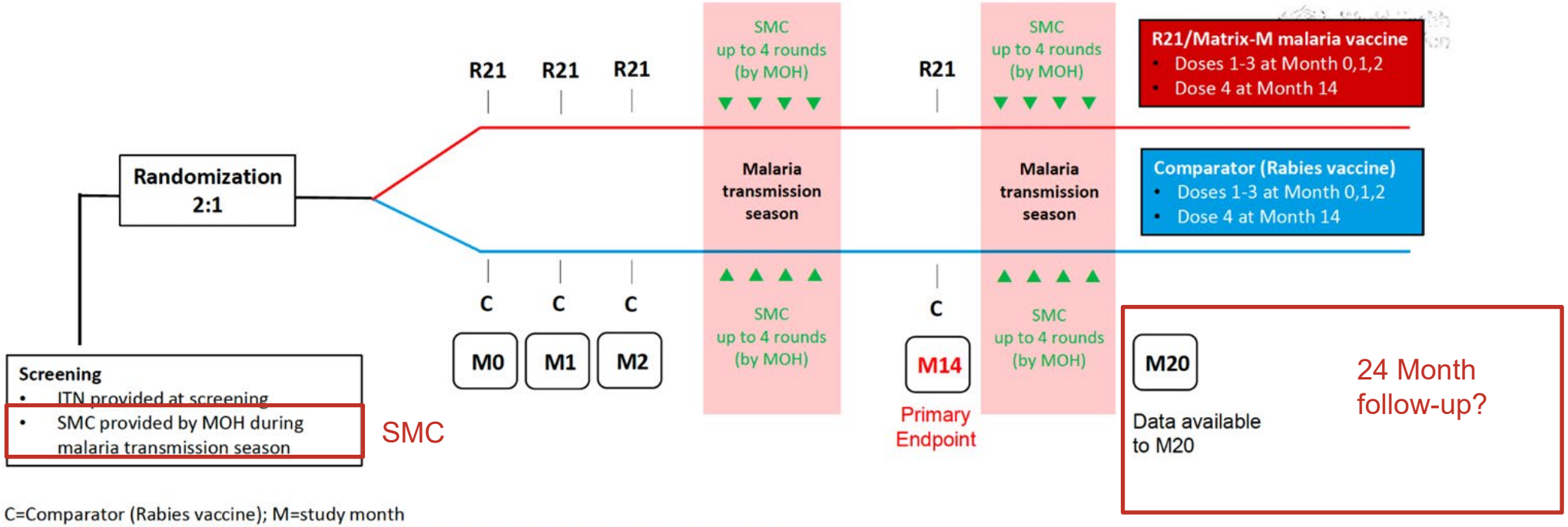
World Health Organization

Seasonal administration (n=2,400), ages 5-36 months at first vaccination Age range up to 3 years

2 sites: Nanoro, Burkina Faso and Bougouni, Mali

Primary endpoint (shown in red): 12 months post dose-3 (M14)

Data available through 18-months follow-up post dose 3 (M20)



C=Comparator (Rabies vaccine); M=study month

Recruited according to age group (5-12 months, 13-24 months, 25-36 months), gender and site

R21 Data availability to inform models

Trial summary

R21/Matrix-M Phase 3 Trial Design (VAC078)
Age-based, or "standard" administration

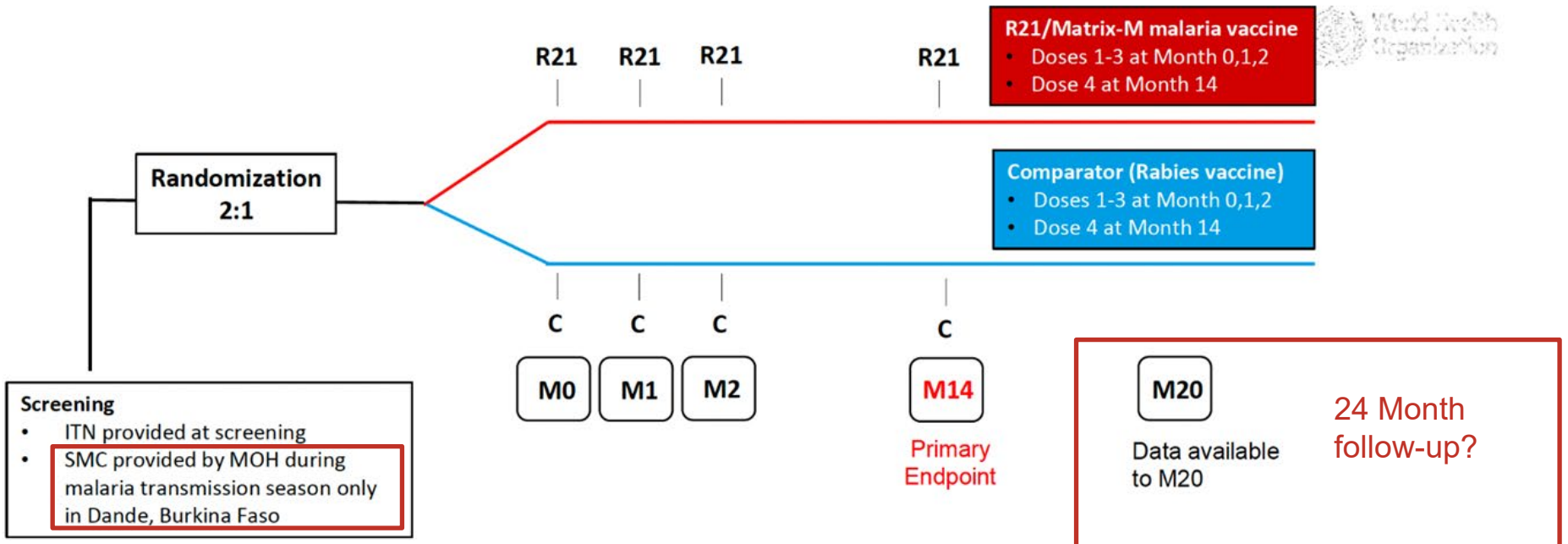
World Health Organization

Age-based ("standard") administration (n=2,400), ages 5-36 months at first vaccination Age range up to 3 years

3 sites: Dande, Burkina Faso; Kilifi, Kenya and Bagamoyo, Tanzania

Primary endpoint (shown in red): 12 months post dose-3 (M14)

Data available through 18-months follow-up post dose 3 (M20)



C=Comparator (Rabies vaccine); M=study month

Recruited according to age group (5-12 months, 13-24 months, 25-36 months), gender and site

R21 Data availability to inform models

Current request: via VIMC a co-ordinated request was sent to Oxford (coordination between GAVI, BMGF, WHO and modelling groups (Telethon Kids Institute/Swiss TPH & University of Abomey-Calavi (Benin))

REQUESTED

The VIMC modeling teams anticipate needing data like what was shared in the SAGE Yellow Book from September 2023, with more detail and longer follow-up period. This would be aggregated data, which we assume is more feasible from a data sharing perspective, although individual-level data would be welcome. This would include:

1) **Phase 3 data** from seasonal (Nanaro, Bougouni) and perennial (Dandé, Bagamoyo, Kilifi) sites, disaggregated by trial site.

2) For all sites, similar to what has already been reported, **3-monthly data on (1) case incidence; (2) number of individuals in each group; (3) person year at risk, for both control and vaccine arms. Similarly, 3-monthly vaccine efficacy (unadjusted and adjusted).**

3) The most up-to-date phase 3 trial follow-up time results to date, ideally 24 months or longer.

4) **Disaggregated results by age**. Appreciating the wide range of ages vaccinated in some sites (5-36 months at first vaccine), the modellers believe disaggregation of the results into age ranges at vaccination will be essential to account for existing immunity and different age patterns of malaria disease outcomes. Some age-stratified results were reported in the SAGE Yellow Book (split into 5-17 months and 18-36 months). In addition, and essential if disaggregation of results by age is not possible, the modellers would need the distribution of ages at first vaccine.

R21 Data availability to inform models

Current request: via VIMC a co-ordinated request was sent to Oxford (coordination between GAVI, BMGF, WHO and modelling groups (Telethon Kids Institute/Swiss TPH & University of Abomey-Calavi (Benin))

Of note

- We propose to use Phase 3 aggregated data at 3 monthly intervals.
- We do not have data access/ GAVI is awaiting feedback from PIs
- We do not intend to use Ab data or individual level data**

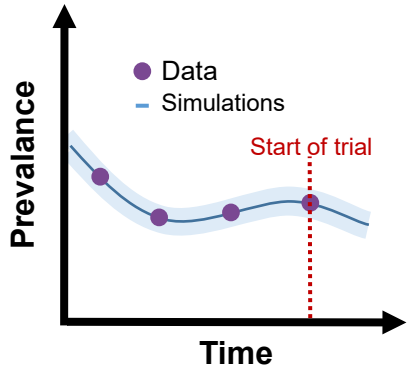
ANALYSIS PLAN

VACCINE MODEL CALIBRATION

Methodology Overview: calibration of vaccine

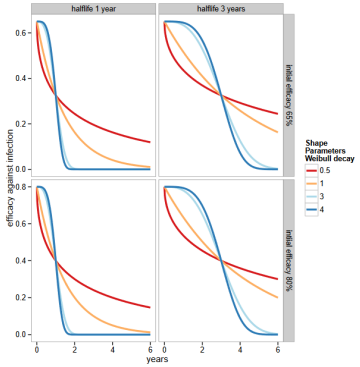
R21 vaccine properties are defined as underlying protection against infection (sporozoite action)

Step 1: History matching to trial site



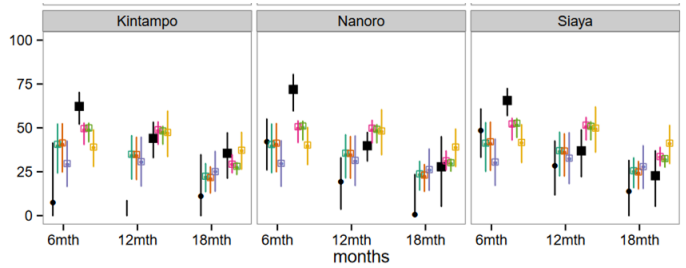
Calibrate base model to trial site in absence of new vaccine intervention

Step 2: Calibrate vaccine model to Phase 3 results



Estimate vaccine parameters for initial efficacy against infection, decay shape, duration (half-life)

Step 3: Validation of model parameters

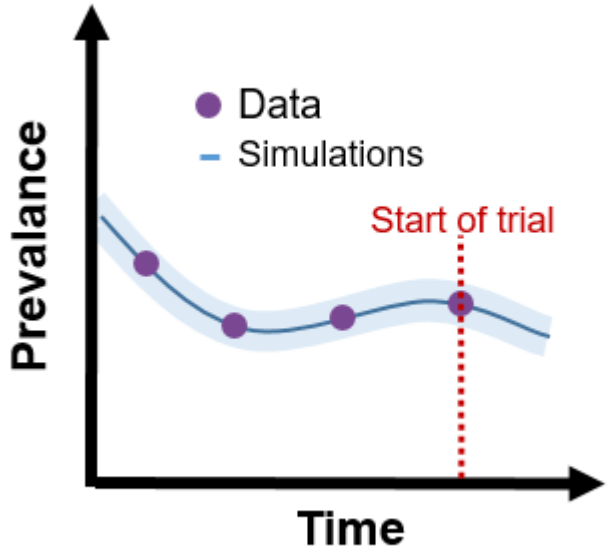


Match predictions to trial data on vaccine efficacy against clinical disease in sites not use for fitting (Phase 2 results?)

Methodology Overview: calibration of vaccine

STEP 1: History Matching

History matching of trial sites dynamics pre-trial



Methodology:

Validated **Bayesian Optimization approach** developed at the group of Melissa Penny (Git Repository & Rieker *et al*)
We calibrate EIR and temporal dynamics matching observed disease dynamics

Data Required (publicly available, or as indicated in the published Phase 2/3 papers):

- Demographic details
- Historical intervention coverage
  - ✓ ITN
  - ✓ **SMC**,
  - ✓ IRS etc
- Historical treatment coverage
- Seasonality indicators

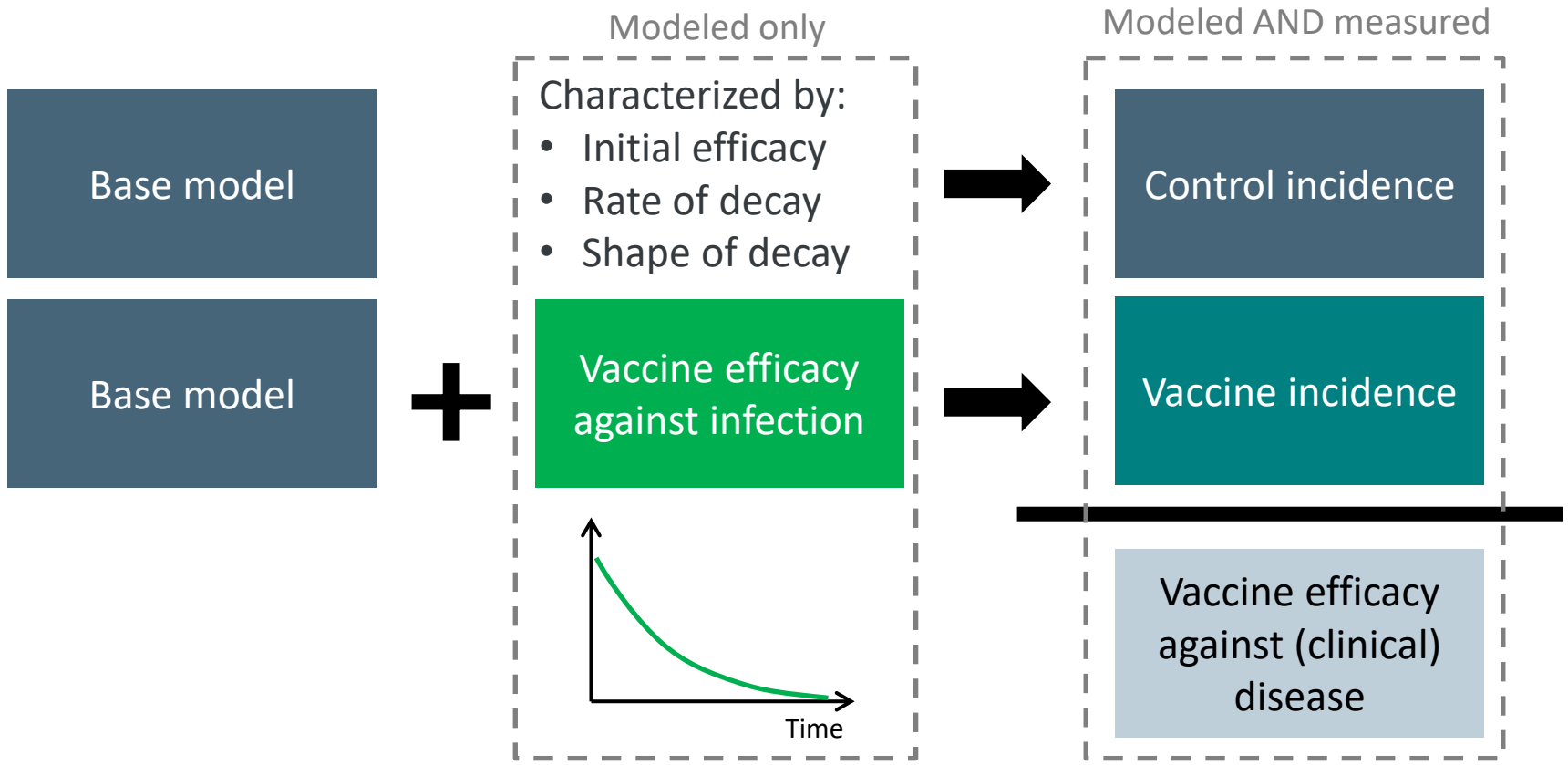
→ ***Fit to: site & time specific prevalence and morbidity (modelled from MAP, or as reported)***

Methodology Overview: calibration of vaccine

STEP 2: Calibrate vaccine properties to Phase 3 results

Calibrate underlying vaccine properties using incidence results from trial (note we are not fitting against reported vaccine clinical efficacy against disease)

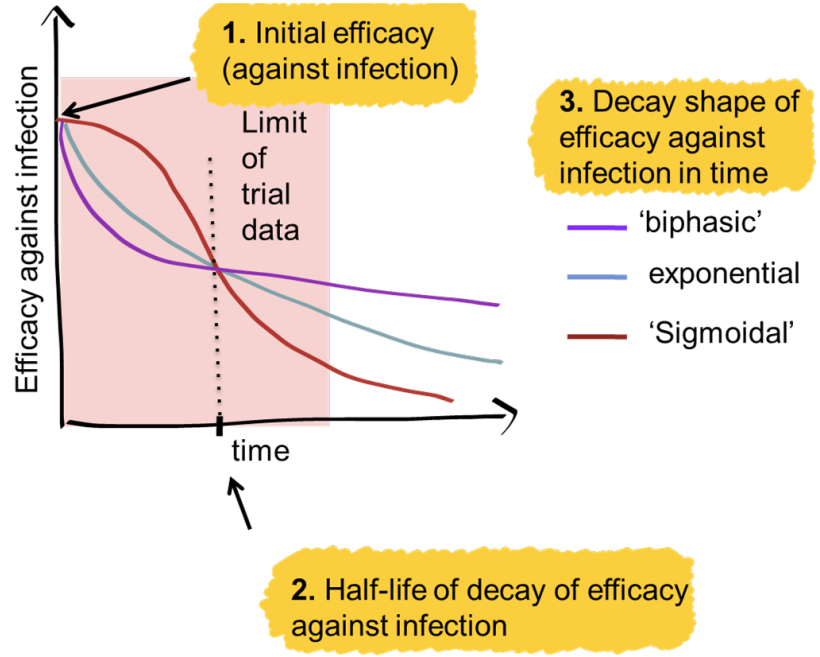
VE against infection vs. VE against clinical disease



Methodology Overview: calibration of vaccine

STEP 2: Calibrate vaccine properties to Phase 3 results

Calibrate underlying vaccine properties using incidence results from trial (note we are not fitting against reported vaccine clinical efficacy against disease)



→ *Fit to: site & time specific incidence in control & intervention groups*
→ *Obtains: optimised parameter values* for vaccine initial efficacy, decay shape, and half-life duration

Methodology:
Validated **Bayesian Optimization approach** developed at the group of Melissa Penny (Git Repository & Rieker *et al*)
Note:
1) We will fit to all trial sites; and suggest Phase 2 results could be used as a validation step
2) Methods tested on synthetic data

Data Required:
- Vaccine coverage, and *age disaggregation* at first vaccine
- All trial endpoints
  - In both arms
  - Disaggregated by age
  - At 3-monthly timepoints

Further considerations:
- SMC-SPAQ coverage (seasonal)***
- Site specific access to treatment

Methodology Overview: calibration of vaccine

STEP 2: Calibrate vaccine properties to Phase 3 results

Calibrate underlying vaccine properties using incidence results from trial (note we are not fitting against reported vaccine clinical efficacy against disease)

SMC+R21: synergistic or additive?

1) SMC coverage data is likely incomplete – our preferred approach is to model both interventions (with SMC coverage cycles close to observed pre- and during Phase 3 trial)

2) As alternative: we plan to test assumptions of modelling SMC prior and during the trial. Thus we will explore additive vs synergistic effects

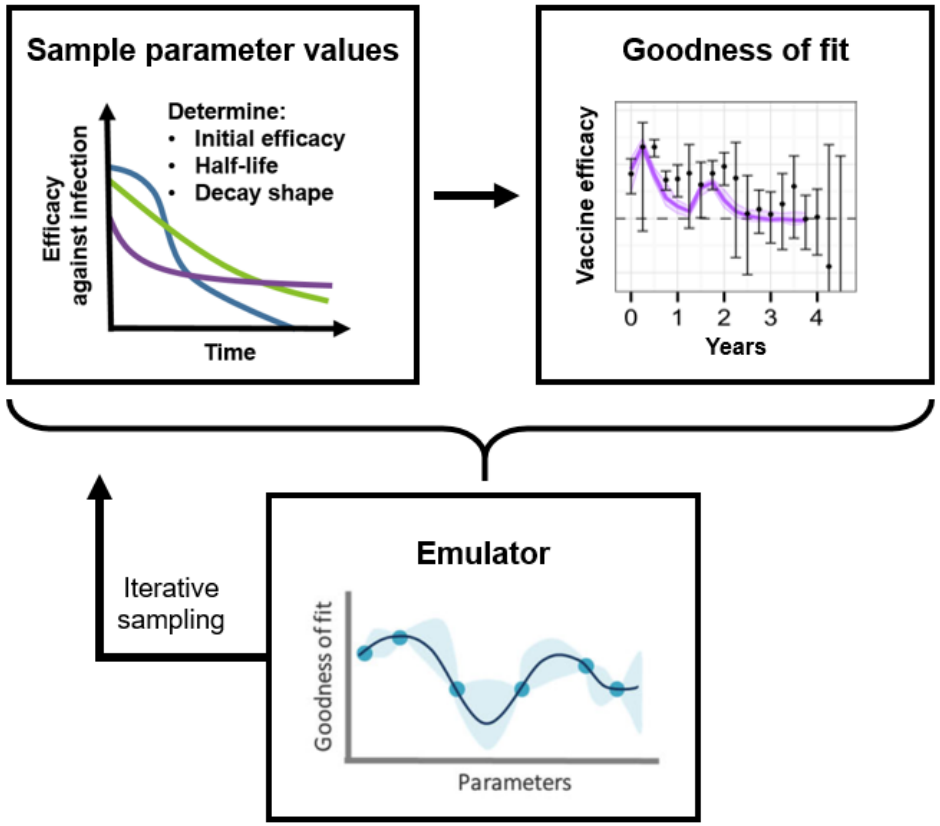
3) SMC is likely to be important due to age at first vaccination 5-36 months (require also disaggregation by age (at very least split into 5-17 months and 18-36 months, as per Datoo *et al 2024*).

Methodology Overview: calibration of vaccine

STEP 1 and 2: Bayesian Optimisation approach

Bayesian optimization approach to identify the most likely vaccine parameter values:

1. Sample parameter values for the parameter of interest (initial efficacy, decay shape and duration of protection) from the parameter space
2. Run simulations for each parameter combination and assess the fit of the simulation to the clinical trial data.
3. Train an emulator to learn the relation between the input parameters (initial efficacy, …) and the clinical trial data fit.
4. Use the trained emulator to predict the fit of the data over the whole parameter space.
5. Resample points that are predicted to have the highest fit and iteratively repeat the process until convergence to an optimal parameter set

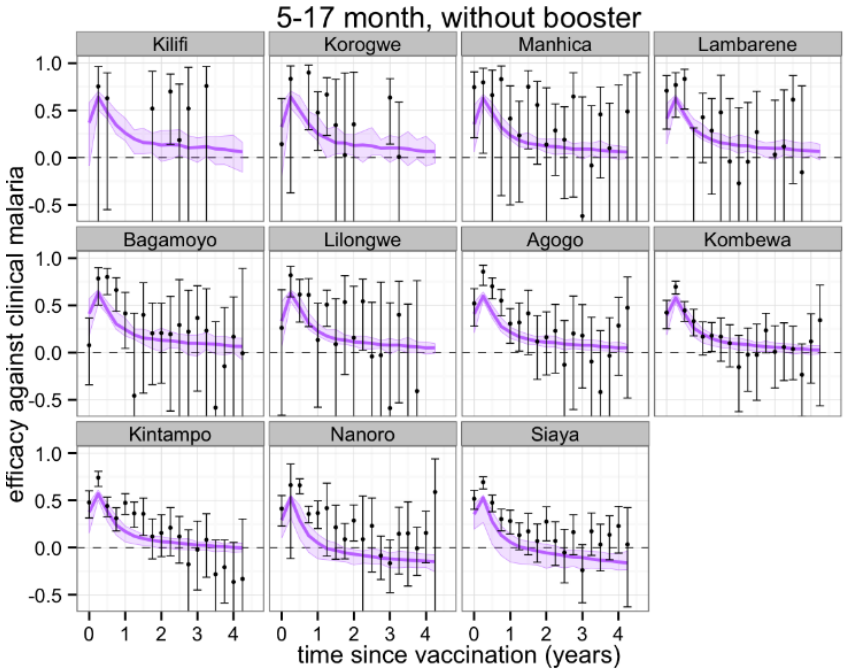


Methodology Overview: calibration of vaccine

STEP 3: Potential validation

Compare model predictions using vaccine properties informed by Phase 3 followup to results from the phase 1/2b randomized controlled trial in children aged 5-17 months in Nanoro, Burkina Faso.
(high malaria transmission)

Example Plot only



Penny *et al.* (2016)

Methodology:
Goodness of fit between predicted and calculated vaccine efficacy against clinical disease in Phase 1/2b site

Data Required:

- Calculated vaccine efficacy against clinical disease
  - Adjusted & unadjusted
  - Disaggregated by age
  - Vaccine efficacy

Feedback: calibration of vaccine

Risks and limitation of available data

Granularity of data: considerations for using 3-monthly data

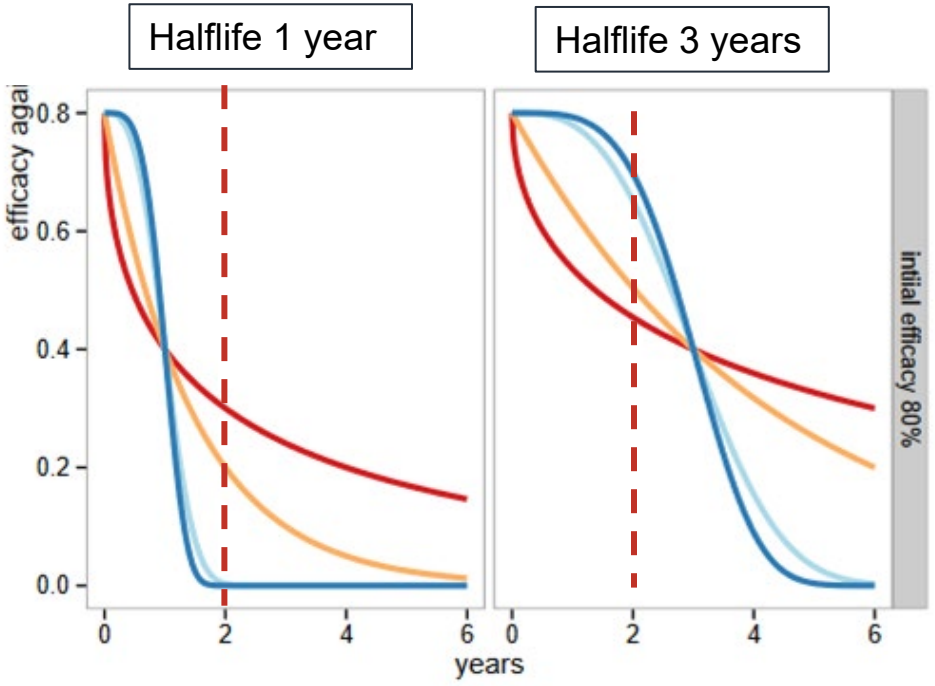
- Making reliable point estimates requires more granular data so complete 3-monthly data is our preferred way forward
- **BACKUP PLAN:** Will it be sufficient to use published **12-month primary endpoint?**

Duration of follow up: limitation of 24 month (or back up 12- or 18-month) follow up

- Currently available data are for 12-month follow up on all sites and 18-month follow up on 2 seasonal sites (24-month follow up data should be forthcoming)
  - There may be risk of properly capturing the correct decay profile and duration of protection *(illustration on right)*
  - What about limited followup of primary series before booster?
- Mitigation: sensitivity analysis of vaccine duration for calibration/validation and for PHI and CEA

Validation using small number of sites with both seasonal & perennial profiles

- Limited number of Phase 3 sites (seasonal & perennial) so we may not have enough data to reserve multiple sites for validation from Phase 3, hence our Phase 2 proposal. But Nanoro is high transmission only



limitation: red line marks end of currently available follow up data

ANALYSIS PLAN

Predictions of R21 potential PUBLIC HEALTH IMPACT

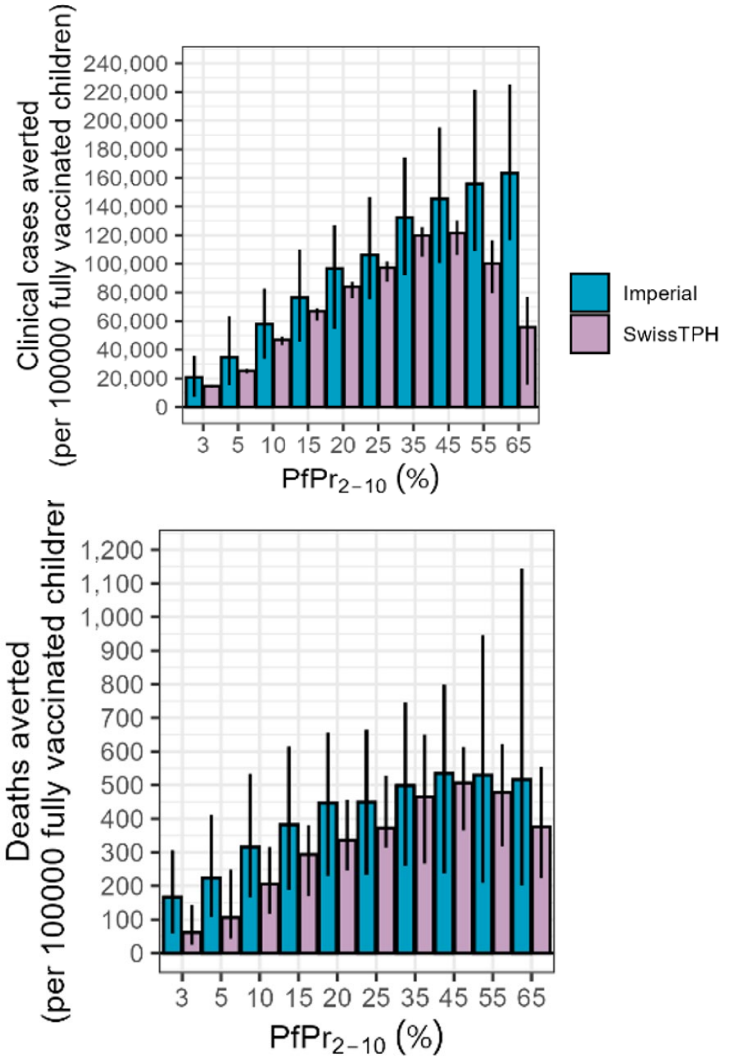
Public health impact estimation

Analysis plan:

Aiming to provide comparable PHI and CEA to Imperial

- Using calibrated and validated OpenMalaria model, will run a range of scenarios to estimates public health impact
- **Scenarios:**
  - Range of archetypal modelling settings: perennial and seasonal, a range of prevalence levels including low-transmission settings with prevalence <10%, range of levels of access to care
    - PHI for EPI routine delivery
    - PHI for Seasonal delivery (with and without codelivery with SMC)
  - *May include history of ongoing childhood interventions: SMC, ITNs, IRS*
- **Vaccine intervention:**
  - Different ranges of coverage and drop out
  - Deployment: to be confirmed with WHO (seasonal with hybrid first? and EPI)
  - Intervention modelled with full sensitivity analysis on a range of vaccine model profiles
- **Outputs**: public health impact estimates of uncomplicated malaria, severe malaria, hospitalisations and mortality and DALYS

Examplar plots from RTS,S



Plus sensitivity analysis on vaccine properties

Public health impact estimation

Analysis plan:

Aiming to provide comparable PHI and CEA to Imperial

Harmonized

- **Demographics**
  Typical of African populations.
- **Transmission settings**
  PfPr_{2-10} of 3% to 75%. Perennial, seasonality, endemic equilibrium.
- **Interventions**
  Current levels of vector control, access to effective care, SMC
- **Delivery strategies** (and age)
- **Coverage**
- **Time horizon**
  Impact measured over 15 years (suggest we analyze 5, and 10 years)

Not harmonized

- **Models:** Model structure
  Non-trial data used in model fitting
  Case definitions
- **Vaccine profile**
  Each group best-fit to
  phase III data

Public health impact estimation

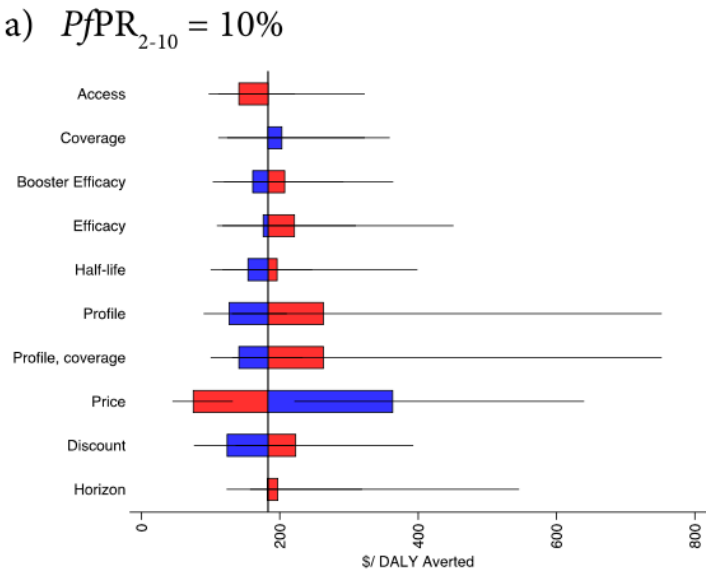
Analysis plan:

Sensitivity analysis

We propose, time pending, several sensitivity analyses (for PHI and CEA) of the following

- impact of vaccine duration, decay
- Boosting efficacy
- SMC coverage/modelling
- Age of vaccination

Example from Penny et al 2016



ANALYSIS PLAN

Predictions of R21
COST-EFFECTIVENESS

Cost-effectiveness

Examplar plots from RTS,S

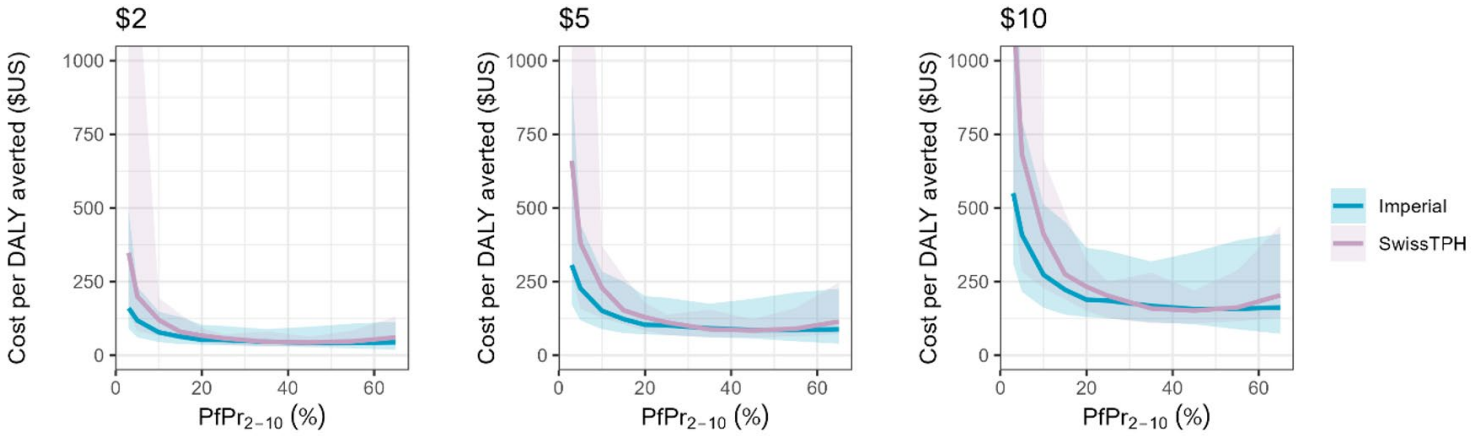
Analysis plan:

Aiming to provide comparable CEA to Imperial

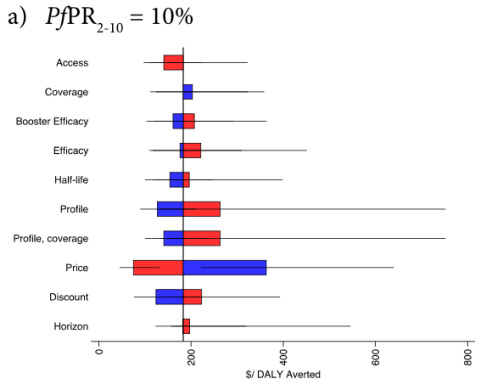
- Methodology: we propose to use similar methodology previously used for RTS,S/R21 CEA for perennial settings, and similar for R21 seasonal deployment as for Schmid et al. with updated data on costs of vaccine and consumables and vaccine delivery
  - Use the public health impact estimates from OpenMalaria to calculate cost effectiveness
  - Costs will be estimated from a health-care provider prospective

- **Outputs: incremental cost-effectiveness ratios (ICERs) as cost per *clinical case, hospitalized malaria, direct malaria severe case, direct malaria mortality and disability-adjusted life years (DALYs)* averted.**

Examplar from RTS,S/AS01 modelling analysis



Example from Penny et al 2016



QUESTIONS to IVIR-AC

Questions to IVIRAC

Suggested by Telethon Kids (not limited to the following)

1. We proposed approaches to use **aggregated data**. Should individual level data be used in preference?
2. Concerning **antibody data** – does IVIR-AC propose an additional modelling group analyze/modelling the antibody data for interpretation of vaccine duration given its high importance for public health impact?
3. Assessment on appropriateness **of vaccine representation in each case of data availability**. Specifically, in the absence of sufficient 3 month follow up data, is fitting only an initial efficacy and half-life (with heavy priors) sufficient for our modelling to be considered an accurate representation of the R21 vaccine? How likely are we to estimate vaccine duration with limited follow-up after primary series, and after booster. Noting duration is a big driver of PHI
4. Technical feedback to both modelling groups on modelling of **ongoing and intervention history** in the trial sites for the model calibration to clinical data, namely **SMC**, IRS and ITNs (SMC will be important to identify or test assumptions on additive vs synergistic effect)
5. Technical feedback to both modelling groups on modelling other interventions (specifically SMC) for predictions of public health impact.
6. Suitability of validation – how to support the ability of models to predict in *Pf*PR settings with which we do not have data or validation?
7. (lower priority) Technical advice on fitting algorithms.

APPENDIX

Model parameterisation

Summary of data required

Step	Data (for each trial site)	Source
Calibration: History matching	Model inputs: ● Demographic details ● Historical intervention coverage (ITN, SMC, IRS) ● Historical treatment coverage ● Seasonality indicators ● Prevalence, morbidity, mortality estimates	● World Population Projections ● Malaria Atlas Project
Calibration: Capture the trial sites	● Vaccine coverage ● SMC-SPAQ coverage (seasonal) ● Site specific access to treatment	● MAP ● Datoo 2023 ● SAGE Yellow Book, Sept 2023
Calibration: Match time points outcomes for data we have extracted	● Incidence and time at risk ○ by control & vaccination arms ○ disaggregate by age ○ 12 month & 18 month follow up (Plan A) ○ 3-monthly summary data (until 18 mo follow up) (Plan B)	● Datoo 2023 ● SAGE Yellow Book, Sept 2023
Validation: matching vaccine efficacy against clinical disease	● Calculated vaccine efficacy against clinical disease ○ Adjusted & unadjusted ○ Disaggregated by age	● Datoo 2023 ● SAGE Yellow Book, Sept 2023

Imperial assumptions: Cost-Effectiveness

Aim: to produce comparable estimates and to align to the data used by Imperial

Cost of R21/Matrix-M vaccination	Consumables (per dose, *corresponding to respective vaccine price*): US$ 0.69 US$ 0.79 US$ 1.24	https://doi.org/10.1016/j.vaccine.2023.01.043
	Delivery (per dose): US$ 1.33 (age-base) US$ 3.35 (seasonal) US$ 2.09 (hybrid)	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10111920/ (https://cdn.who.int/media/docs/default-source/immunization/mvip/full-evidence-report-on-the-rtss-as01-malaria-vaccine-for-sage-mpag-(sept2021).pdf)
Vaccine price	US$ 2.00 US$ 3.00 US$ 4.00 per dose (excluding cost of consumables and delivery)	R21/Matrix-M Phase 3 trial; American Society of Tropical Medicine and Hygiene (ASTMH) Annual Meeting – 2022
Cost of malaria case management	US$ 6.00 (child) and US$ 9.60 (adult) per clinical case treated US$ 12.84 (child) and US$ 16.44 (adult) per severe case treated	WHO Choosing Interventions that are Cost-Effective (WHO-CHOICE); The Global Fund Pooled Procurement Mechanism Reference Pricing

Source: SAGE Sept 2023, 7.1 Report on Malaria, Imperial College London - Table 31.
R21/MM PHI & CE Model Assumptions

Modelling the public health impact and cost-effectiveness of the R21/Matrix-M malaria vaccine

IVIR-AC Meeting, 26 February 2024

Background summary

As of October 2023, WHO recommends two vaccines for the prevention of *Plasmodium falciparum* malaria in children. This includes RTS,S/AS01 (RTS,S) and R21/Matrix-M (R21). Demand for malaria vaccines is high, and, to date, 20 countries have been approved by Gavi, the Vaccine Alliance, to receive support for introduction. However, supply capacity for RTS,S is limited. R21 is anticipated to be manufactured at higher scale and at a lower cost than RTS,S, helping to ease the supply shortage. Gavi has included R21 in its malaria program, and UNICEF expects to begin delivering R21 in mid-2024. Beginning in 2024, the cumulative supply availability of the two WHO-recommended malaria vaccines is expected to meet the high demand, enabling more countries to introduce and scale up the vaccine in areas where malaria is a public health risk.

The WHO recommendation for R21 was based largely on results from clinical trials showing high vaccine efficacy and no major safety concerns. Additionally, modelling conducted by Imperial College used data from the R21 Phase 2 and 3 trials, combined with a mathematical transmission model, to estimate the public health impact and cost-effectiveness of R21 using different delivery strategies and across a range of transmission intensities. Based on 3 years of immunogenicity and clinical data from the Phase 2b trial in Nanoro, Burkina Faso, a fitted relationship between anti-CSP antibody titres and vaccine efficacy against clinical malaria was modelled. This fitted relationship was validated by comparing the model-predicted vaccine efficacy to the observed vaccine efficacy in the five R21 Phase 3 trial sites over a 12- to 18-month period. The antibody-efficacy relationship was integrated into the Imperial mathematical transmission model to estimate clinical and severe malaria cases, malaria deaths, and DALYs averted. Using these modelled public health impact estimates, cost-effectiveness was estimated over a 15-year time horizon in a range of transmission intensities from 3% to 65% *P. falciparum* prevalence ($Pf PR_{2-10}$) in both perennial and seasonal settings. Several vaccination schedules were also analysed: 1) age-based vaccination (3 doses at 6,7, and 8 months of age with a 4^{th} dose given one year later); 2) seasonal vaccination (3-doses given before the seasonal malaria peak with a 4^{th} dose one year later, also before the seasonal peak); and 3) a hybrid of the two approaches (3-dose primary series given age-based and dose 4 given one year later before the seasonal peak). The option of a 5^{th} dose one year after dose 4 was also included in these vaccination schedules.

Considering an assumed price of $3 per dose, the estimated cost per DALY averted for R21 appears comparable to other existing malaria interventions and childhood vaccines in Africa, noting that there is a significant amount of context-specific variation in the cost-effectiveness of the vaccine as well as other interventions. Cost-effectiveness was higher at higher transmission intensities across all implementation and dose regimens. In seasonal settings, cost-effectiveness was similar using either age-based, seasonal or hybrid vaccination. Incremental cost-effectiveness ratios were generally lowest for age-based implementation with four doses. In the lower transmission non-seasonal Phase 3 trial sites (Kenya and Tanzania), the model estimates for vaccine efficacy were outside the upper 95% confidence bound of the observed trial data, reflecting potential uncertainty in both the trial and model estimates in these settings.

In this IVIR-AC session, Imperial College will present their modelled impact and cost-effectiveness analysis for review. During the evidence review for the WHO recommendation of R21, the Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Group (MPAG) requested that modelling of impact and cost-effectiveness be conducted using inputs from the Phase 3 trial data rather than Phase 2 trial, and that additional independent cost-effectiveness analysis be conducted to

complement that already completed. Therefore, Telethon Kids Institute (PI Melissa Penny previously Swiss TPH) will present their previously validated individual-based malaria model and approach to calibrate R21 vaccine efficacy and duration/decay depending on different levels of access to Phase 3 data. They will present their plans for an impact and cost-effectiveness analysis of R21/Matrix-M, aligned with Imperial College predictions for a range of vaccine deployment scenarios. Alignment will include making projections of impact in generic prevalence settings, aligned costs etc.

Technical presentations:

1. Presentation of modelled estimates of impact and cost-effectiveness of R21/Matrix-M (Imperial College)
2. Description of proposed modelling of impact and cost-effectiveness of R21/Matrix-M (Telethon Kids Institute)

Questions to IVIR-AC:

1. To what extent does the Imperial modelling analysis estimate the impact and cost-effectiveness of the R21 vaccine ***across transmission intensities, seasonal patterns, and settings using of different malaria interventions (e.g., seasonal malaria chemoprevention)***?
    a. Is the impact in low transmission settings overestimated?
2. For any gaps identified in question 1, to what extent are these due to:
    a. Model structure or
    b. Uncertainties in the data informing model parameters
    c. (e.g., vaccine antibody dynamics, vaccine efficacy, duration of protection)
3. What comments or recommendations does IVIR-AC have on the proposed analysis based on the Telethon Kids Institute model to address questions 1 and 2?
4. Are there suggestions on how can parameter estimates be improved?
    a. For example, can currently available Phase 3 data better inform the models? Which uncertainties in the estimates would still remain? (to address level of data detail required to inform additional modelling by both groups)

Background reading describing/comparing the models of malaria dynamics discussed in this session

We have provided the main paper and supplement of the following publication:

> Penny et al, 2016, *Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models*, https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00725-4/fulltext#supplementaryMaterial

as background documentation. Note the models have not changed substantially since 2016 so the comparison and description of the models provided in the Lancet publication still holds.

We suggest to review:

- Summary descriptions of the Imperial College and Telethon Kids/Swiss TPH (OpenMalaria) models and modelling assumptions in
    - Methods section of main paper
    - Supplementary materials - Section 1 on pages 6-14 which includes Figures to compare epidemiological relationships of the models (for example prevalence-incidence and age patterns by disease definition)
    - Box S1.1: Descriptions of the four malaria models p7
    - Table S1.1. Detailed descriptions of the models p15
    - Table S1.2 Malaria case definitions in the four models p19
- Background descriptions of modelling of vaccine profiles for RTS,S for reference only - Supplementary materials Section 2, starting page 22
- A comparison and differences in the predicted impact of RTS,S at different parasite prevalence levels are also provided in the main paper and supplement.
    - Of note see Figure 2 main paper, and Tables S4.1 supplement (p39)

Telethon Kids/Swiss TPH analysis plan: R21 analysis and predictions of public health impact and cost-effectiveness

WHO IVIR-AC meeting 26-29th Feb 2024

Melissa Penny, Daniela Figueroa-Downing, Lydia Braunack-Mayer, Thiery Masserey, Josephine Malinga, Andrew Shattock

Contact: melissa.penny@uwa.edu.au melissa.penny@telethonkids.org.au

Outline

BACKGROUND (Model OpenMalaria, RTS,S/AS01 modelling, &= R21 Modelling)

MODEL CALIBRATION (Analysis plan: approach & data)

PUBLIC HEALTH IMPACT ESTIMATION (Analysis plan)

COST-EFFECTIVENESS ANALYSIS (Analysis plan)

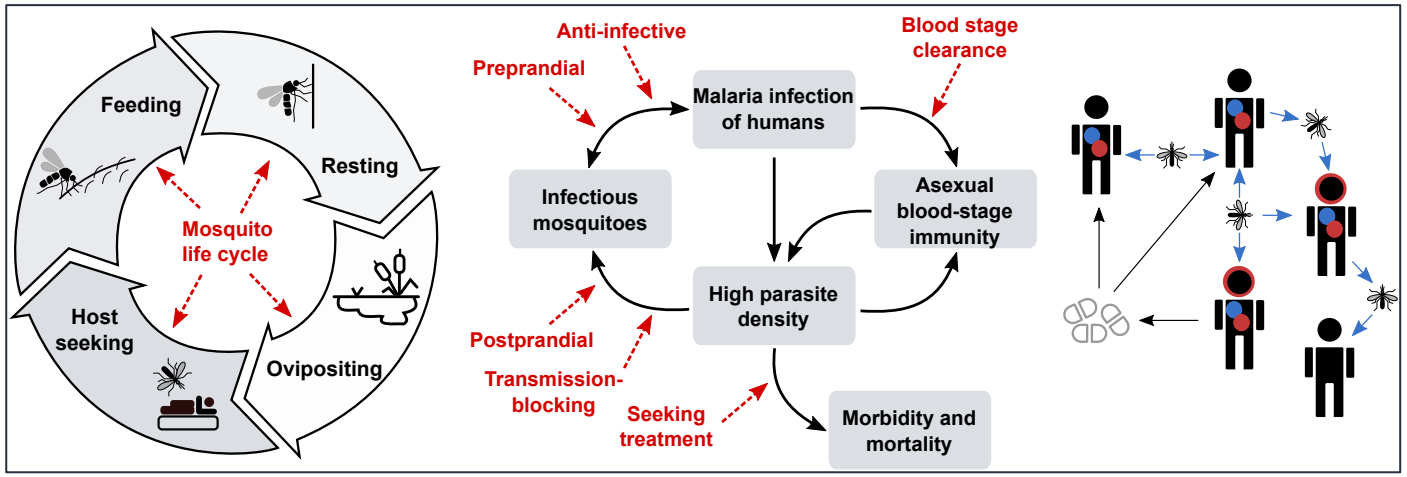
Background

Background: OpenMalaria & vaccine modelling

Telethon Kids and Swiss TPH malaria model: OpenMalaria

OpenMalaria is **an individual-based, stochastic model of malaria transmission and disease progression** that includes dynamics of mosquito infectiousness, human host infection, blood-stage parasite densities, incidence of severe malaria, hospitalization, and mortality.
The model has been previously reviewed with IVIR-AC in 2013-2015 (part of our modelling work on RTS,S)

OpenMalaria: Individual-based stochastic simulator of malaria epidemiology and control (*Plasmodium falciparum*)
https://github.com/SwissTPH/openmalaria/wiki



Within-host + intervention dynamics *within* population models

OpenSource C++: developed and in use since 2006
(many applications, validated, updated calibrations, used by many groups)

Source: Theresa Reiker et al

Parasite densities
Infectiousness
Number of infections
Immunity
Drug level

Infectiousness
Mosquito density
Feeding cycle
Parasite development
seasonality

Health System
Drugs & quality
Adherence
Compliance

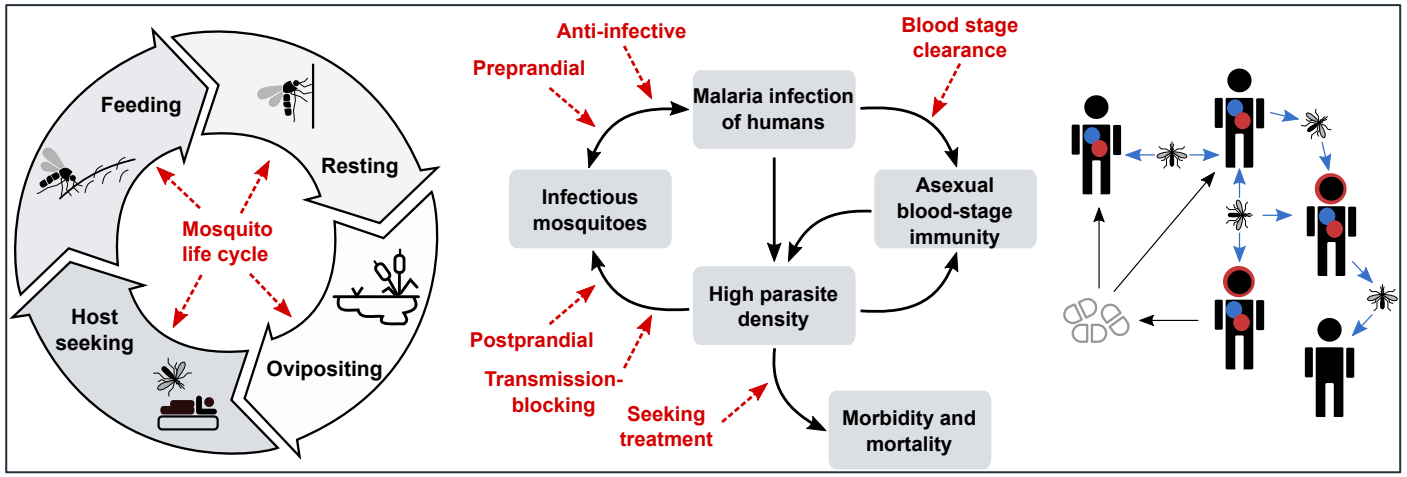
Drugs
Vector Control (IRS, ITNs)
Vaccines
Mass treatment
Reactive strategies

Background: OpenMalaria & vaccine modelling

Telethon Kids and Swiss TPH malaria model: OpenMalaria

OpenMalaria is **an individual-based, stochastic model of malaria transmission and disease progression** that includes dynamics of mosquito infectiousness, human host infection, blood-stage parasite densities, incidence of severe malaria, hospitalization, and mortality.
The model has been previously reviewed with IVIR-AC in 2013-2015 (part of our modelling work on RTS,S)

OpenMalaria: Individual-based stochastic simulator of malaria epidemiology and control (*Plasmodium falciparum*)
https://github.com/SwissTPH/openmalaria/wiki



Within-host + intervention dynamics *within* population models

OpenSource C++: developed and in use since 2006
(many applications, validated, updated calibrations, used by many groups)

Source: Theresa Reiker et al

Highlight: model functionality

- **Mechanistic acquisition of immunity**

For **RTS,S vaccine**:

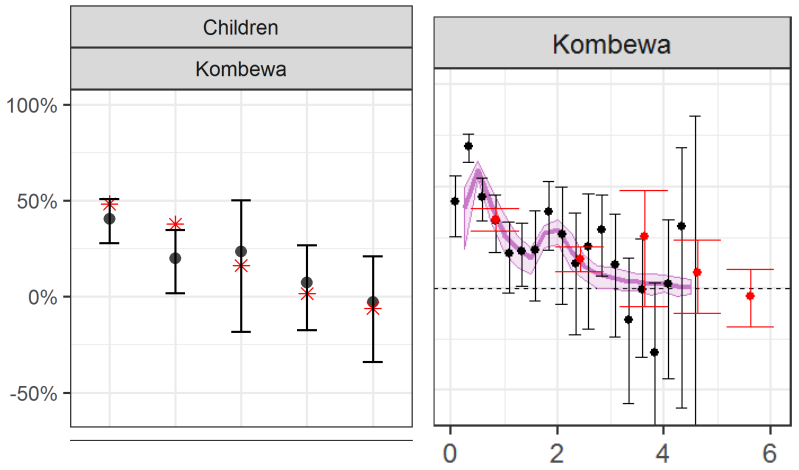
- Model was **calibrated to (a) historical characteristics of trial sites** and; **(b) trial implementation characteristics**
- To **match clinical endpoints** of the trial
- OpenMalaria models RTS,S or R21 as it functions: **prevention of sporozoites and therefore infection**

Background: Model comparisons & validation

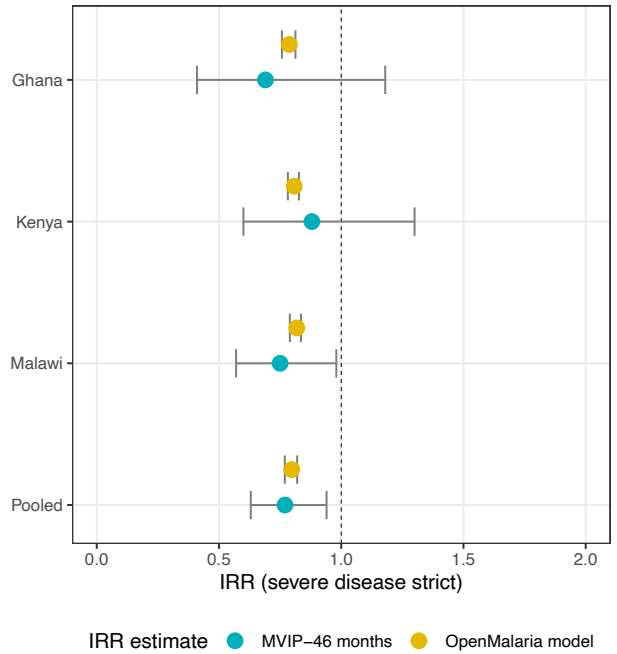
RTS,S modelling and validation

Our model was also employed for model comparisons of impact and economic analyses for RTS,S, carried out in 2013, 2015, 2018, and 2021, under the close collaboration and coordination with PATH and the WHO.

Extensive model validation has been conducted against the 7 year follow-up of RTS,S, and the 24 month MVIP severe disease IRR



Model validataion 7 year follow-up pf the Phase 3 RTS,S Clinical trial



2023 MVIP comparison to OpenMalaria
Model-based IRRs for severe malaria were found to be **consistent** with IRRs from final MVIP results at 46 months:

Source: reports to WHO 2018, and 2023

Background: Model comparisons

Vaccine model comparison and RTS,S predictions of public health impact and cost-effectiveness

Our model was also employed for model comparisons of impact and economic analyses for RTS,S, carried out in 2013, 2015, 2018, and 2021, under the close collaboration and coordination with PATH and the WHO.

Clinical Trial Data

Detailed Phase 3 vaccine results

Models

models informed by **trial data** and **historical data** on malaria dynamics

Swiss TPH

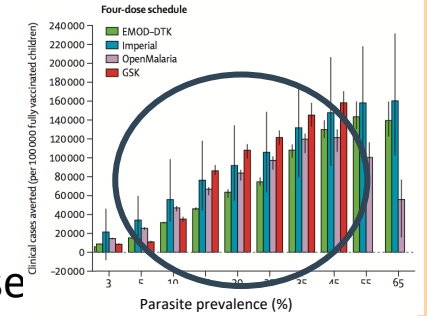
INSTITUTE FOR DISEASE MODELING
INTELLECTUAL VENTURES

gsk GlaxoSmithKline Vaccines

Imperial College London

Simulations: Future Use Case

- Effectiveness: future public health impact
- Beyond trial settings
- Impact on mortality
- Economic analysis
- Target settings for use



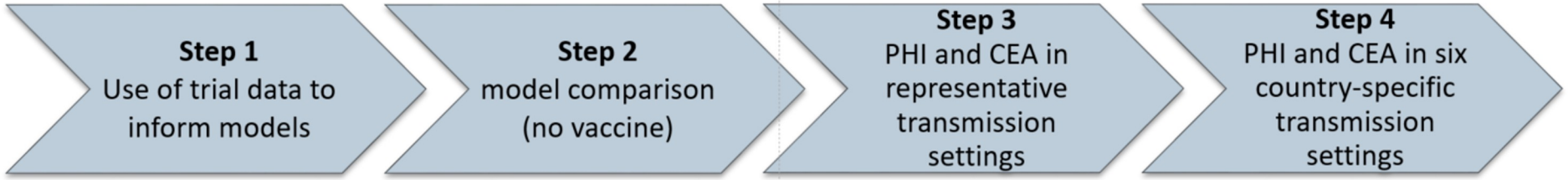
Penny, Verity, Bever et al. **Lancet** 2016, **387:**367

Background: Model comparisons

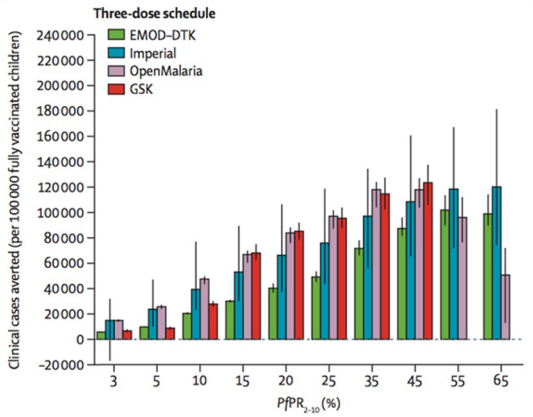
Vaccine model comparison and RTS,S predictions of public health impact and cost-effectiveness

Our model was also employed for model comparisons of impact and economic analyses for RTS,S, carried out in 2013, 2015, 2018, and 2021, under the close collaboration and coordination with PATH and the WHO.

Summary of RTS,S modelling in 2013 - 2015 (Penny *et al.* (2016) and MPAG-SAGE reports)

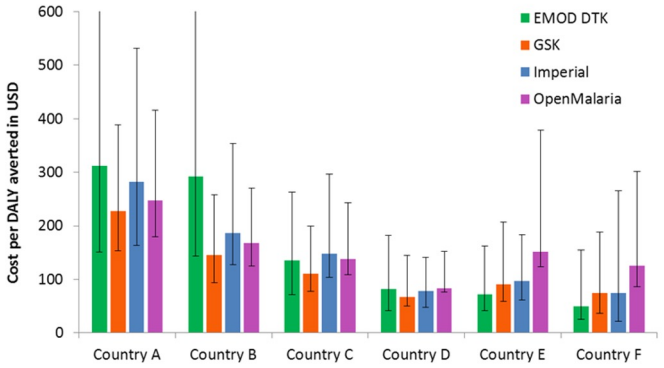


Step 3



Generic settings

Step 4



Country specific

All covered in background documents

Source: reports to WHO 2015

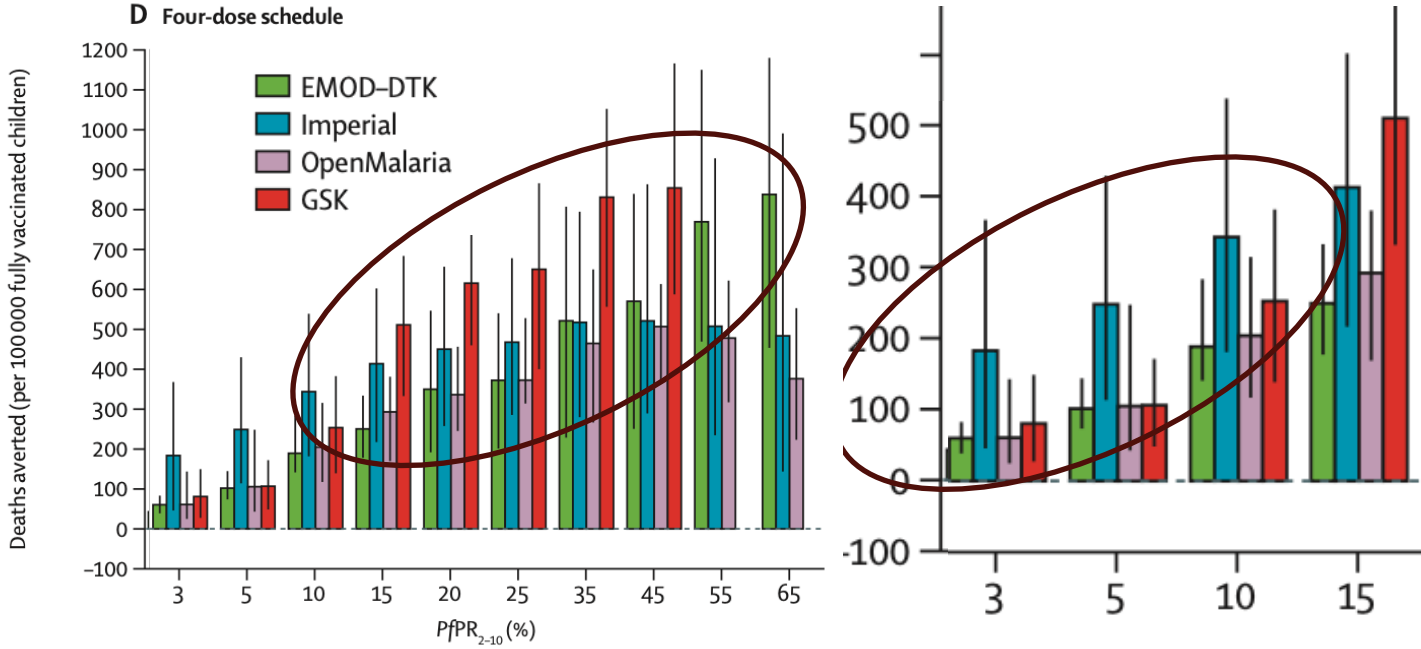
Background: Model comparisons

Vaccine model comparison and RTS,S predictions of public health impact and cost-effectiveness

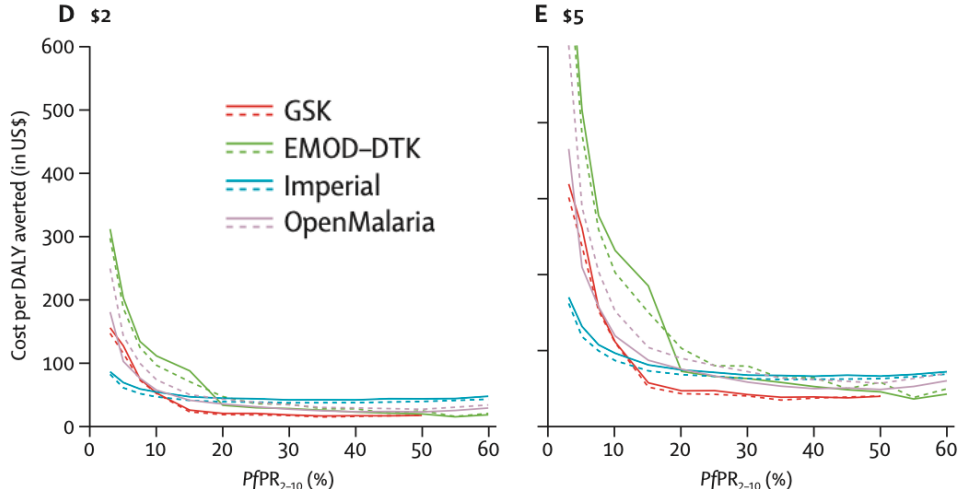
- There are some differences between the predictions of the models, especially at *low transmission settings*. Thus, we should determine if this difference is also observed for R21.
- Each established malaria transmission model has different structural assumptions and is validated to different historical data *(see background material, Supplement of Penny 2016)*

Multiple models were needed to inform projections of vaccine impact beyond clinical trial data

PHI



ICERs

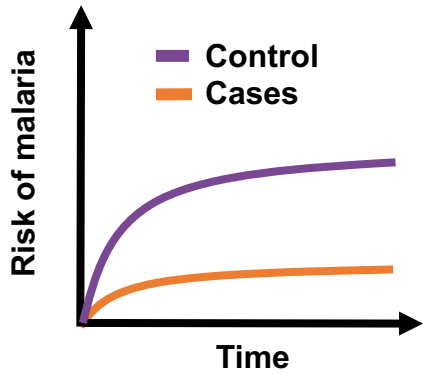


Source: Penny *et al* .2016

Background: Summary of analysis plan

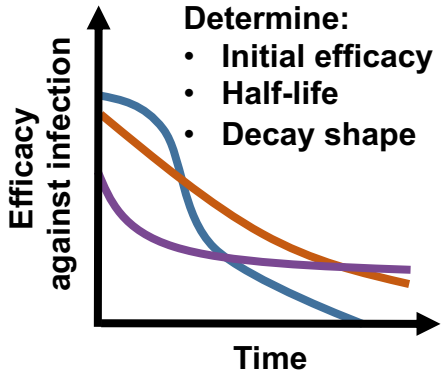
At request of WHO and IVIR-AC we have developed an analysis plan to complement the impact and cost-effectiveness estimates already provided to WHO from Imperial college

Review clinical data



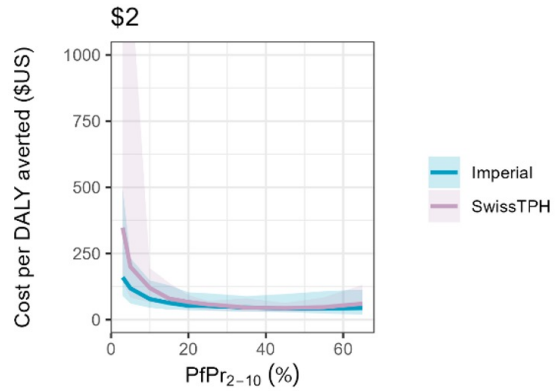
Phase 3 data

Vaccine Model calibration



Informed by trial data and historical data

Predicted health impact and cost effectiveness



Calculate events averted, ICERs, and DALYs using the model

Plan A: Using 3-monthly aggregate data ***(preferred)***
Plan Backup: Using 12 month and 18 month summary data

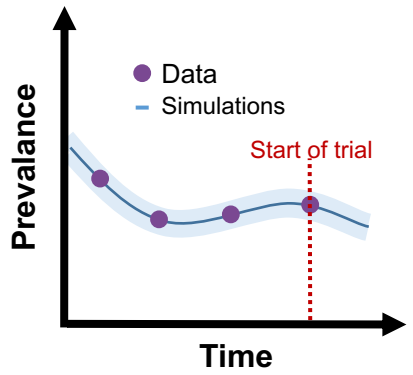
ANALYSIS PLAN

VACCINE MODEL CALIBRATION

Methodology Overview: calibration of vaccine

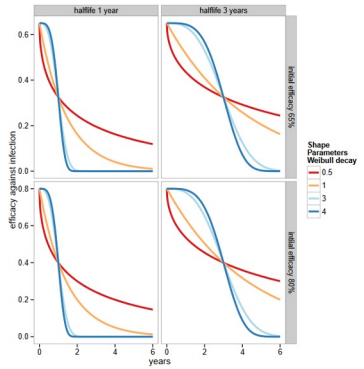
R21 vaccine properties are defined as underlying protection against infection (sporozoite action)

Step 1: History matching to trial site



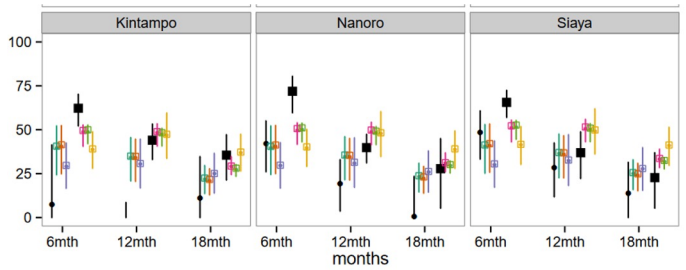
Calibrate base model to trial site in absence of new vaccine intervention

Step 2: Calibrate vaccine model to Phase 3 results



Estimate vaccine parameters for initial efficacy against infection, decay shape, duration (half-life)

Step 3: Validation of model parameters

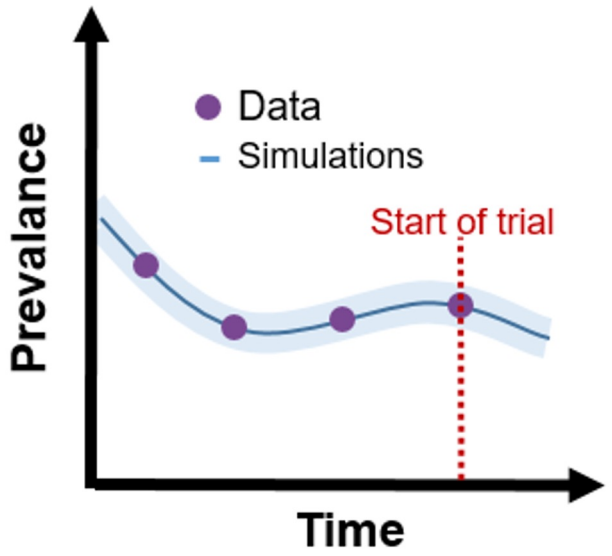


Match predictions to trial data on vaccine efficacy against clinical disease in sites not use for fitting (Phase 2 results?)

Methodology Overview: calibration of vaccine

STEP 1: History Matching

History matching of trial sites dynamics pre-trial



Methodology:

Validated **Bayesian Optimization approach** developed at the group of Melissa Penny (Git Repository & Rieker *et al*)
We calibrate EIR and temporal dynamics matching observed disease dynamics

Data Required (publicly available, or as indicated in the published Phase 2/3 papers):

- Demographic details
- Historical intervention coverage
  - ✓ ITN
  - ✓ **SMC**,
  - ✓ IRS etc
- Historical treatment coverage
- Seasonality indicators

→ ***Fit to: site & time specific prevalence and morbidity (modelled from MAP, or as reported)***

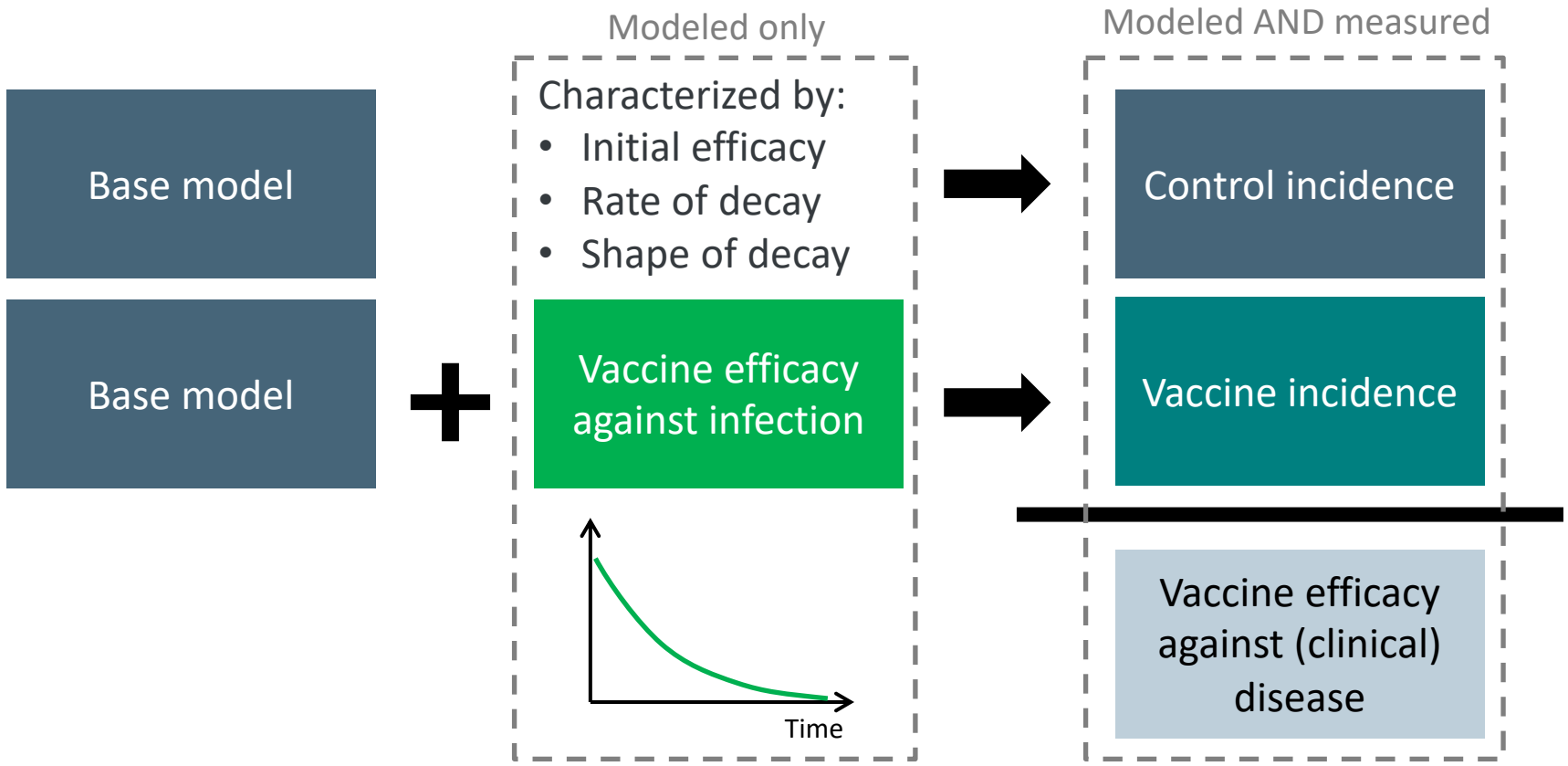
Methodology Overview: calibration of vaccine

STEP 2: Calibrate vaccine properties to Phase 3 results

Calibrate underlying vaccine properties using incidence results from trial (note we are not fitting against reported vaccine clinical efficacy against disease)

VE against infection vs. VE against clinical disease

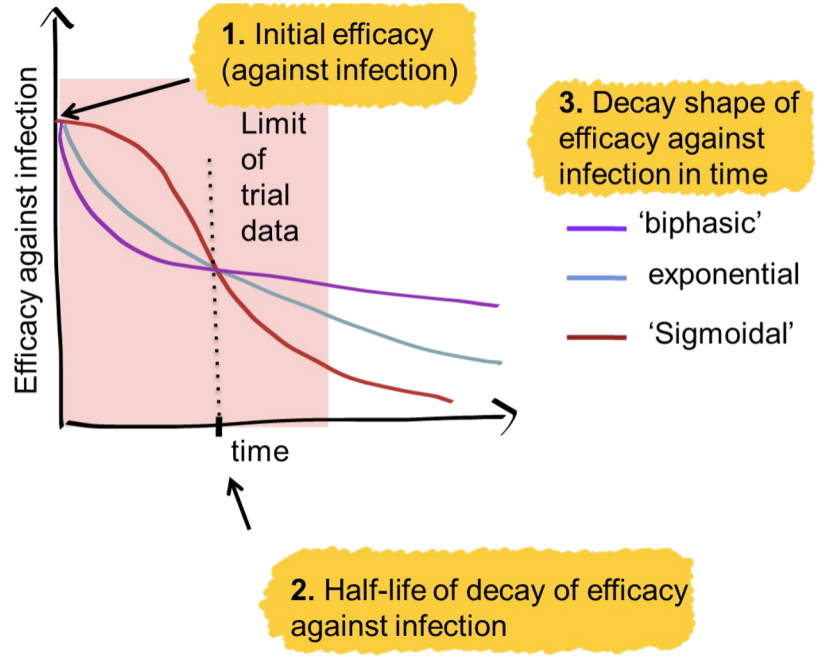
In-silico trial (control and vaccine cohorts as per trial)



Methodology Overview: calibration of vaccine

STEP 2: Calibrate vaccine properties to Phase 3 results

Calibrate underlying vaccine properties using incidence results from trial (note we are not fitting against reported vaccine clinical efficacy against disease)



→ *Fit to: site & time specific incidence in control & intervention groups*

→ *Obtains: optimised parameter values* for vaccine initial efficacy, decay shape, and half-life duration

Methodology:

Validated **Bayesian Optimization approach** developed at the group of Melissa Penny (Git Repository & Rieker *et al*)

Note:

1) *We will fit to all trial sites; and suggest Phase 2 results could be used as a validation step*
2) *Methods tested on synthetic data*

Data Required:

- Vaccine coverage, and *age disaggregation* at first vaccine
- All trial endpoints
  - In both arms
  - Disaggregated by age
  - At 3-monthly timepoints

Further considerations:

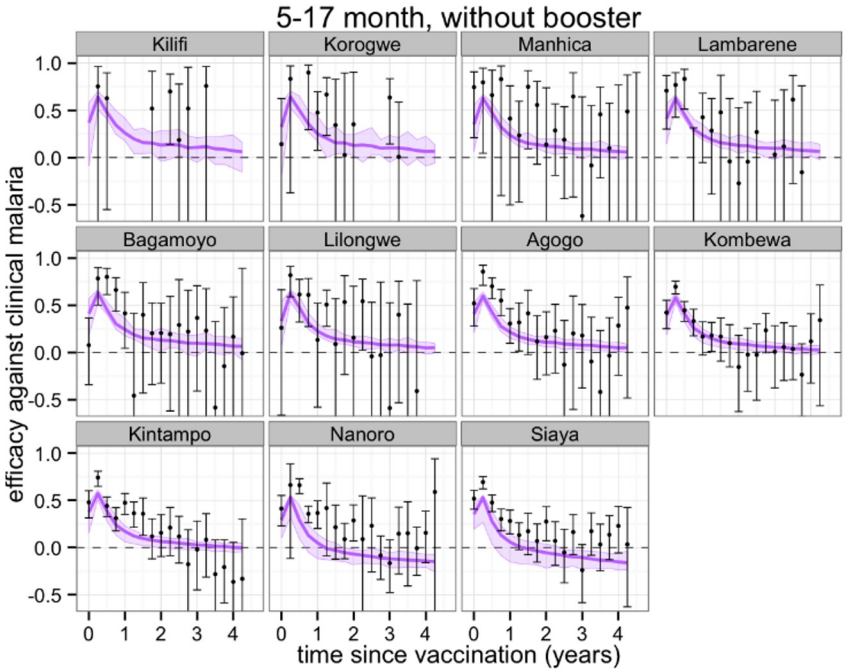
- SMC-SPAQ coverage (seasonal)***
- Site specific access to treatment

Methodology Overview: calibration of vaccine

STEP 3: Potential validation

Compare model predictions using vaccine properties informed by Phase 3 followup to results from the phase 1/2b randomized controlled trial in children aged 5-17 months in Nanoro, Burkina Faso.
(high malaria transmission)

Example Plot only



Penny *et al.* (2016)

Methodology:
Goodness of fit between predicted and calculated vaccine efficacy against clinical disease in Phase 1/2b site

Data Required:

- Calculated vaccine efficacy against clinical disease
  - Adjusted & unadjusted
  - Disaggregated by age
  - Vaccine efficacy

ANALYSIS PLAN

Predictions of R21 potential PUBLIC HEALTH IMPACT

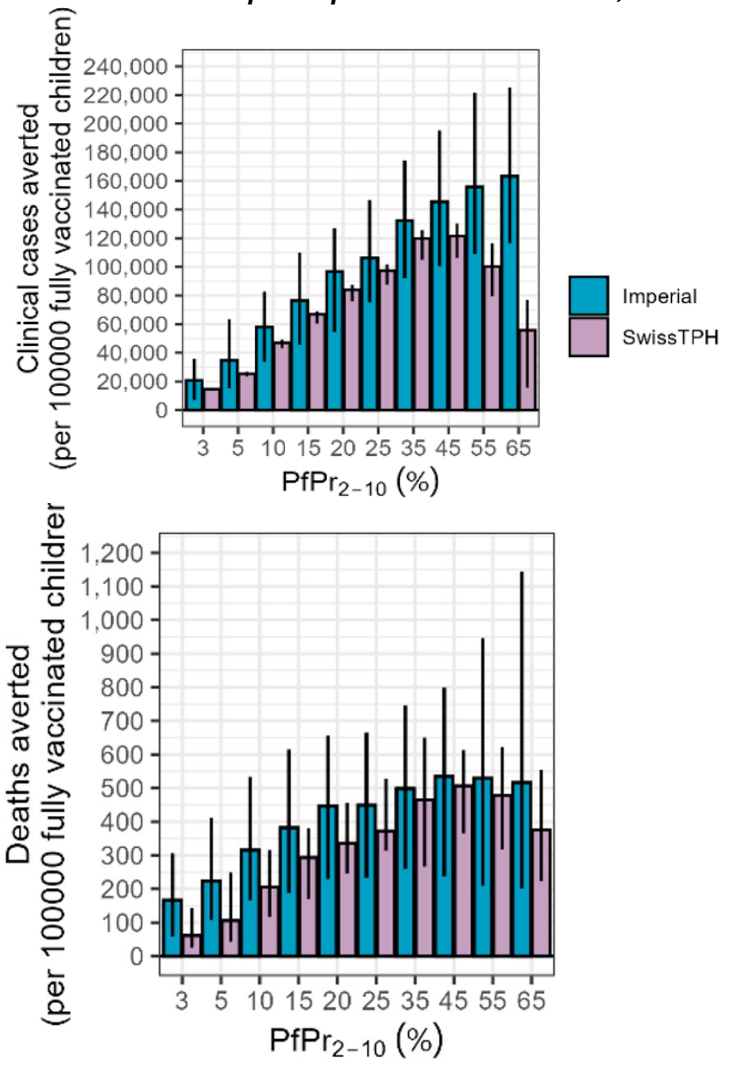
Public health impact estimation

Analysis plan:

Aiming to provide comparable PHI and CEA to Imperial

- Using calibrated and validated OpenMalaria model, will run a range of scenarios to estimate potential public health impact of R21
- **Scenarios:**
  - Range of archetypal modelling settings: perennial and seasonal, a range of prevalence levels including low-transmission settings with prevalence <10%, range of levels of access to care
    - PHI for EPI routine delivery
    - PHI for Seasonal delivery (with and without codelivery with SMC)
    - Hybrid
  - *May include history of ongoing childhood interventions: SMC, ITNs, IRS*
- **Vaccine intervention:**
  - Different ranges of coverage and drop out
  - Deployment: to be confirmed with WHO (seasonal with hybrid first? and EPI)
  - Intervention modelled with full sensitivity analysis on a range of vaccine model profiles
- **Outputs**: public health impact estimates of uncomplicated malaria, severe malaria, hospitalisations and mortality and DALYS

Examplar plots from RTS,S



Plus sensitivity analysis on vaccine properties

ANALYSIS PLAN

Predictions of R21
COST-EFFECTIVENESS

Cost-effectiveness

Examplar plots from RTS,S

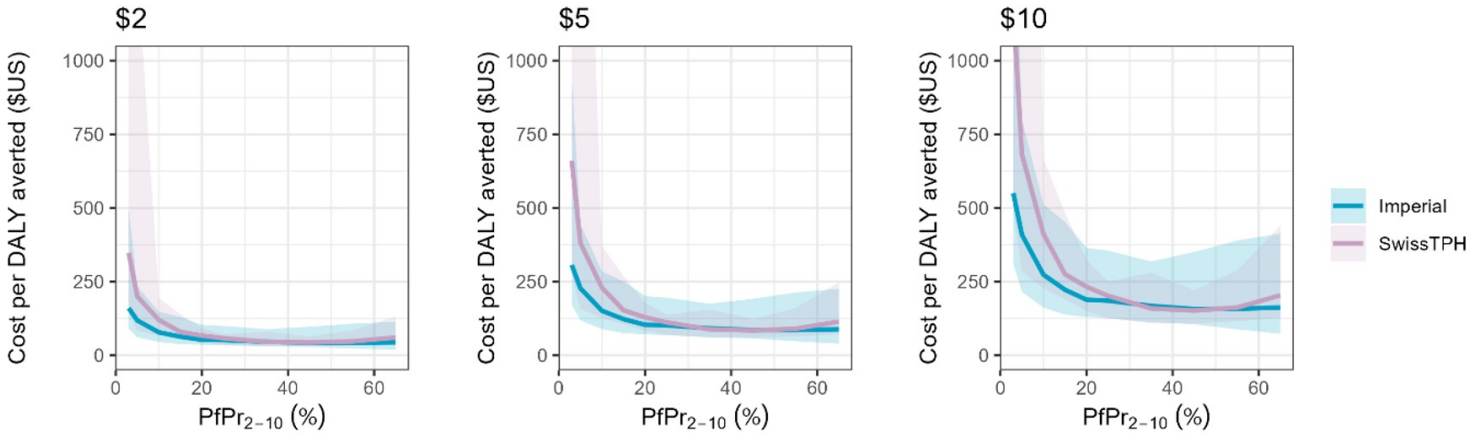
Analysis plan:

Aiming to provide comparable CEA to Imperial

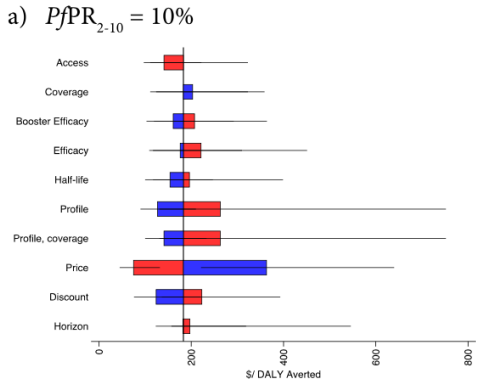
- Methodology: we propose to use similar methodology previously used for RTS,S/R21 CEA for perennial settings, and similar for R21 seasonal deployment as for Schmid et al. with updated data on costs of vaccine and consumables and vaccine delivery
  - Use the public health impact estimates from OpenMalaria to calculate cost effectiveness
  - Costs will be estimated from a health-care provider prospective

- **Outputs: incremental cost-effectiveness ratios (ICERs) as cost per *clinical case, hospitalized malaria, direct malaria severe case, direct malaria mortality and disability-adjusted life years (DALYs)* averted.**

Examplar from RTS,S/AS01 modelling analysis



Example from Penny et al 2016



Background published articles for Session 1

1. Schmit, N., Topazian, H. M., Natama, H. M., Bellamy, D., Traoré, O., Somé, M. A., Rouamba, T., Tahita, M. C., Bonko, M. D. A., Sourabié, A., Sorgho, H., Stockdale, L., Provstgaard-Morys, S., Aboagye, J., Woods, D., Rapi, K., Datoo, M. S., Lopez, F. R., Charles, G. D., McCain, K., … Winskill, P. (2024). The public health impact and cost-effectiveness of the R21/Matrix-M malaria vaccine: a mathematical modelling study. *The Lancet. Infectious diseases*, S1473-3099(23)00816-2. Advance online publication. https://doi.org/10.1016/S1473-3099(23)00816-2

2. Penny, M. A., Verity, R., Bever, C. A., Sauboin, C., Galactionova, K., Flasche, S., White, M. T., Wenger, E. A., Van de Velde, N., Pemberton-Ross, P., Griffin, J. T., Smith, T. A., Eckhoff, P. A., Muhib, F., Jit, M., & Ghani, A. C. (2016). Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. *Lancet (London, England)*, *387*(10016), 367–375. https://doi.org/10.1016/S0140-6736(15)00725-4

World Health Organization

Session 2

Meta-Analysis of Economic Evaluations of Vaccines

Meta-Analysis of Economic Evaluations (MAEE) of Vaccines

For IVIR-AC recommendations

MAEE IVIR-AC subgroup and project team

World Health Organization | IVB

27 February 2024

Agenda for today's session

- **Background information** – Karene Yeung (WHO IVB)
- **Overview of existing MAEE studies, gaps and challenges** – Nathorn Chaiyakunapruk (University of Utah)
- **Proposal of research agenda to guide the advice on how the work of MAEE of vaccines should be continued** – Alexandra Hogan (IVIR-AC Subgroup Chair)
- **Q&A and discussion** – with IVIR-AC members

Background information

Karene Yeung
WHO/IVB/IAI/VOV

Background

- Growing pressure on how to allocate scarce resources and choose among competing priorities
- Important role of the use of evidence from economic evaluations (EEs) in vaccine introduction and implementation decisions
- Data and expertise may not be available in countries (especially but not exclusively LMICs) to conduct economic evaluations
- Concerns about transferability of economic evidence from one to another
- Unmanageable amounts of information and conflicting findings

Background

- Systematic reviews: synthesize existing economic evidence efficiently, descriptively and qualitatively
- Meta-analyses: quantitative pooling of results from multiple studies to create a more reliable estimates
- Utility of MAEE is subject to scientific debate

Background

- In March 2021, IVIR-AC considered several MAEE examples and provided feedback on the value and limitations of using MAEE
- Highlighted techniques to be developed to address methodological issues
- Recommended a documentation to describe and explain major sources of variation and heterogeneity in estimates from EEs and uncertainty of sampling

2021, 96, 133–144 No 17

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

30 APRIL 2021, 96th YEAR / 30 AVRIL 2021, 96e ANNÉE
No 17, 2021, 96, 133–144
http://www.who.int/wer

Contents

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

Sommaire

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

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

The IVIR-AC recommendations are based on discussions during a virtual meeting of the IVIR-AC held 1–5 March 2021.

COVID-19 vaccine modelling

The WHO COVID-19 Vaccine Impact Modelling Subgroup of the WHO Strategic Advisory Group of Experts on Immunization (SAGE) Working Group on COVID-19 Vaccines provides modelling guidance to inform global policy recommendations related to prioritization of COVID-19 vaccines. In September 2020, IVIR-AC reviewed an initial set of modelling questions developed by the Subgroup. These were part of a Request for Information that was shared with modelling groups which have since presented work on these topics to the SAGE Working Group and Subgroup. In January 2021, the Subgroup issued a Request for Proposals (RFP) that addressed priority questions and gaps in modelling evidence. The results of the RFP, expected in mid-2021, will enable SAGE to further develop vaccine product-specific guidance and policy recommendations. To inform this process, IVIR-AC was asked to identify additional priority areas for vaccine modelling and ways to incorporate additional evidence into the SAGE *Evidence to Recommendations* (E2R) process.[1]

[1] Evidence to recommendations for COVID-19 vaccines: evidence framework (https://www.who.int/publications/i/item/WHO-2019-nCoV-SAGE-Framework-Evidence-2020-1; accessed March 2021).

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

Les recommandations de l'IVIR-AC présentées ici sont basées sur les discussions qui ont eu lieu lors d'une réunion virtuelle du Comité qui s'est tenue du 1er au 5 mars 2021.

Modélisation des vaccins contre la COVID-19

Le sous-groupe de l'OMS chargé de la modélisation de l'impact des vaccins anti-COVID-19 au sein du groupe de travail sur les vaccins anti-COVID-19 du Groupe stratégique consultatif d'experts de l'OMS (SAGE) sur la vaccination fournit des conseils en matière de modélisation afin d'éclairer les recommandations stratégiques mondiales relatives à l'établissement des priorités de vaccination contre la COVID-19. En septembre 2020, l'IVIR-AC a examiné une première série de questions de modélisation préparées par le sous-groupe. Celles-ci faisaient partie d'une demande d'information partagée avec des groupes de modélisation qui ont depuis présenté des travaux sur ces sujets au groupe de travail et au sous-groupe du SAGE. En janvier 2021, le sous-groupe a émis un appel à propositions visant à répondre aux questions prioritaires et à combler les lacunes dans les données de modélisation. Les résultats de cet appel à propositions, attendus pour le milieu de l'année 2021, permettront au SAGE de poursuivre l'élaboration d'orientations et de recommandations stratégiques spécifiques aux différents vaccins. A cette fin, il a été demandé à l'IVIR-AC d'identifier d'autres domaines prioritaires pour la modélisation des vaccins et des moyens d'intégrer des données probantes supplémentaires dans le processus du SAGE pour élaborer des recommandations à partir des preuves scientifiques (*Evidence to Recommendations*).[1]

[1] Evidence to recommendations for COVID-19 vaccines: evidence framework (https://www.who.int/publications/i/item/WHO-2019-nCoV-SAGE-Framework-Evidence-2020-1; consulté en mars 2021).

133

Weekly Epidemiological Record No 17, 2021, 96, 133–144.

Formulation of IVIR-AC subgroup

Main objective: To facilitate an ecosystem utilizing MAEE of vaccines to support policy and decision-making globally, regionally or in the settings with limited data availability

Subgroup members:

1. Alexandra Hogan *(chair, IVIR-AC member)*
2. Rakesh Aggarwal *(IVIR-AC member)*
3. Kathy Leung *(IVIR-AC member)*
4. Jessica Ochalek
5. Richmond Owus
6. Francis Ruiz
7. Stéphane Verguet
8. Merryn Voysey
9. Marcia Weaver

Writing group members

1. Nathorn Chaiyakunapruk, University of Utah (lead)
2. Mark Jit, London School of Hygiene & Tropical Medicine
3. Simon Procter, London School of Hygiene & Tropical Medicine
4. Sajesh Veettil, International Medical University in Malaysia

Overview of existing MAEE studies, gaps and challenges

Nathorn Chaiyakunapruk
Department of Pharmacotherapy
University of Utah College of Pharmacy

How to pool EE with MA?

Use incremental net benefit (INB)

$INB = \Delta E\ (K) - \Delta C$; K= Cost-effectiveness threshold; ΔE = incremental effect , ΔC = incremental cost

- Overcome the problem of using a ratio measure (ICER)
- Require an explicit cost-effectiveness threshold (K)

Data harmonization process[1]

- Standardize different money units and years by converting to purchasing power parity (PPP) adjusted to US$ for the latest year of analysis
- Estimation of variance for INB
  - $Equation\ 1: Var(INB) = K^2\sigma^2_{\Delta E} + \sigma^2_{\Delta C} - 2K\sigma_{\Delta E \Delta C}$
  - $Equation\ 2: Var(INB) = K^2\sigma^2_{\Delta E} + \sigma^2_{ICER}$
- As data for estimating variance available variably across EEs, five scenarios were developed to obtain variances and covariance

[1] Bagepally BS, Chaikledkaew U, Chaiyakunapruk N, Attia J, Thakkinstian A. Meta-analysis of economic evaluation studies: data harmonisation and methodological issues. BMC Health Serv Res. 2022 Feb 15;22(1):202.

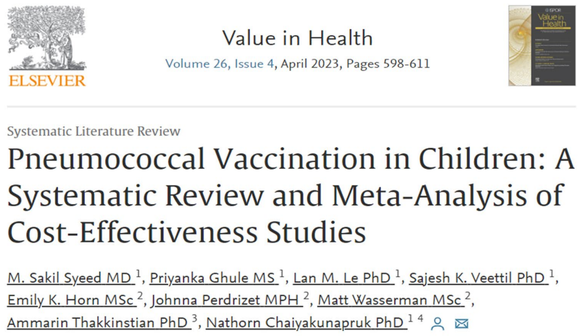
Analytical approach for MAEE

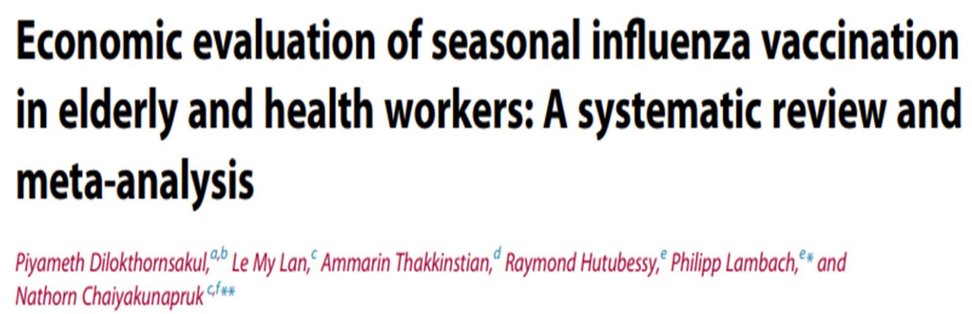
Pooling with inverse variance approach: fixed-effects vs random-effects

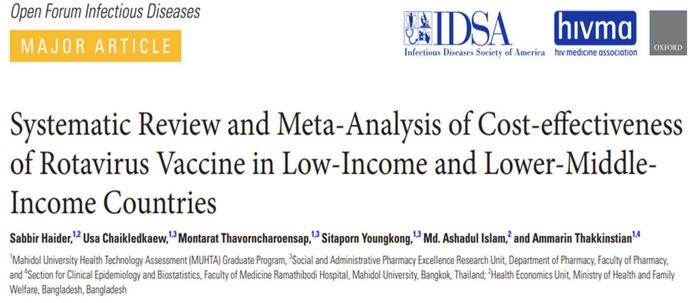
Stratified by **country income level** (e.g., low, lower-middle, upper-middle, and high), **perspective** (e.g., societal, health care or payer, etc.), **model type** (Markov, decision tree, or others) etc.

Exploring heterogeneity (Q and I^2) & Publication bias (Funnel plot & Egger)

Application of MAEE







Gaps & Challenges

1. Heterogeneity in MAEE

- Approximately two-thirds of analyses in recently published MAEEs showed evidence of substantial heterogeneity[1] (particularly unexplained)
  - Documentation is desired to describe and explain major sources of variation and heterogeneity : *IVIR-AC March 2021*[2]
  - There is a need to develop a standardized approach to handle it.
  - *Potential solution* Meta-regression might be a potential solution & other approaches

2. Study weighting in MAEE

- For EE studies uncertainty intervals depend on how thoroughly the modelers have investigated uncertainty; therefore, larger intervals may reflect relatively better-quality studies that should not be down-weighted
- *Potential solutions*
  - Analysis with unweighted pooling or weighting based on study quality: *IVIR-AC March 2021*[2] There is a need to "develop a grid of criteria for assessing study quality to enable quantitative assessment and weighting": *IVIR-AC March 2021*[2]
  - Other methods- Complementary approach to MAEE using random-effects model could be combining uncertainty distributions from studies through weighted convolution: presented at IHEA World Congress, July 2023

[1] *Veettil SK, Syeed MS, Noviyan R, Thakkinstian A, Chaiyakunapruk N. Does meta-analysis of economic evaluations have the potential to play a role in healthcare decision-making in the United States? J Med Econ. 2022 Jan-Dec;25(1):750-754.*

[2] https://www.who.int/publications/i/item/weekly-epidemiological-record-no-17-2021-96-133-144

Gaps & Challenges

3. Quantifying EEs: other approaches, if any

- Which indicator should be meta-analyzed (Cost, QALY, ICER or INB)?
- *Potential solution*
  - separately analyze the numerator and denominator then re-combine into an ICER
  - Any other approaches?

4. No formal evaluation of perception from demand side on the value of MAEE

- The methodology of MAEE is evolving.
- Lack of full understanding on how policy makers perceive on the value of an ecosystem using MAEE of vaccines (and in other therapeutic areas) to support policy and decision-making.
- *Potential solution*: Conduct a study to understand the value and perception from policy makers

[1] *Veettil SK, Syeed MS, Noviyan R, Thakkinstian A, Chaiyakunapruk N. Does meta-analysis of economic evaluations have the potential to play a role in healthcare decision-making in the United States? J Med Econ. 2022 Jan-Dec;25(1):750-754.*

[2] https://www.who.int/publications/i/item/weekly-epidemiological-record-no-17-2021-96-133-144

Proposal of research agenda to guide the advice on how the work of MAEE of vaccines should be continued

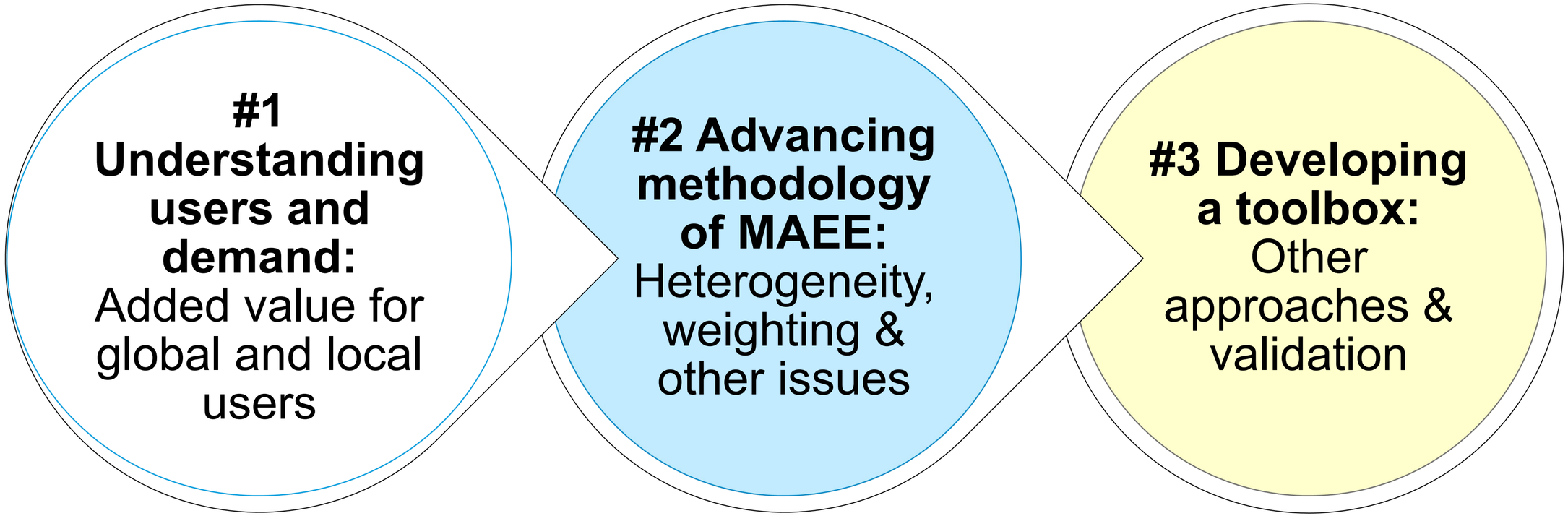
Alexandra Hogan

MAEE IVIR-AC Subgroup Chair

Summary of outcomes from the subgroup on 8 Dec 2023 meeting and subsequent conversations

- Highlighted the importance of understanding the users of and their demand for MAEE
  - Two types of users (global and local level users) were suggested, and the potential use cases of MAEE for each of these types of users was discussed
- Technical aspects of MAEE identified, such as:
  - The range of approaches for performing meta-analyses
  - Uncertainty and heterogeneity
  - Study quality and weighting
  - Estimation of product versus non-product costs
- Discussed issue of validating outcomes of MAEE in settings where local data are not available
- Identified the need for a resource or tool for MAEE that could be used in different settings
- A research agenda was proposed

Proposed research agenda



Proposed research agenda

#1 Understanding users of and demand for MAEE

Overall objective: To understand the demand and value of using MAEE to support policy and decision-making globally, regionally or in settings with limited resources

Phase 1a: Literature review

- Aims: To identify MAEEs conducted in various therapeutic areas; map out their key characteristics, findings and factors that may affect the finding of MAEE estimates; and identify how recommendations made by NITAGs and HTA agencies are informed by economic evidence
- Output: Summary of potential use cases of MAEE, which provides context for users at the local and global levels in the facilitator guide for phase 1b

Phase 1b: Qualitative interviews with potential local and global users

- Aims: To understand their perception of, demand for and ways they use MAEE
- Output: Recommendations for the optimal contexts in which MAEE can be used, and which kind of MAEE methodology would best meet user requirements

Proposed research agenda

#2 Advancing methodology of MAEE

Overall objective: To advance methodology of MAEE by addressing the existing methodological challenges

Phase 2a: Handling heterogeneity

- Aims: To explore the influence of structural uncertainty, parametric uncertainty, and setting-specific variation on heterogeneity
- Output: Guidance on how MAEE analysis should be performed to minimize heterogeneity

Phase 2b: Handling weighting

- Aims: To develop methods for meta-analyses with unweighted pooling and weighting based on study quality
- Output: Guidance on weighting approach in MAEE analysis

Phase 2c: Exploring other methodological issues

- Aims: To identify other methodological issues around MAEE

Proposed research agenda

#3 Developing tools for context-specific economic evidence that can contribute to an overall toolbox for using evidence in vaccine decision-making

- To develop a tool with a manual for local users to input their local values and generate results to help decision-making
  - Considering existing transferability of EE tools or checklists, existing MAEE approaches (e.g., INB approach or IHME approach), and the findings of phases 1 and 2
- To conduct validation of results
  - Through a comparison of results of using different MAEE approaches with locally produced high-quality EE

Timeline

Timeline															
Project phase	**2024**												**2025**		
	Jan	**Feb**	**Mar**	**Apr**	**May**	**Jun**	**Jul**	**Aug**	**Sep**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**	**Mar**
IVIR-AC meeting															
#1a Literature review															
#1b Qualitative interview															
#2a Method of MAEE – heterogeneity															
#2b Method of MAEE – weighting															
#2c Exploring other methodological issues															
#3 Developing a toolbox															
Update to IVIR-AC															
Present final products to IVIR-AC															

Questions to IVIR-AC

1. Review and provide feedback on the identified gaps and challenges of MAEE
2. Review and provide feedback on the proposed research agenda
3. Advice on how the work of MAEE of vaccines should be continued

Q&A and discussion

Guiding document of background materials for
IVIR-AC session 2 Meta-Analysis of Economic Evaluations of Vaccines

Background Document 1: 00_walkthrough_document

- **Description:** A guiding document of background materials
- **Prioritization:** 1 of 3

Background Document 2: 01_Slides_MAEE_OverviewGapsChallenges

- **Description:** A slide deck summarizing the existing Meta-Analysis of Economic Evaluations (MAEE) studies, gaps and challenges. IVIR-AC is asked to review this summary (and the associated studies [background documents 4-11] and provide feedback on the identified gaps and challenges.
- **Prioritization:** 1 of 3

Background Document 3: 02_SubgroupMeetingSummary_ResearchAgenda

- **Description:** A document summarizing the main outcomes from the first IVIR-AC subgroup meeting and the proposed research agenda. IVIR-AC is asked to review this document and provide feedback on the proposed research agenda as the proposed next steps to guide the advice on how the work of MAEE of vaccines should be continued.
- **Prioritization:** 1 of 3

Background Document 4: 03_WER9617

- **Description:** Weekly epidemiological record of the summary of March 2021 IVIR-AC meeting with the MAEE session summary on pages 138-140
- **Prioritization:** 2 of 3

Background Document 5: 04_Pang1999_UseOfMAEE

- **Description:** The first working paper on MAEE
- **Prioritization:** 2 of 3

Background Document 6: 05_Crespo2014_COMER

- **Description:** A methodology paper on MAEE
- **Prioritization:** 2 of 3

Background Document 7: 06_Bagepally2022_DataHarmonisation

- **Description:** A modified methodology paper with a step-by-step data harmonization process to conduct MAEE
- **Prioritization:** 2 of 3

Background Document 8: 07_Haider2019_MAEE_rotavirus

- **Description:** MAEE study on rotavirus vaccine
- **Prioritization:** 3 of 3

Background Document 9: 08_Udayachalerm2022_MAEE_zoster

- **Description:** MAEE study on zoster vaccine
- **Prioritization:** 3 of 3

Background Document 10: 09_Dilokthornsakul2022_MAEE_influenza

- **Description:** MAEE study on influenza vaccine
- **Prioritization:** 3 of 3

Background Document 11: 10_Syeed2023_MAEE_pneumococcal

- **Description:** MAEE study on pneumococcal vaccine
- **Prioritization:** 3 of 3

Overview of existing MAEE studies, gaps and challenges

Nathorn Chaiyakunapruk

Department of Pharmacotherapy

University of Utah College of Pharmacy

How to pool EE with MA?

Use incremental net benefit (INB)

$INB = \Delta E\ (K) - \Delta C$; K= Cost-effectiveness threshold; ΔE = incremental effect , ΔC = incremental cost

- Overcome the problem of using a ratio measure (ICER)
- Require an explicit cost-effectiveness threshold (K)

Data harmonization process[1]

- Standardize different money units and years by converting to purchasing power parity (PPP) adjusted to US$ for the latest year of analysis
- Estimation of variance for INB
  - $Equation\ 1: Var(INB) = K^2\sigma^2_{\Delta E} + \sigma^2_{\Delta C} - 2K\sigma_{\Delta E \Delta C}$
  - $Equation\ 2: Var(INB) = K^2\sigma^2_{\Delta E} + \sigma^2_{ICER}$
- As data for estimating variance available variably across EEs, five scenarios were developed to obtain variances and covariance

[1] Bagepally BS, Chaikledkaew U, Chaiyakunapruk N, Attia J, Thakkinstian A. Meta-analysis of economic evaluation studies: data harmonisation and methodological issues. BMC Health Serv Res. 2022 Feb 15;22(1):202.

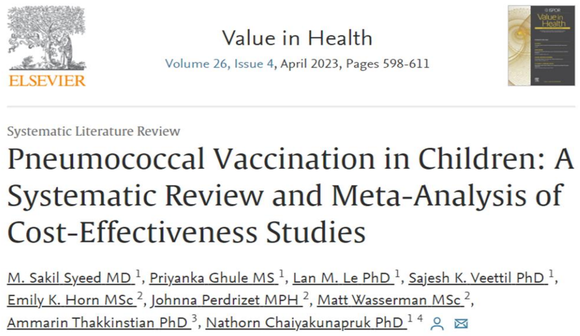
Analytical approach for MAEE

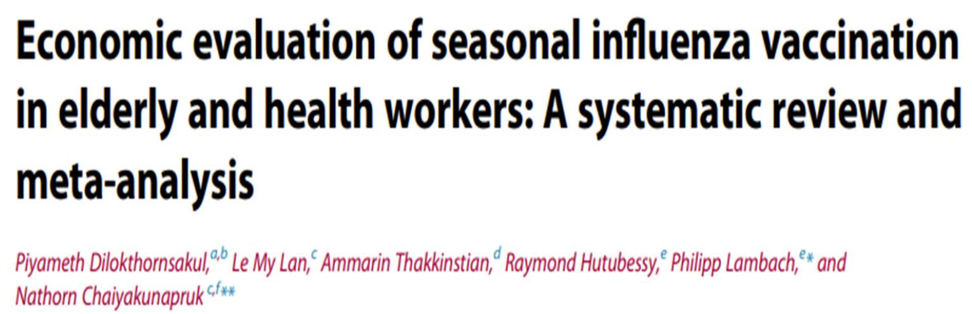
Pooling with inverse variance approach: fixed-effects vs random-effects

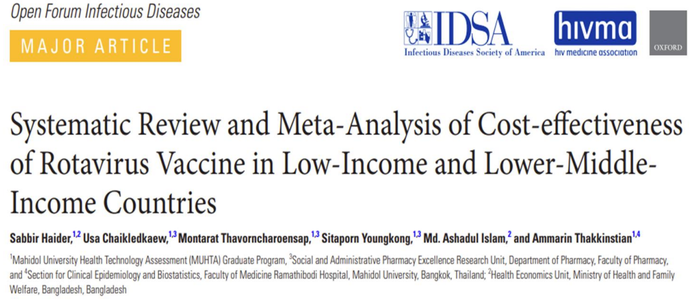
Stratified by **country income level** (e.g., low, lower-middle, upper-middle, and high), **perspective** (e.g., societal, health care or payer, etc.), **model type** (Markov, decision tree, or others) etc.

Exploring heterogeneity (Q and I^2) & Publication bias (Funnel plot & Egger)

Application of MAEE







Gaps & Challenges

1. Heterogeneity in MAEE

- Approximately two-thirds of analyses in recently published MAEEs showed evidence of substantial heterogeneity[1] (particularly unexplained)
  - Documentation is desired to describe and explain major sources of variation and heterogeneity : *IVIR-AC March 2021*[2]
  - There is a need to develop a standardized approach to handle it.
  - *Potential solution* Meta-regression might be a potential solution & other approaches

2. Study weighting in MAEE

- For EE studies uncertainty intervals depend on how thoroughly the modelers have investigated uncertainty; therefore, larger intervals may reflect relatively better-quality studies that should not be down-weighted
- *Potential solutions*
  - Analysis with unweighted pooling or weighting based on study quality: *IVIR-AC March 2021*[2] There is a need to "develop a grid of criteria for assessing study quality to enable quantitative assessment and weighting": *IVIR-AC March 2021*[2]
  - Other methods- Complementary approach to MAEE using random-effects model could be combining uncertainty distributions from studies through weighted convolution: presented at IHEA World Congress, July 2023

[1] *Veettil SK, Syeed MS, Noviyan R, Thakkinstian A, Chaiyakunapruk N. Does meta-analysis of economic evaluations have the potential to play a role in healthcare decision-making in the United States? J Med Econ. 2022 Jan-Dec;25(1):750-754.*

[2] https://www.who.int/publications/i/item/weekly-epidemiological-record-no-17-2021-96-133-144

Gaps & Challenges

3. Quantifying EEs: other approaches, if any

- Which indicator should be meta-analyzed(Cost, QALY, ICER or INB)?
- *Potential solution*
  - separately analyze the numerator and denominator then re-combine into an ICER
  - Any other approaches?

4. No formal evaluation of perception from demand side on the value of MAEE

- The methodology of MAEE is evolving.
- Lack of full understanding on how policy makers perceive on the value of an ecosystem using MAEE of vaccines (and in other therapeutic areas) to support policy and decision-making.
- *Potential solution*: Conduct a study to understand the value and perception from policy makers

[1] *Veettil SK, Syeed MS, Noviyan R, Thakkinstian A, Chaiyakunapruk N. Does meta-analysis of economic evaluations have the potential to play a role in healthcare decision-making in the United States? J Med Econ. 2022 Jan-Dec;25(1):750-754.*

[2] https://www.who.int/publications/i/item/weekly-epidemiological-record-no-17-2021-96-133-144

Summary of the first meeting: IVIR-AC subgroup on MAEE of vaccines (8th Dec 2023)

Background

The use of evidence from economic evaluations (EEs) is likely to play an increasingly important role in vaccine introduction and implementation decisions that lead to sustained and optimal use of prioritized vaccines. However, many countries, especially but not exclusively low- and middle-income countries (LMICs), may not have data, available resources, or expertise to conduct EEs that require complex modelling, such as transmission dynamic models of vaccination. Until such capacity and expertise is developed, decision-makers from these countries would then need to rely on evidence from existing EEs from other countries. However, there are concerns about the transferability of such evidence from one policy setting to another or from one country to another. Moreover, decision-makers are often challenged by unmanageable amounts of information and conflicting findings from EEs. Systematic reviews of EEs (SREEs) can provide an efficient mechanism to synthesize existing economic evidence to answer a specific value question. However, SREEs provide only descriptive and qualitative evidence. Meta-analyses are useful for pooling results from multiple studies to generate more reliable quantitative estimates. Application of this approach to EEs is now under consideration.[1] Previously, Crespo et al. (2014) suggested statistical methods for performing meta-analysis of EEs (MAEEs) to generate quantitative evidence.[2] The incremental net benefit (INB) is used as the outcome of interest in this approach, rather than the incremental cost-effectiveness ratio (ICER), as ICER is a ratio measure that does not meet normality assumptions and has the ambiguity of negative values. Recently, this method was further modified by Bagepally et al. (2022) and was devised as a step-by-step data harmonization process to bring together inconsistently reported (e.g., money units) or missing data (e.g., data to estimate the variance of INB) from different EEs to facilitate performing MAEEs (Appendix 1).[3] This INB approach has been applied to meta-analysis of EE of vaccines such as PCV (Syeed et al., 2023),[4] herpes zoster (Udayachalerm S, 2022),[5] seasonal influenza (Dilokthornsakul et al., 2022),[6] and rotavirus (Haider S, 2019).[7] Separately, IHME has developed its own methodology for conducting meta-regression of EE of immunization programmes such as HPV (Rosettie et al., 2021)[8] and rotavirus (Janko et al., 2022)[9] (Appendix 1).

In March 2021, the Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC) considered several examples of MAEEs and provided feedback on the value and limitations of performing MAEEs using the INB approach.[10] The IVIR-AC (2021) acknowledged the heterogeneity among the EE literature, highlighted that MAEE is not straightforward and that standard meta-analysis techniques may not be directly applicable, and that the techniques need to be developed to address methodological issues around MAEE, but also agreed that MAEE could facilitate decision-making in countries without context-specific EEs. The committee recommended that documentation is desired to describe and explain major sources of variation and heterogeneity in EE estimates. In July 2023, methodological and practical experience on performing MAEE of vaccines, potential applications, and challenges were presented at the 15th International Health Economics Association (IHEA) World Congress on Health Economics in Cape Town, South Africa. Participants acknowledged its limitations and usefulness and discussed potential use in an adaptive Health Technology Assessment (HTA). Subsequently, the IVIR-AC subgroup on MAEE of vaccines was set up with the main objective of facilitating an ecosystem utilizing MAEE of vaccines to support policy and decision-making globally, regionally, or in settings with limited data availability. At the first meeting, which was held on 8th December 2023, the subgroup members discussed and agreed upon the main outcome and scope of the product of the subgroup and suggested the research agenda in this area.

Summary of recommendations

1. The subgroup highlighted the importance of understanding the local and global users of and their demand for MAEE. For example, for which context MAEE is most suitable? What types of decisions can be informed by MAEE? Why would MAEE be used rather than other frameworks? What is the demand and desire to use MAEE by decision-makers? In particular, it is important to understand how EEs are used to inform decision-making, as this will drive the methodology of MAEE. For instance, some decision-makers apply particular decision rules around quantitative measures of the uncertainty around economic efficiency measures (such as the ICER or NMB). Knowing how these are used would then drive how MAEEs should propagate uncertainty in individual EEs into summary estimates.

   Two types of users (global and local level users) were suggested.

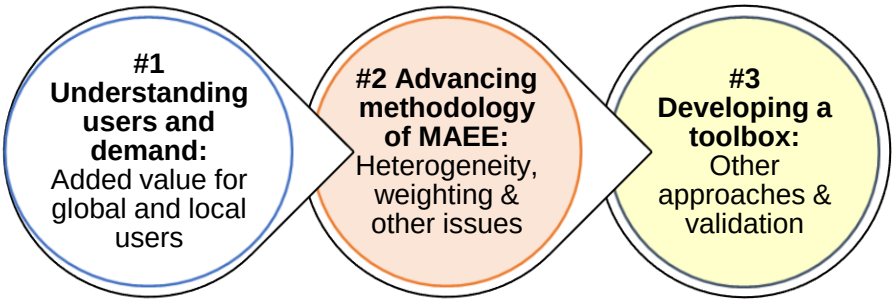
   For global-level users, e.g., WHO. Quantitative summary estimates, with an explanation of what factors influencing the outcomes (e.g., INB, ΔE (incremental health effects), and ΔC (incremental costs)), could be provided. This will help explain or even reduce heterogeneity from the analysis. Incremental costs may need to be further disaggregated into vaccine procurement costs (which are highly context-dependent and may not be part of the formal remit of HTA agencies or NITAGs to consider) and cost offsets to the health service and/or society (which are important benefits of vaccination). Some EEs may not allow such disaggregation; however, these are likely to be lower quality studies since reporting guidelines such as CHEERS recommend disaggregating costs and health effects in reports of EEs. For global end-users, MAEE may be applied across an income group or a geographic region or both, rather than for individual countries, therefore there could be ranges of values that could be drawn on as needed for a particular vaccine.

   For local-level users, e.g., individual countries. A tool available for countries to be able to input their local values and generate results to help decision-making, could be developed. This could be part of a broader toolbox concept to facilitate use of economic (and other) evidence in vaccine decision-making. The approach might be utilized through MAEE or meta-regression. A more advanced step could be to develop league tables that present cost-effective interventions selected by ranking ICERs from the lowest to the highest, such as those developed by the Institute for Health Metrics and Evaluation (IHME) group or by the WHO-CHOICE approach. A further step could even be to present the separated meta-analyses of cost-effectiveness which allows each country to use them for their context.

2. Other technical aspects of MAEE (e.g., heterogeneity and weighting) were not discussed in detail at this meeting. However, previous discussions have emphasised the need to weigh studies according to study quality rather than relying on reported uncertainty measures without assessing how comprehensive the study has been in capturing all sources of uncertainty (including structural uncertainty).
3. An additional question was raised of how to validate the outcomes of the MAEE exercise in a setting where local data are not available.
4. Other approaches for performing meta-analysis were also discussed in subsequent conversations among subgroup members (Appendix 1).

Research agenda

An overall research agenda is outlined in the following figure.



1. Understanding users of and demand for MAEE: The overall objective is to understand the demand and value of using MAEE to support policy and decision-making globally, regionally or in settings with limited resources.
    a. Phase 1a: The writing group will perform a literature review identifying MAEEs conducted in various therapeutic areas, and map out their key characteristics, findings, and factors that may affect the finding of MAEE estimates. They will also review guidelines about how recommendations made by NITAGs and HTA agencies are informed by EE evidence (and particularly how they consider sources of heterogeneity and uncertainty, as well as evidence from other countries). The output will be the summary of potential use cases of MAEE, which provides context for users at the local and global levels in the facilitator guide for phase 1b.
    b. Phase 1b: The writing group will perform qualitative interviews with potential local and global users specifically in LMICs to understand their perception of, demand for and ways they use MAEE. The output will help generate recommendations for the optimal contexts in which MAEE can be used, and what kind of MAEE methodology would best meet user requirements.

2. Advancing methodology of MAEE: The overall objective is to advance methodology of MAEE by addressing the existing methodological challenges.
    a. Phase 2a: The writing group will explore the influence of structural uncertainty, parametric uncertainty, and setting-specific variation (e.g., income country level, funding, etc.) on heterogeneity. A list of influential parameters will be obtained from both tornado diagrams from included EE studies and those parameters not included in the tornado diagram, as they may represent uncertainty not captured in the analysis. The writing group will assess their impact on heterogeneity possibly using a meta-regression approach. However, it is likely that a standard list of parameters and model features that are influential cannot be developed because this is likely to be disease-specific. Instead, the output could help to inform a guidance framework on how MAEE analysis should be performed to minimize heterogeneity. This framework will be developed through methodological exploration by the writing group and the advisory committee, considering the way users of MAEEs use EEs.
    b. Phase 2b: The writing group will develop methods for meta-analyses with unweighted pooling and weighting based on study quality. A grid of criteria for assessing study quality will be developed with

focus on the quality of uncertainty assessment in EE studies. Additionally, the writing group will also explore ways of combining uncertainty distributions from studies e.g. through weighted convolution. The writing group will compare the findings generated by meta-analyses with unweighted pooling, quality-based weighted pooling, and weighted convolution method, and assess their statistical features. The output will help generate a guidance on weighting approach in MAEE analysis.

c. Phase 2c: Identification of other methodological issues around MAEEs through discussion among the writing group and advisory group, literature review and consultations with users of EEs.

3. Developing tools for context-specific economic evidence that can contribute to an overall toolbox for using evidence in vaccine decision-making: The writing group may develop a tool with a manual for local users to input their local values and generate results to help decision-making. Existing transferability of economic evaluation tools or checklists may be used to guide the development of the manual for the proposed toolbox.[11] The toolbox could be informed by existing MAEE approaches e.g. the INB approach or the IHME approach (Appendix 1). However, it will adapt these approaches based on the findings of steps (1) and (2). Validation of the results will be done through a comparison of results of using different MAEE approaches with locally produced high-quality EE. The writing group will explore quantitative synthesis of various economic efficiency measures, e.g., INB and non-INB measures such as separately conducted meta-analyses of ΔE and ΔC, or even splitting the ΔC further to product and non-product costs to generate threshold cost per dose as outcome (Appendix 2).

References:

1. Pang F et al. The use of meta-analysis in economic evaluation. Centre for Health Economics, University of York; 1999 Nov.
2. Crespo C et al. Comparative efficiency research (COMER): meta-analysis of cost-effectiveness studies. BMC Medical Research Methodology 2014;14(1):139.
3. Bagepally BS, Chaikledkaew U, Chaiyakunapruk N, Attia J, Thakkinstian A. Meta-analysis of economic evaluation studies: data harmonisation and methodological issues. BMC Health Serv Res. 2022 Feb 15;22(1):202.
4. Syeed MS, et al. Pneumococcal Vaccination in Children: A Systematic Review and Meta-Analysis of Cost-Effectiveness Studies. Value Health. 2023 Apr;26(4):598-611.
5. Udayachalerm S, et al. Incremental net monetary benefit of herpes zoster vaccination: a systematic review and meta-analysis of cost-effectiveness evidence. J Med Econ. 2022 Jan-Dec;25(1):26-37.
6. Dilokthornsakul P, et al. Economic evaluation of seasonal influenza vaccination in elderly and health workers: A systematic review and meta-analysis. EClinicalMedicine. 2022 Apr 21;47:101410.
7. Haider S, et al. Systematic Review and Meta-Analysis of Cost-effectiveness of Rotavirus Vaccine in Low-Income and Lower-Middle-Income Countries. Open Forum Infect Dis. 2019 Mar 8;6(4):ofz117.
8. Janko MM, et al. Cost-effectiveness of rotavirus vaccination in children under five years of age in 195 countries: A meta-regression analysis. Vaccine. 2022 Jun 21;40(28):3903-3917.
9. Rosettie KL, et al. Cost-effectiveness of HPV vaccination in 195 countries: A meta-regression analysis. PLoS One. 2021 Dec 20;16(12):e0260808.
10. https://www.who.int/publications/i/item/weekly-epidemiological-record-no-17-2021-96-133-144
11. Heupink LF, Peacocke EF, Sæterdal I, Chola L, Frønsdal K. Considerations for transferability of health technology assessments: a scoping review of tools, methods, and practices. Int J Technol Assess Health Care. 2022 Nov 2;38(1):e78.

Appendix 1 Summary of all approaches for performing meta-analysis of economic evaluations

1. INB approach: In this approach, improvements in health outcomes are valued at a CE threshold of $ per QALY averted, which converts them to cost units. The benefit in cost units is calculated net of the intervention cost and cost offsets. The INB and variance are estimated according to the five data extraction scenarios based on the availability of data reported in EE studies[3] and pooled across studies stratified by country income level, perspective, and other important factors, using a random-effect model. A positive INB favours the intervention as cost-effective, whereas a negative INB favours the comparator with the intervention being not cost-effective. A limitation of this approach is that it requires an explicit assumption about the cost-effective threshold.

2. Adjusted ICERs: In IHME's approach, the adjusted ICERs are the product of two estimates: a) the meta-regression analysis of ICERs in quadrant 2, and b) a logistic regression analysis of the probability that a cost-effective result is in quadrant 4 vs 2. The predicted ICERs are adjusted downward by an estimated probability. Cost-effective interventions are selected by ranking ICERs from lowest to highest rather than relying on a threshold. A limitation is that the analyses currently exclude results in quadrants 1 and 3. *[1= more costly, less effective; 2= more costly, more effective; 3= less costly, less effective; and 4= less costly, more effective].*

3. Separate meta-analyses of the numerator (ΔC) and the denominator (ΔE): In this approach, predictions are based on separate analyses that are combined into ratios and categorized in quadrants. The limitation is the sample size because some articles report only as ICERs or quadrants. Recently, more articles may be reporting the numerator and denominator in addition to the ICERs and quadrants. ICERs have the additional undesirable property that the ICER is a nonlinear function of the denominator, which violates the assumptions used in the standard additive model used to calculate the pooled effect estimate.

Appendix 2 Discussion on splitting product and non-product costs to calculate threshold cost

There have been a number of discussions among subgroup members about splitting ΔC further to product and non-product costs with the purpose to support transferability of the pooled data. This may allow distinguishing between tradeable and non-tradeable resources, or at least give an indication of the extent to which costs are driven by imported commodities in the analysed studies. Splitting the ΔC to product (i.e., the price paid to the manufacturer for the vaccine), and non-product costs may allow calculation of the threshold cost. Countries might then input their own CET to determine what their threshold cost per dose should be. The disadvantage is that it requires publications to report non-product costs and utilities separately. However, challenges remain in practice to remove product costs from the analysis.

Timeline

Project phase	Project Year 2024 (In months)											
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
IVIR-AC meeting												
#1a Literature review												
#1b Qualitative interview												
#2a Method of MAEE – heterogeneity												
#2b Method of MAEE – weighting												
#2c Exploring other methodological issues												
#3 Developing a toolbox												
IVIR-AC meeting												

We will compile a report detailing our findings and new approaches and present it at the next IVIR-AC meeting and share it with other research communities through published journal articles and conference presentations. Target audience would be policy makers at global and local levels. As we also aim to improve methodology, another group of target audiences will be researchers utilizing our method. We will also provide the summary of our lessons learned from the interviews to those who provided information.

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

30 APRIL 2021, 96th YEAR / 30 AVRIL 2021, 96e ANNÉE
No 17, **2021**, **96**, 133–144
http://www.who.int/wer

Contents

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

Sommaire

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

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

The IVIR-AC recommendations are based on discussions during a virtual meeting of the IVIR-AC held 1–5 March 2021.

COVID-19 vaccine modelling

The WHO COVID-19 Vaccine Impact Modelling Subgroup of the WHO Strategic Advisory Group of Experts on Immunization (SAGE) Working Group on COVID-19 Vaccines provides modelling guidance to inform global policy recommendations related to prioritization of COVID-19 vaccines. In September 2020, IVIR-AC reviewed an initial set of modelling questions developed by the Subgroup. These were part of a Request for Information that was shared with modelling groups which have since presented work on these topics to the SAGE Working Group and Subgroup. In January 2021, the Subgroup issued a Request for Proposals (RFP) that addressed priority questions and gaps in modelling evidence. The results of the RFP, expected in mid-2021, will enable SAGE to further develop vaccine product-specific guidance and policy recommendations. To inform this process, IVIR-AC was asked to identify additional priority areas for vaccine modelling and ways to incorporate additional evidence into the SAGE *Evidence to Recommendations* (E2R) process.[1]

[1] Evidence to recommendations for COVID-19 vaccines: evidence framework (https://www.who.int/publications/i/item/WHO-2019-nCoV-SAGE-Framework-Evidence-2020-1; accessed March 2021).

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

Les recommandations de l'IVIR-AC présentées ici sont basées sur les discussions qui ont eu lieu lors d'une réunion virtuelle du Comité qui s'est tenue du 1er au 5 mars 2021.

Modélisation des vaccins contre la COVID-19

Le sous-groupe de l'OMS chargé de la modélisation de l'impact des vaccins anti-COVID-19 au sein du groupe de travail sur les vaccins anti-COVID-19 du Groupe stratégique consultatif d'experts de l'OMS (SAGE) sur la vaccination fournit des conseils en matière de modélisation afin d'éclairer les recommandations stratégiques mondiales relatives à l'établissement des priorités de vaccination contre la COVID-19. En septembre 2020, l'IVIR-AC a examiné une première série de questions de modélisation préparées par le sous-groupe. Celles-ci faisaient partie d'une demande d'information partagée avec des groupes de modélisation qui ont depuis présenté des travaux sur ces sujets au groupe de travail et au sous-groupe du SAGE. En janvier 2021, le sous-groupe a émis un appel à propositions visant à répondre aux questions prioritaires et à combler les lacunes dans les données de modélisation. Les résultats de cet appel à propositions, attendus pour le milieu de l'année 2021, permettront au SAGE de poursuivre l'élaboration d'orientations et de recommandations stratégiques spécifiques aux différents vaccins. A cette fin, il a été demandé à l'IVIR-AC d'identifier d'autres domaines prioritaires pour la modélisation des vaccins et des moyens d'intégrer des données probantes supplémentaires dans le processus du SAGE pour élaborer des recommandations à partir des preuves scientifiques *(Evidence to Recommendations)*.[1]

[1] Evidence to recommendations for COVID-19 vaccines: evidence framework (https://www.who.int/publications/i/item/WHO-2019-nCoV-SAGE-Framework-Evidence-2020-1; consulté en mars 2021).

Summary of IVIR-AC feedback and recommendations

IVIR-AC commended the tremendous work of the Subgroup in summarizing the outputs from 30 different modelling groups and confirmed that the modelling supports vaccine prioritization as described in the SAGE Roadmap.[2]

IVIR-AC recommended:

- for SAGE to modify the *E2R* tables to enable product comparisons, to use product-specific characteristics in models, and to consider prioritizing products for specific populations or countries on the basis of modelled parameters and feasibility of implementation;
- inclusion of additional modelling questions;[3]
- evaluation of the models' suitability for addressing particular questions and consideration of including more diverse model types (e.g. immune dynamics or population genetics);
- modelling the impact of new variants, prioritizing vaccine effectiveness, and including feasibility of vaccine implementation when determining vaccine formulation priorities;
- maintaining ongoing surveillance systems that collect high-quality data on duration of immunity, vaccine-specific effectiveness, and short- and long-term vaccine safety issues; and
- improving and informing models by filling the evidence gap on social and behavioural drivers of vaccination and interventions to address these (non-pharmaceutical interventions).

Optimizing COVID- 19 vaccine costing

The E2R "resource use" criterion required as part of COVID-19 vaccine-specific recommendations utilized by SAGE presents several challenges. IVIR-AC provided feedback on how best to interpret and apply the criterion to global and country-level costing for decision-making on COVID-19 vaccination. IVIR-AC also discussed the most appropriate approaches/tools for estimation of COVID-19 vaccine-related costs.

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

L'IVIR-AC a salué le travail considérable accompli par le sous-groupe pour résumer les résultats de 30 groupes de modélisation différents et a confirmé que la modélisation aide à l'établissement des priorités de vaccination tel que décrit dans la feuille de route du SAGE.[2]

L'IVIR-AC a recommandé:

- au SAGE de modifier les tableaux des recommandations élaborées à partir des preuves scientifiques de manière à pouvoir comparer les produits, d'utiliser les caractéristiques spécifiques des différents produits dans les modèles, et d'envisager la priorisation des produits pour des populations ou des pays particuliers sur la base des paramètres modélisés et de la faisabilité de la mise en œuvre;
- d'intégrer des questions de modélisation supplémentaires;[3]
- d'évaluer l'aptitude des modèles à répondre à des questions particulières et d'envisager la possibilité d'inclure des types de modèles plus divers (par exemple la dynamique immunitaire ou la génétique des populations);
- de modéliser l'impact des nouveaux variants, de hiérarchiser l'efficacité vaccinale et de prendre en compte de la faisabilité de leur mise en œuvre lors de la détermination des priorités en matière de formulations des vaccins;
- de maintenir des systèmes de surveillance continue qui collectent des données de qualité sur la durée de l'immunité, sur l'efficacité spécifique des différents vaccins et sur la sécurité des vaccins à court et à long terme; et
- d'améliorer et d'alimenter les modèles grâce au recueil de données probantes, actuellement insuffisantes, sur les facteurs sociaux et comportementaux de la vaccination et les interventions nécessaires pour y répondre (interventions non pharmaceutiques).

Optimisation de l'établissement des coûts de la vaccination contre la COVID-19

Le critère «utilisation des ressources» des recommandations élaborées à partir des preuves scientifiques, requis dans le cadre des recommandations spécifiques aux différents vaccins anti-COVID-19 et utilisé par le SAGE, pose plusieurs difficultés. L'IVIR-AC a présenté ses observations sur la meilleure façon d'interpréter et d'appliquer ce critère au calcul des coûts aux niveaux mondial et national en vue de la prise de décisions concernant la vaccination contre la COVID-19. Le Comité a également discuté des approches/outils les plus appropriés pour estimer ces coûts.

[2] WHO SAGE roadmap for prioritizing uses of COVID-19 vaccines in the context of limited supply (https://www.who.int/publications/m/item/who-sage-roadmap-for-prioritizing-uses-of-covid-19-vaccines-in-the-context-of-limited-supply; accessed March 2021).

[3] For instance: What are the effects of prior infection on vaccine efficacy? What is the acceptable lower limit of vaccine effectiveness for specific priority groups? What is the impact of vaccine hesitancy at the national level? What is the appropriate vaccination strategy for settings with no cases? In the context of supply shortages for 2-dose vaccines, should the focus be on vaccinating as many people as possible with one dose or preserving the vaccine supply to ensure that the second dose can be administered at the recommended interval? What is the benefit and immunological impact of alternative dosing strategies (e.g. 6-month booster), based on clinical evidence of waning immunity? What is the best dosing combination?

[2] Feuille de route du SAGE de l'OMS pour l'établissement des priorités concernant l'utilisation des vaccins anti-Covid-19 dans un contexte d'approvisionnement limité (https://www.who.int/fr/publications/m/item/who-sage-roadmap-for-prioritizing-uses-of-covid-19-vaccines-in-the-context-of-limited-supply; consulté en mars 2021).

[3] Par exemple: Quels sont les effets d'une précédente infection sur l'efficacité des vaccins? Quelle est la limite inférieure acceptable de l'efficacité vaccinale pour des groupes prioritaires donnés? Quel est l'impact de la réticence à la vaccination au niveau national? Quelle stratégie de vaccination envisager pour les milieux où il n'y a pas de cas? Dans le contexte d'une pénurie de vaccins nécessitant l'administration de 2 doses, faut-il privilégier la vaccination du plus grand nombre de personnes possible avec une seule dose ou gérer le stock de vaccins de manière à pouvoir administrer la seconde dose à l'intervalle recommandé? Quels sont les avantages et l'impact immunologique d'autres stratégies de vaccination (par exemple une dose de rappel tous les 6 mois), d'après les données cliniques disponibles sur la baisse de l'immunité? Quelle est le meilleur schéma posologique?

Summary of IVIR-AC feedback and recommendations

IVIR-AC stressed that the health sector perspective alone is not sufficient to decide vaccine rollout as it will not capture the macroeconomic impact of COVID-19. Consequently, the Advisory Committee recommended:

- to evaluate, interpret and communicate COVID-19 vaccine resources needed within the context of broader cost implications (e.g. global economic impact estimated at US$ 28 trillion by the International Monetary Fund);
- to consider the breadth of health system's constraints and cost implications; and
- to account for health systems strengthening, at least within the discussion of benefits (including the potential for enhanced testing and treatment, and for strengthening non-COVID-19 essential services).

IVIR-AC provided guidance on estimation approaches and tools, as follows:

- Collect and analyse detailed, case-relevant costs (e.g. delivery and human resources costs) for country-level decision-making.
- Prioritize the use of different types of cost estimates for global-level resource mobilization and budgeting.
- Consider the substantial budget impact in low- and middle-income countries (LMICs), including health system constraints such as limited human resources (in both numbers and skills) and physical infrastructure for vaccine delivery (e.g. cold chain capacity, vaccination sites).
- Consider the potential opportunity costs of vaccine rollout – i.e. that vaccination can significantly take human resources away from their regular duties and may jeopardize the maintenance of essential health services in the short term.
- Consider how COVID-19 vaccination can help strengthen local health systems, including, for instance: the development of adult immunization delivery platforms; the development of responsive testing, diagnosis and treatment capacity; and the strengthening of non-COVID essential services (e.g. current Expanded immunization programmes) in the long term.

IVIR-AC highlighted the importance of cost and resource estimates within economic evaluations at the local, country level, which will depend on local vaccine prices, coverage targets, vaccine delivery strategies (e.g. campaign vs. routine delivery), human resources implications, and cold chain maintenance investments.

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

L'IVIR-AC a souligné que la perspective du secteur de la santé ne suffit pas à elle seule pour décider du déploiement des vaccins, car elle ne permet pas de saisir l'impact macroéconomique de la COVID-19. Par conséquent, le Comité a recommandé:

- d'évaluer, d'interpréter et de communiquer les ressources nécessaires pour la vaccination contre la COVID-19 en tenant compte d'incidences financières plus larges (par exemple l'impact économique mondial estimé à 28 billions de dollars américains par le Fonds monétaire international);
- de prendre en considération l'étendue des contraintes des systèmes de santé et les incidences financières pour ces derniers;
- de tenir compte du renforcement des systèmes de santé, au moins dans le cadre du débat sur les avantages (notamment la possibilité d'améliorer le dépistage et le traitement, et de renforcer les services essentiels non liés à la COVID-19).

L'IVIR-AC a fourni les conseils suivants concernant les approches et les outils d'estimation des coûts:

- recueillir et analyser les coûts détaillés et pertinents à la situation (par exemple les coûts de la délivrance et des ressources humaines) aux fins de la prise de décisions au niveau national;
- établir des priorités dans l'utilisation de différents types d'estimations des coûts en vue de la mobilisation des ressources et la budgétisation au niveau mondial;
- tenir compte de l'impact budgétaire important dans les pays à revenu faible et intermédiaire, notamment en raison des contraintes des systèmes de santé telles que des ressources humaines limitées (en termes d'effectifs et de compétences) et de l'infrastructure nécessaire pour la délivrance des vaccins (par exemple la chaîne du froid, les sites de vaccination);
- tenir compte des coûts d'opportunité potentiels du déploiement des vaccins: la vaccination peut en effet détourner notablement les ressources humaines de leurs tâches habituelles et peut compromettre le maintien des services de santé essentiels à court terme;
- examiner la manière dont la vaccination contre la COVID-19 peut contribuer à renforcer les systèmes de santé locaux, par exemple par la mise en place de plateformes de vaccination des adultes; le développement de capacités réactives de dépistage, de diagnostic et de traitement; et le renforcement des services essentiels non liés à la COVID-19 (par exemple les programmes élargis de vaccination actuels) sur le long terme;

L'IVIR-AC a souligné l'importance des estimations des coûts et des ressources dans les évaluations économiques locales et nationales, qui dépendront des prix des vaccins au niveau local, des objectifs de couverture, des stratégies d'administration des vaccins (campagnes de vaccination ou vaccination systématique par exemple), des incidences en termes de ressources humaines et des investissements dans la chaîne du froid.

Measles case fatality ratios

Until now, static age- and country-specific case fatality ratios (CFRs), established by expert opinion and informed by a review of CFR studies in LMICs,[4] have provided the basis for WHO's measles mortality estimates. The review consists of literature with known limitations, including varying case definitions and a lack of representativeness among countries. Newer approaches include a predictive model to estimate CFRs, as outlined in an updated review.[5] To further optimize CFR estimation, the London School of Hygiene and Tropical Medicine presented a new methodology that builds on the updated review utilizing a Bayesian meta-regression platform with spatial disaggregation. IVIR-AC was asked to advise how best to leverage current methods and to give feedback on fixed versus dynamic model trade-offs, additional primary data needs, future approaches for best outputs, and how to navigate plans for estimates in the short term and beyond.

Summary of IVIR-AC feedback and recommendations

Welcoming the extensive literature review and development of a new methodology, IVIR-AC:

- stated that continued updating of the model/data as new studies become available is challenging but necessary;
- strongly recommended that funds and human resources be made available to support the ongoing literature and data review, model developments and generation of CFRs, predictions and projections;
- agreed there is little value in static age- and country-specific CFRs, and that time-varying and updatable CFRs are needed with incidence terms informed by dynamic models; and
- noted that time-varying CFRs will be sensitive to covariate selection and parameter estimates, which may present future methodological challenges.

With respect to the covariates that inform CFR modelling, IVIR-AC supported:

- a clear rationale for covariates that have an explicit link to CFRs and that represent poverty and socio-economic inequalities;

Taux de létalité due à la rougeole

Jusqu'à présent, les estimations OMS de la mortalité due à la rougeole reposaient sur les taux de létalité statiques selon l'âge et le pays, établis par des experts et éclairés par une revue des études sur les taux de létalité dans les pays à revenu faible et intermédiaire.[4] Cette revue porte sur la littérature dont les limites sont connues, notamment des définitions de cas variables et un manque de représentativité parmi les pays. Les approches plus récentes comprennent un modèle prédictif pour estimer les taux de létalité, comme décrit dans une revue actualisée.[5] Pour optimiser davantage l'estimation des taux de létalité, la London School of Hygiene and Tropical Medicine a présenté une nouvelle méthode qui s'appuie sur la revue actualisée en utilisant une plateforme de métarégression bayésienne avec désagrégation spatiale. Il a été demandé à l'IVIR-AC de fournir des conseils sur la meilleure façon d'exploiter les méthodes actuelles et de faire des observations sur les compromis entre modèles fixes et dynamiques, sur les besoins supplémentaires en données primaires, sur les approches futures pour obtenir les meilleurs résultats, et sur la façon de guider les plans pour obtenir des estimations à court terme et au-delà.

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

Se félicitant de cette revue approfondie de la littérature et de l'élaboration d'une nouvelle méthode, l'IVIR-AC:

- a indiqué que l'actualisation continue du modèle et des données au fur et à mesure que de nouvelles études deviennent disponibles est difficile mais nécessaire;
- a fortement recommandé que des fonds et des ressources humaines soient mis à disposition pour appuyer la revue continue de la littérature et des données, le développement de modèles et la génération des taux de létalité, des prédictions et des projections;
- est convenu que les taux de létalité statiques selon l'âge et le pays ont peu d'intérêt et que des taux de létalité variables dans le temps et actualisables sont nécessaires avec des éléments d'incidence éclairés par des modèles dynamiques; et
- a noté que les taux de létalité variables dans le temps seront sensibles au choix des covariables et aux estimations des paramètres, ce qui pourrait poser des difficultés méthodologiques futures.

En ce qui concerne les covariables utiles à la modélisation des taux de létalité, l'IVIR-AC est favorable à:

- une justification claire des covariables qui ont un lien explicite avec les taux de létalité et qui représentent la pauvreté et les inégalités socio-économiques;

[4] Wolfson LJ et al. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. Int J Epidemiol. 2009;38(1):192–205 (https://pubmed.ncbi.nlm.nih.gov/19188207/; accessed March 2021).

[5] Portnoy A et al. Estimates of case-fatality ratios of measles in low-income and middle-income countries: a systematic review and modelling analysis. Lancet Glob Health. 2019;7(4):E472–81 (https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30537-0/fulltext; accessed March 2021).

[4] Wolfson LJ et al. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. Int J Epidemiol. 2009;38(1):192–205 (https://pubmed.ncbi.nlm.nih.gov/19188207/; consulté en mars 2021).

[5] Portnoy A et al. Estimates of case-fatality ratios of measles in low-income and middle-income countries: a systematic review and modelling analysis. Lancet Glob Health. 2019;7(4):E472–81 (https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30537-0/fulltext; consulté en mars 2021).

- possible use of 1) a theoretical model of causal factors that influence disease incidence and progression, and 2) geographical and other markers which represent the most vulnerable populations; and
- possible inclusion of covariates on the short- versus long-term impact of COVID-19 on health-care capacity and the impact on vaccination coverage.

Noting the need for ongoing primary empirical data collection, IVIR-AC encouraged:

- acknowledgement of the importance of vitamin A therapy on CFRs;
- investments in strengthening outbreak investigation and evaluation activities to generate additional primary data;
- creation of a standard CFR study protocol and a structured data collection tool to improve comparability of studies;
- development of a unified research protocol; and
- validation of model predictions against new CFR estimates.

For future approaches IVIR-AC recommended:

- transparency and availability of flexible/analytical methods with user-friendly R[6] packages, clear documentation in a newsletter including bug fixes, discussion forums and case studies; and
- documentation/publication of the methodology in open access peer-reviewed journals.

Overview of the Vaccine Impact Modelling Consortium

The *Vaccine Impact Modelling Consortium* (VIMC)[7] is a multinational collaboration of 16 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. They published a comprehensive modelling study[8] and data visualization tool[9] on the impact of vaccination against 10 pathogens in 98 LMICs. The VIMC collaborates with WHO on the *Immunization Agenda 2030 (IA 2030) Vaccine Impact Estimates* and on COVID-19-related projects, including modelling the impact of interruptions in routine and supplementary immunizations on vaccine preventable diseases (VPDs) in the context of COVID-19.

- l'utilisation éventuelle 1) d'un modèle théorique de facteurs de causalité qui influent sur l'incidence et la progression de la maladie, et 2) de marqueurs géographiques et autres qui représentent les populations les plus vulnérables; et
- l'inclusion éventuelle de covariables pour l'impact à court et à long terme de la COVID-19 sur les capacités des soins de santé et sur la couverture vaccinale.

Notant la nécessité d'un recueil continu de données empiriques primaires, l'IVIR-AC a encouragé:

- la prise en compte de l'importance du traitement par la vitamine A pour les taux de létalité;
- des investissements pour renforcer les activités d'investigation et d'évaluation des épidémies afin de générer des données primaires supplémentaires;
- l'élaboration d'un protocole standard pour les études sur les taux de létalité et d'un outil de recueil de données structuré pour améliorer la comparabilité des études;
- l'élaboration d'un protocole de recherche unifié; et
- la validation des prédictions du modèle par rapport aux nouvelles estimations des taux de létalité.

Pour les approches futures, l'IVIR-AC a recommandé:

- la transparence et la disponibilité de méthodes souples/analytiques avec des paquets R[6] faciles à utiliser, une documentation claire rassemblée dans un bulletin comprenant des corrections de bugs, des forums de discussion et des études de cas; et
- la documentation/publication de la méthode dans des revues à comité de lecture en libre accès.

Aperçu du Vaccine Impact Modelling Consortium

Le *Vaccine Impact Modelling Consortium*[7] est une collaboration multinationale de 16 groupes de recherche financés par l'Alliance Gavi et la Fondation Bill & Melinda Gates. Ce Consortium vise à fournir une approche plus durable, efficace et transparente de la génération des estimations de la charge de morbidité et de l'impact des vaccins. Il a publié une étude de modélisation[8] et un outil de visualisation des données[9] sur l'impact de la vaccination contre 10 agents pathogènes dans 98 pays à revenu faible et intermédiaire. Le Consortium collabore avec l'OMS sur les estimations de l'impact des vaccins dans le cadre du *Programme pour la vaccination à l'horizon 2030* et sur des projets liés à la COVID-19, notamment la modélisation de l'impact des interruptions de la vaccination systématique et des activités de vaccination supplémentaire sur les maladies à prévention vaccinale dans le contexte de la COVID-19.

[6] See https://www.r-project.org/ (accessed March 2021).

[7] See https://www.vaccineimpact.org/ (accessed March 2021).

[8] Li X et al. Estimating the health impact of vaccination against ten pathogens in 98 low-income and middle-income countries from 2000 to 2030: a modelling study. Lancet. 2021;397(10272):398–408 (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32657-X/fulltext; accessed March 2021).

[9] See https://montagu.vaccineimpact.org/2020/visualisation/ (accessed March 2021).

[6] Voir https://www.r-project.org/ (consulté en mars 2021).

[7] Voir https://www.vaccineimpact.org/ (consulté en mars 2021).

[8] Li X et al. Estimating the health impact of vaccination against ten pathogens in 98 low-income and middle-income countries from 2000 to 2030: a modelling study. Lancet. 2021;397(10272):398–408 (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32657-X/fulltext; consulté en mars 2021).

[9] Voir https://montagu.vaccineimpact.org/2020/visualisation/ (consulté en mars 2021).

Summary of IVIR-AC feedback and recommendations

While IVIR-AC members acknowledged VIMC's main objective being to provide GAVI[10] and the Bill & Melinda Gates Foundation[11] with estimates of global vaccine impact, the committee still encouraged modelling of indirect impacts – particularly hospitalizations and immunizations – on the health-care system.

IVIR-AC suggested further clarification on:

- how the model accounts for early detection tools with vaccines such as human papillomavirus (HPV) and hepatitis B virus (HBV) which primarily impact adulthood;
- how to ensure that dynamic models are used for diseases for which herd immunity may be important; and
- any group of VPDs for which the effects of vaccinations in different years are interdependent.

IVIR-AC provided feedback on different methodological issues, namely:

VIMC supporting models:

The utility of the Impact Estimates (IE) method depends on how often coverage estimates are revised and the magnitude of changes in coverage.

General Strategy for VIMC:

Since it seems that IE would work only for small perturbations in coverage estimates, members of IVIR-AC asked whether simple analytics could be developed to check if IE is likely to be robust for a given revision of coverage. It would also be helpful to clarify whether mortality rates from United National World Population Prospects (UNWPP) have accounted for deaths due to VPDs when they are used in the VIMC calculations and to know the assumption regarding the impact of vaccines on death rates in UNWPP.

Interim estimates:

Proposed case study: Does IE provide robust approximation of the effect of coverage drop attributable to COVID-19?

Meta-analysis of economic evaluations

Meta-analyses (MA) are useful for quantitative pooling of results from multiple studies to create more reliable estimates of the effectiveness of an intervention. Application of this approach to economic evaluations (EE) is under consideration and may be useful in countries that lack the capacity to do their own cost-effectiveness (CE)

[10] See https://www.gavi.org/ (accessed March 2021).

[11] See https://www.gatesfoundation.org/ (accessed March 2021).

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

Si les membres de l'IVIR-AC ont reconnu que l'objectif principal du Consortium était de fournir à l'Alliance Gavi[10] et à la Fondation Bill & Melinda Gates[11] des estimations de l'impact des vaccins à l'échelle mondiale, le Comité a néanmoins encouragé la modélisation des impacts indirects – en particulier les hospitalisations et les vaccinations – sur le système des soins de santé.

L'IVIR-AC a suggéré de clarifier plus avant:

- la manière dont le modèle tient compte des outils de détection précoce avec des vaccins tels que ceux contre le papillomavirus humain (PVH) et le virus de l'hépatite B (VHB) qui ont principalement un impact à l'âge adulte;
- la façon de s'assurer que des modèles dynamiques sont utilisés pour les maladies pour lesquelles l'immunité collective peut être importante; et
- les groupes de maladies à prévention vaccinale pour lesquels les effets des vaccinations à différents moments (années) sont interdépendants.

L'IVIR-AC a présenté des observations sur différentes questions méthodologiques, présentées ci-après.

Modèles pour le Consortium

L'utilité de la méthode pour établir les estimations d'impact dépend de la fréquence de la révision des estimations de la couverture et de l'ampleur de l'évolution de la couverture.

Stratégie générale pour le Consortium

Puisque les estimations d'impact semblent ne s'appliquer que pour des changements minimes dans les estimations de la couverture, les membres de l'IVIR-AC ont demandé s'il était possible de développer une méthode analytique simple pour vérifier la robustesse des estimations d'impact pour une révision donnée de la couverture. Il serait également utile de préciser si les taux de mortalité issus des United National World Population Prospects (UNWPP) ont pris en compte les décès dus aux maladies à prévention vaccinale lorsqu'ils sont utilisés dans les calculs du Consortium et de connaître l'hypothèse concernant l'impact des vaccins sur les taux de mortalité utilisée dans les UNWPP.

Estimations provisoires

Proposition d'étude de cas: Les estimations d'impact fournissent-elles une approximation robuste de l'effet de la baisse de la couverture attribuable à la COVID-19?

Méta-analyses des évaluations économiques

Les méta-analyses sont utiles pour le regroupement quantitatif des résultats de plusieurs études afin de créer des estimations plus fiables de l'efficacité d'une intervention. L'application de cette approche aux évaluations économiques est à l'étude et pourrait s'avérer utile dans les pays qui n'ont pas la capacité de réaliser leurs propres études coût-efficacité.

[10] Voir https://www.gavi.org/ (consulté en mars 2021).

[11] Voir https://www.gatesfoundation.org/ (consulté en mars 2021).

studies. However, the utility of MA for EE is subject to scientific debate following publication of the first methodology paper by Crespo *et al*[12] in 2014 and a systematic review on the use of MA for EE studies[13] in 2019. IVIR-AC considered several examples (rotavirus vaccine, anticoagulants, diabetes medications) and provided feedback on the value and limitations of using MA for EE.

Summary of IVIR-AC feedback and recommendations

IVIR-AC agreed that:

- MA for EE could facilitate decision-making in countries without context-specific EEs.
- The EE literature is heterogeneous, highly dependent on input parameters, methodological and with modelling choices in each study, which can make it difficult for informing global-level decision-making and policy.
- MA of CE studies is not straightforward, as the incremental cost-effectiveness ratio (ICER) is not normally distributed, 95% confidence intervals for the ICER cannot be validly estimated, and interpretation of the ICER is not straightforward (e.g. a negative ICER could indicate a cost-saving or dominated strategy).

IVIR-AC recommended that:

- High-quality, locally-produced and context-/country-specific EE should be maintained as the priority for decision-making over MA for EE.

Harmonization of inputs across studies:

- Consistent currency years should be used for costs (e.g. 2021 $).
- There should be a focus on scenarios in order to extract variance/covariance of incremental costs and incremental effectiveness separately.
- Caution is required when assuming that incremental effectiveness is distributed normally because this may not be the case for infectious disease interventions.
- Contextual differences in the stratification of EEs should be considered.

Toutefois, l'utilité des méta-analyses des évaluations économiques fait l'objet d'un débat scientifique depuis la publication du premier article méthodologique de Crespo *et al.*[12] en 2014 et d'une revue systématique sur l'utilisation des méta-analyses pour les études d'évaluations économiques[13] en 2019. L'IVIR-AC a examiné plusieurs exemples (vaccin contre le rotavirus, anticoagulants, médicaments pour le diabète) et a présenté des observations sur la valeur et les limites de l'utilisation des méta-analyses pour les évaluations économiques.

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

L'IVIR-AC est convenu de ce qui suit:

- les méta-analyses des évaluations économiques pourraient faciliter la prise de décisions dans les pays ne disposant pas d'évaluations économiques spécifiques au contexte;
- la littérature sur les évaluations économiques est hétérogène et ces évaluations dépendent fortement des paramètres d'entrée, de la méthodologie et des choix de modélisation de chaque étude; l'exploitation de ces évaluations pour éclairer la prise de décisions et les politiques peut donc s'avérer difficile;
- les méta-analyses des études coût-efficacité ne sont pas simples, car le rapport coût-efficacité différentiel (ICER) ne suit pas une distribution normale, les intervalles de confiance à 95% pour l'ICER ne peuvent pas être estimés de manière valable, et l'interprétation de l'ICER est délicate (par exemple un ICER négatif peut indiquer une stratégie d'économie ou une stratégie dominée).

Recommandations de l'IVIR-AC:

- continuer à privilégier des évaluations économiques de qualité, produites localement et spécifiques au contexte/pays dans la prise de décisions par rapport aux méta-analyses des évaluations économiques.

Harmonisation des données d'entrée utilisées dans les études

- Utiliser des années monétaires cohérentes pour les coûts (par exemple $ 2021).
- Mettre l'accent sur les scénarios afin d'extraire séparément la variance/covariance des coûts différentiels et de l'efficacité différentielle.
- Faire preuve de prudence lorsqu'on suppose que l'efficacité différentielle suit une distribution normale, car cela peut ne pas être le cas pour les interventions en matière de maladies infectieuses.
- Prendre en compte les différences contextuelles dans la stratification des évaluations économiques.

[12] Crespo C et al. Comparative efficiency research (COMER): meta-analysis of cost-effectiveness studies. BMC Med Res Methodol. 2014;14:139.

[13] Systematic review journal: submitted 2019; BMJ Open Diabetes Res Care. 2020;8(1):e001020; Open Forum Infect Dis. 2019;6(4):ofz117; Value Health. 2019;22(12):1458–69.

[12] Crespo C et al. Comparative efficiency research (COMER): meta-analysis of cost-effectiveness studies. BMC Med Res Methodol. 2014;14:139.

[13] Systematic review journal: submitted 2019; BMJ Open Diabetes Res Care. 2020;8(1):e001020; Open Forum Infect Dis. 2019;6(4):ofz117; Value Health. 2019;22(12):1458–69.

Synthesis of EE estimates:

- When pooling estimates of incremental net benefits across studies, the estimates should be unweighted or weighted by study quality instead of by inverse variance.
- Develop a grid of criteria for assessing study quality to enable quantitative assessment and weighting.
- Exclude poor-quality studies from sensitivity analyses.

Additional desirable outputs:

- Document and explain major sources of variation and heterogeneity in the CE/ICER estimates, as well as uncertainty about the selected sample of studies, in order to identify regions where more studies are needed.
- To the extent that it is feasible, provide estimates for typical country groupings.

As a "public good" IVIR-AC recommended:

- An open-access data-sharing repository should be created to gather all underlying inputs, data sources, codes and detailed documentation.
- Synergies with other efforts/groups should be considered.

Full Public Health Value of Vaccines – influenza vaccine

In order to inform the implementation of a seasonal influenza vaccine programme and to drive innovative research for next-generation influenza vaccines for LMICs, WHO aims to develop a Full Public Health Value of Vaccines (FPHVV) assessment for influenza vaccines. As a first step, WHO developed methods and approaches for developing use cases and country archetypes for seasonal influenza vaccine. IVIR-AC provided feedback on the overall methodology for developing and validating these draft use cases and country archetypes.

Summary of IVIR-AC feedback and recommendations

IVIR-AC agreed that:

- Country decision-making processes are relevant to consider and are unique to each country. Seasonal influenza vaccine is one of several new vaccines being recommended for introduction in many countries and for which principles and scenarios exist to guide both the decision-making and the process. Use cases and country archetypes are other innovative approaches.
- The approach to developing use cases addresses an important policy need and is important for informing country programme strategies, market-shaping

Synthèse des estimations des évaluations économiques

- Lors du regroupement des estimations des avantages nets différentiels issues des études, il convient de ne pas pondérer les estimations ou de les pondérer par la qualité de l'étude plutôt que par l'inverse de la variance.
- Elaborer une grille de critères d'évaluation de la qualité des études pour permettre une évaluation quantitative et une pondération.
- Exclure les études de mauvaise qualité des analyses de sensibilité.

Autres résultats souhaitables

- Documenter et expliquer les principales sources de variation et d'hétérogénéité dans les estimations des données coût-efficacité/ICER, ainsi que l'incertitude concernant l'échantillon d'études sélectionné, afin d'identifier les régions où davantage d'études sont nécessaires.
- Dans la mesure du possible, fournir des estimations pour des groupes de pays types.

Considérant qu'il s'agit d'un «bien public», l'IVIR-AC a recommandé:

- la création d'un référentiel de partage de données en libre accès pour rassembler tous les intrants sous-jacents, les sources de données, les codes et les documents détaillés;
- la mise en place de synergies avec d'autres travaux/groupes.

La pleine valeur des vaccins pour la santé publique – vaccin contre la grippe

Afin d'éclairer la mise en œuvre d'un programme de vaccination contre la grippe saisonnière et de stimuler une recherche innovante sur les vaccins antigrippaux de nouvelle génération pour les pays à revenu faible et intermédiaire, l'OMS cherche à mettre en place une évaluation de la pleine valeur des vaccins pour la santé publique concernant les vaccins antigrippaux. Dans un premier temps, l'OMS a élaboré des méthodes et des approches pour développer des scénarios d'utilisation et des archétypes de pays pour le vaccin contre la grippe saisonnière. L'IVIR-AC a fourni des observations sur la méthodologie globale de développement et de validation de ces projets de scénarios d'utilisation et d'archétypes de pays.

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

L'IVIR-AC est convenu de ce qui suit:

- il est pertinent de prendre en compte les processus de décision nationaux, qui sont propres à chaque pays. Le vaccin contre la grippe saisonnière est l'un des nombreux nouveaux vaccins dont l'introduction est recommandée dans de nombreux pays et pour lesquels il existe des principes et des scénarios pour guider à la fois la prise de décisions et le processus. Les scénarios d'utilisation et les archétypes de pays constituent d'autres approches innovantes;
- l'élaboration de scénarios d'utilisation répond à un besoin politique important et est très utile pour éclairer les stratégies des programmes nationaux, la structuration du

and possibly short-term product development. This approach should be undertaken. However, as the value proposition is developed further there will need to be clarification as to how the approach informs a value proposition for universal influenza vaccines (even as first step), as well as broader country-level and global strategic goals.

IVIR-AC recommended that:

- Concerns about the conceptual framework, the dimensions and the country archetypes/use cases should be clarified.
- The conceptual framework and the pathway should be elaborated from a use case for current influenza vaccines to universal influenza vaccines.

- The public health goals of seasonal influenza vaccines in different countries should be understood before considering the product characteristics and target population.
- The definition of geographical location should be considered.
- The use of data-clustering techniques to define archetypes should be explored; in this regard it could be helpful to include a data scientist in the team.
- Market, policy and programmatic factors should be considered – including procurement mechanisms, strength of the National Immunization Technical Advisory Group, service delivery, decision-making factors, cold chain and vaccine hesitancy. A country's delivery capacity could also be taken into account – such as high capacity (e.g., annual adult influenza vaccine given prior to pandemic; high access; multiple service points; trained workforce), low capacity (e.g., no previous adult influenza vaccination prior to pandemic; limited service access with remote communities; significant workforce limitations or need for training), and medium capacity.

- There must be consideration of how COVID-19 vaccine implementation may change the overall approach, use case and future availability of seasonal and pandemic influenza vaccines.

Immunization Agenda 2030 (IA 2030) – vaccine impact estimates

In September 2020, IVIR-AC gave recommendations on the framework and methods proposed for estimating future deaths averted due to vaccination, as part of the *IA2030 Agenda: A Global Strategy to Leave No One Behind.*[14] At its March 2021 meeting, IVIR-AC evaluated follow-up to previous recommendations, reviewed

marché et éventuellement le développement de produits à court terme. Cette approche doit être entreprise. Toutefois, au fur et à mesure de l'élaboration de la proposition de valeur, il conviendra de clarifier la manière dont cette approche éclaire une proposition de valeur pour les vaccins antigrippaux universels (même dans un premier temps), ainsi que des objectifs stratégiques plus larges aux niveaux national et mondial.

Recommandations de l'IVIR-AC:

- il convient de clarifier les préoccupations concernant le cadre conceptuel, les dimensions et les archétypes de pays/scénarios d'utilisation;
- le cadre conceptuel et le cheminement doivent être élaborés à partir d'un scénario d'utilisation des vaccins antigrippaux actuels jusqu'aux vaccins antigrippaux universels;
- il est nécessaire de comprendre les objectifs de santé publique des vaccins contre la grippe saisonnière dans les différents pays avant d'envisager les caractéristiques des produits et la population cible;
- il convient d'envisager la définition de l'emplacement géographique;
- l'utilisation de techniques de regroupement de données pour définir les archétypes mérite d'être explorée; à cet égard, il pourrait être utile d'inclure un spécialiste en science des données dans l'équipe;
- les facteurs liés au marché, aux politiques et aux programmes doivent être pris en compte, notamment les mécanismes d'achat, la solidité des groupes consultatifs techniques nationaux sur la vaccination, la prestation de services, les facteurs décisionnels, la chaîne du froid et la réticente à l'égard des vaccins. La capacité de prestation d'un pays pourrait également être prise en compte: capacité élevée (par exemple un vaccin annuel contre la grippe chez l'adulte administré avant la pandémie; un large accès; de multiples points de service; une main-d'œuvre formée), faible capacité (par exemple aucune vaccination contre la grippe chez l'adulte avant la pandémie; un accès limité aux services dans les communautés éloignées; une main-d'œuvre très limitée ou insuffisamment formée) et capacité moyenne;
- il faut examiner la manière dont la mise en œuvre des vaccins contre la COVID-19 peut modifier l'approche globale, le scénario d'utilisation et la disponibilité future des vaccins contre la grippe saisonnière et pandémique.

Programme pour la vaccination à l'horizon 2030 – estimations de l'impact des vaccins

En septembre 2020, l'IVIR-AC a formulé des recommandations sur le cadre et les méthodes proposés pour estimer les futurs décès évités grâce à la vaccination, dans le cadre du *Programme pour la vaccination à l'horizon 2030: Une stratégie mondiale pour ne laisser personne de côté.*[14] Lors de sa réunion de mars 2021, l'IVIR-AC a évalué le suivi des recommandations précé-

[14] Immunization Agenda 2030: A Global Strategy to Leave No One Behind. https://www.who.int/teams/immunization-vaccines-and-biologicals/strategies/ia2030 (accessed 26 March 2021).

[14] 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 le 26 mars 2021).

updates to proposed methodologies, and evaluated preliminary results.

Summary of IVIR-AC feedback and recommendations

- For the statistical modelling, IVIR-AC recommended giving more details on:
  - the different input covariates; variance of the covariates; explanations of observed uncertainties; and the advantages and disadvantages of the different models tested;
  - how the model accounts for the attributable reduction in mortality that is not due to vaccines (e.g. the differences in health-care services across VPDs, between countries and over time);
  - how the IA2030 impact model accounts for herd immunity.
- IVIR-AC further recommended presenting vaccine impact estimates for high-income countries separately as it was unclear whether use of the IA2030 statistical model to extrapolate the VIMC estimates to these countries would produce results consistent with existing high-income country estimates (i.e. from WHO's Regional Office for Europe, the Centers for Disease Control and Prevention in the USA and Public Health England). Validation was needed to ensure consistency.
- IVIR-AC reiterated the importance of communicating information on key WHO websites in a clear and accessible manner. The "deaths averted" figure currently available is widely used but its sources and references are hard to find.
- IVIR-AC stressed the need to clarify whether the mortality rates from UNWPP have accounted for deaths due to VPDs when they are used to parameterize the IA2030 impact model.

IA 2030 costing

WHO collaborates with the International Vaccine Access Center (IVAC) at Johns Hopkins University to generate global and regional cost estimates for implementing the IA2030 Global Strategy from 2021 to 2030. These estimates include vaccine costs (vaccine price, cost of injection supplies, freight costs) and immunization delivery costs (labour, storage, transportation, other capital costs and other recurrent costs). IVIR-AC gave feedback on the proposed costing methodology and identification of data gaps between IVAC's previous model[15] and IA2030 objectives.

dentes, examiné les mises à jour des méthodes proposées et évalué les résultats préliminaires.

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

- Pour la modélisation statistique, l'IVIR-AC a recommandé de donner plus de détails sur:
  - les différentes covariables d'entrée; la variance des covariables; les explications des incertitudes observées; et les avantages et inconvénients des différents modèles testés;
  - la manière dont le modèle tient compte de la fraction attribuable de la réduction de la mortalité qui n'est pas due aux vaccins (par exemple les différences dans les services de soins de santé pour les différentes maladies à prévention vaccinale, entre les pays et dans le temps);
  - la manière dont le modèle d'estimation de l'impact tient compte de l'immunité collective.
- L'IVIR-AC a également recommandé de présenter séparément les estimations de l'impact des vaccins pour les pays à revenu élevé, car il n'est pas certain que l'utilisation du modèle statistique du Programme pour la vaccination 2030 pour extrapoler les estimations pour le Consortium à ces pays produise des résultats cohérents avec les estimations existantes pour les pays à revenu élevé (c'est-à-dire celles du Bureau régional OMS de l'Europe, des *Centers for Disease Control and Prevention* aux États-Unis d'Amérique et de *Public Health England*). Une validation est nécessaire pour garantir la cohérence.
- L'IVIR-AC a réitéré l'importance de communiquer les informations sur les sites Web clés de l'OMS de manière claire et accessible. Le chiffre des «décès évités» actuellement disponible est largement utilisé, mais ses sources et références sont difficiles à trouver.
- L'IVIR-AC a souligné la nécessité de préciser si les taux de mortalité issus des UNWPP ont pris en compte les décès dus aux maladies à prévention vaccinale lorsqu'ils sont utilisés pour paramétrer le modèle d'impact du Programme pour la vaccination 2030.

Etablissement des coûts du Programme pour la vaccination à l'horizon 2030

L'OMS collabore avec l'International Vaccine Access Center (IVAC) de l'Université Johns Hopkins pour générer des estimations mondiales et régionales des coûts de la mise en œuvre de la stratégie mondiale du Programme pour la vaccination pour la période 2021-2030. Ces estimations comprennent les coûts des vaccins (prix du vaccin, coût du matériel d'injection, frais de transport) et les coûts de la délivrance des vaccins (main-d'œuvre, stockage, transport, autres coûts d'investissement et autres coûts récurrents). L'IVIR-AC a présenté ses observations sur la méthode de calcul des coûts proposée et sur l'identification des lacunes dans les données entre le modèle précédent[15] de l'IVAC et les objectifs du Programme pour la vaccination à l'horizon 2030.

[15] Sim YS et al. Return on investment from immunization against 10 pathogens in 94 low- and middle-income countries, 2011–30. Health Aff. 2020;39(8): (https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2020.00103; accessed March 2021).

[15] Sim YS et al. Return on investment from immunization against 10 pathogens in 94 low- and middle-income countries, 2011–30. Health Aff. 2020;39(8): (https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2020.00103; consulté en mars 2021).

Summary of IVIR-AC feedback and recommendations

The Advisory Committee noted that:

- The proposed plan for analysis is comprehensive and methodologically robust with sensitivity and scenario analysis; the scope, scale and perspective are clearly defined; and the distinction between vaccine cost and delivery cost is helpful in terms of resource generation and allocation.
- Updating the analysis with the latest vaccine demand, coverage and price estimates is a step in the right direction.
- It is important to ensure model availability, transparency and accessibility.

In addition:

- IVIR-AC suggested that future analyses should account for costs incurred by the beneficiaries who are immunized (e.g. transportation, lost productive time due to immunization sessions) in both the public and private sectors. These costs will have implications for potential interventions such as conditional cash transfers or country strategies to strengthen health systems.
- IVIR-AC recommended that future work should incorporate detailed information about public and private sector-specific contributions to coverage rates and variation in prices.
- The communication team should link cost estimates to the vaccine impact estimates as part of the IA2030 Global Strategy.
- IVIR-AC reiterated the importance of timely release of updated costing and impact estimates, including updated methods or source data and limitations. ■

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

Le Comité consultatif a noté que:

- le plan d'analyse proposé est complet et méthodologiquement solide, avec l'analyse de la sensibilité et des scénarios; la portée, l'échelle et la perspective sont clairement définies; et la distinction entre le coût des vaccins et le coût de la délivrance des vaccins est utile en termes de génération et d'allocation des ressources;
- la mise à jour de l'analyse avec les dernières estimations de la demande, de la couverture et du prix des vaccins est un pas dans la bonne direction;
- il est important de garantir la disponibilité, la transparence et l'accessibilité des modèles.

En outre:

- l'IVIR-AC a suggéré que les analyses futures tiennent compte des coûts supportés par les personnes vaccinées (par exemple le transport, le temps de travail perdu en raison des séances de vaccination) dans les secteurs public et privé. Ces coûts auront des répercussions sur les interventions potentielles telles que le versement conditionnel d'une somme d'argent ou les stratégies nationales de renforcement des systèmes de santé;
- l'IVIR-AC a recommandé que les travaux futurs intègrent des informations détaillées sur les contributions spécifiques des secteurs public et privé aux taux de couverture et à la variation des prix;
- l'équipe chargée de la communication doit établir un lien entre les estimations des coûts et les estimations de l'impact des vaccins dans le cadre de la stratégie mondiale du Programme pour la vaccination 2030;
- l'IVIR-AC a réitéré l'importance de la publication en temps utile des estimations actualisées des coûts et de l'impact des vaccins, y compris les méthodes ou les données sources actualisées et leurs limites. ■

How to obtain the WER through the Internet

(1) WHO WWW server: Use WWW navigation software to connect to the WER pages at the following address: **http://www.who.int/wer/**

(2) An e-mail subscription service exists, which provides by electronic mail the table of contents of the WER, together with other short epidemiological bulletins. To subscribe, send a message to **listserv@listserv.who.int**. The subject field should be left blank and the body of the message should contain only the line subscribe wer-reh. A request for confirmation will be sent in reply.

Comment accéder au REH sur Internet?

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

2) Il existe également un service d'abonnement permettant de recevoir chaque semaine par courrier électronique la table des matières du REH ainsi que d'autres bulletins épidémiologiques. Pour vous abonner, merci d'envoyer un message à **listserv@listserv.who.int** en laissant vide le champ du sujet. Le texte lui même ne devra contenir que la phrase suivante: subscribe wer-reh. Une demande de confirmation vous sera envoyée en retour.

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

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

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

Avian influenza	**https://www.who.int/influenza/human_animal_interface**	Grippe aviaire
Buruli ulcer	**http://www.who.int/buruli**	Ulcère de Buruli
Child and adolescent health and development	**http://www.who.int/child_adolescent_health**	Santé et développement des enfants et des adolescents
Cholera	**http://www.who.int/cholera**	Choléra
COVID-19	**https://www.who.int/emergencies/diseases/novel-coronavirus-2019**	Maladie à coronavirus 2019 (COVID-19)
Dengue	**http://www.who.int/denguecontrol**	Dengue
Ebola virus disease	**https://www.who.int/health-topics/ebola/#tab=tab_1**	Maladie à virus Ebola
Emergencies	**https://www.who.int/emergencies**	Situations d'urgence sanitaire
Epidemic and pandemic diseases	**https://www.who.int/emergencies/diseases**	Maladies épidémiques et pandémiques
Eradication/elimination programmes	**http://www.who.int/topics/infectious_diseases**	Programmes d'éradication/élimination
Fact sheets on infectious diseases	**http://www.who.int/topics/infectious_diseases/factsheets**	Aide-mémoires sur les maladies infectieuses
Filariasis	**http://www.filariasis.org**	Filariose
Global Foodborne Infections Network (GFN)	**http://www.who.int/gfn**	Réseau mondial d'infections d'origine alimentaire
Global Health Observatory (GHO) data	**https://www.who.int/gho**	Données de l'Observatoire de la santé mondiale
Global Influenza Surveillance and Response System (GISRS)	**https://www.who.int/influenza/gisrs_laboratory**	Système mondial de surveillance et d'intervention en cas de grippe (GISRS)
Global Outbreak Alert and Response Network (GOARN)	**https://www.who.int/ihr/alert_and_response/outbreak-network/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**	Trypanosomiase humaine africaine
Immunization, Vaccines and Biologicals	**http://www.who.int/immunization**	Vaccination, Vaccins et Biologiques
Influenza	**https://www.who.int/influenza**	Grippe
International Health Regulations	**http://www.who.int/ihr**	Règlement sanitaire international
International travel and health	**http://www.who.int/ith**	Voyages internationaux et santé
Leishmaniasis	**http://www.who.int/leishmaniasis**	Leishmaniose
Leprosy	**http://www.who.int/lep**	Lèpre
Lymphatic filariasis	**http://www.who.int/lymphatic_filariasis**	Filiariose lymphatique
Malaria	**http://www.who.int/malaria**	Paludisme
Middle East respiratory syndrome coronavirus (MERS-CoV)	**https://www.who.int/emergencies/mers-cov**	Coronavirus du syndrome respiratoire du Moyen-Orient (MERS-CoV)
Neglected tropical diseases	**http://www.who.int/neglected_diseases**	Maladies tropicales négligées
Onchocerciasis	**http://www.who.int/onchocerciasis**	Onchocercose
OpenWHO	**https://openwho.org/**	OpenWHO
Outbreak news	**http://www.who.int/csr/don**	Flambées d'épidémies
Poliomyelitis	**http://www.polioeradication.org**	Poliomyélite
Rabies	**http://www.who.int/rabies**	Rage
Schistosomiasis	**http://www.who.int/schistosomiasis**	Schistosomiase
Smallpox	**http://www.who.int/csr/disease/smallpox**	Variole
Soil-transmitted helminthiases	**http://www.who.int/intestinal_worms**	Géohelminthiases
Trachoma	**http://www.who.int/trachoma**	Trachome
Tropical disease research	**http://www.who.int/tdr**	Recherche sur les maladies tropicales
Tuberculosis	**http://www.who.int/tb and/et http://www.stoptb.org**	Tuberculose
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**	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**	Schéma OMS d'évaluation des pesticides
Yellow fever	**http://www.who.int/csr/disease/yellowfev**	Fièvre jaune
Zika virus disease	**https://www.who.int/emergencies/diseases/zika**	Maladie à virus Zika

Background published articles for Session 2

04. Pang, F., Drummond, M., & Song, F. (1999)."The use of meta-analysis in economic evaluation" Working Papers 173chedp. Centre for Health Economics, University of York.

05. Crespo, C., Monleon, A., Díaz, W., & Ríos, M. (2014). Comparative efficiency research (COMER): meta-analysis of cost-effectiveness studies. *BMC medical research methodology*, *14*, 139. https://doi.org/10.1186/1471-2288-14-139

06. Bagepally, B. S., Chaikledkaew, U., Chaiyakunapruk, N., Attia, J., & Thakkinstian, A. (2022). Meta-analysis of economic evaluation studies: data harmonisation and methodological issues. *BMC health services research*, *22*(1), 202. https://doi.org/10.1186/s12913-022-07595-1

07. Haider, S., Chaikledkaew, U., Thavorncharoensap, M., Youngkong, S., Islam, M. A., & Thakkinstian, A. (2019). Systematic Review and Meta-Analysis of Cost-effectiveness of Rotavirus Vaccine in Low-Income and Lower-Middle-Income Countries. *Open forum infectious diseases*, *6*(4), ofz117. https://doi.org/10.1093/ofid/ofz117

08. Udayachalerm, S., Renouard, M. G., Anothaisintawee, T., Thakkinstian, A., Veettil, S. K., & Chaiyakunapruk, N. (2022). Incremental net monetary benefit of herpes zoster vaccination: a systematic review and meta-analysis of cost-effectiveness evidence. *Journal of medical economics*, *25*(1), 26–37. https://doi.org/10.1080/13696998.2021.2008195

09. Dilokthornsakul, P., Lan, L. M., Thakkinstian, A., Hutubessy, R., Lambach, P., & Chaiyakunapruk, N. (2022). Economic evaluation of seasonal influenza vaccination in elderly and health workers: A systematic review and meta-analysis. *EClinicalMedicine*, *47*, 101410. https://doi.org/10.1016/j.eclinm.2022.101410

10. Syeed, M. S., Ghule, P., Le, L. M., Veettil, S. K., Horn, E. K., Perdrizet, J., Wasserman, M., Thakkinstian, A., & Chaiyakunapruk, N. (2023). Pneumococcal Vaccination in Children: A Systematic Review and Meta-Analysis of Cost-Effectiveness Studies. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*, *26*(4), 598–611. https://doi.org/10.1016/j.jval.2022.10.006

11. Rosettie, K. L., Joffe, J. N., Sparks, G. W., Aravkin, A., Chen, S., Compton, K., Ewald, S. B., Mathew, E. B., Michael, D., Pedroza Velandia, P., Miller-Petrie, M. B., Stafford, L., Zheng, P., Weaver, M. R., & Murray, C. J. L. (2021). Cost-effectiveness of HPV vaccination in 195 countries: A meta-regression analysis. *PloS one*, *16*(12), e0260808. https://doi.org/10.1371/journal.pone.0260808

12. Janko, M. M., Joffe, J., Michael, D., Earl, L., Rosettie, K. L., Sparks, G. W., Albertson, S. B., Compton, K., Pedroza Velandia, P., Stafford, L., Zheng, P., Aravkin, A., Kyu, H. H., Murray, C. J. L., & Weaver, M. R. (2022). Cost-effectiveness of rotavirus vaccination in children under five years of age in 195 countries: A meta-regression analysis. *Vaccine*, *40*(28), 3903–3917. https://doi.org/10.1016/j.vaccine.2022.05.042

World Health Organization

Session 3

Global Analysis Estimating the impact of vaccination over 50 years

Global analysis estimating the impact of vaccination over 50 years

For information session
IVIR-AC meeting

28 February 2024

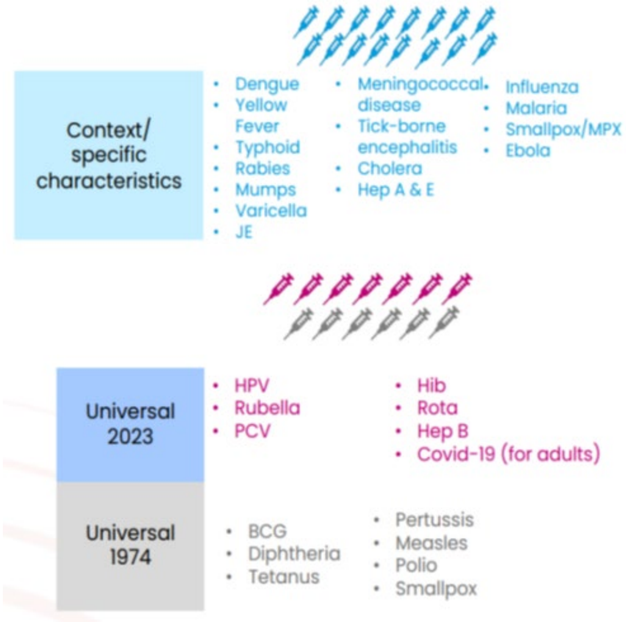
Agenda

1. Background - *Yoonie Sim*
2. Technical presentation – *Dr Helen Johnson*
3. Questions for IVIR-AC
4. Discussion

Background

Analytical contribution to EPI@50

- 2024 marks 50 years since the World Health Assembly resolution formally established the Expanded Programme on Immunization (EPI) on 23 May 1974
- We are conducting **a global level analysis that estimates the health impact of vaccination over the last 50 years**
- The estimates will be released during the World Immunization Week in 2024 (24-30 April). The analysis will be given prominence at the World Health Assembly (27 May – 1 June)
- The estimates will serve as a critical input into the non-branded campaign being developed by coordinating partners from WHO, UNICEF, Gavi, and BMGF



Overview of EPI@50 analysis

- **Historical public health impact** of vaccination for **pathogens within EPI**
  - Time-frame: 50 years (1974-present)
  - Country scope: global and regional (194 countries)
  - Pathogens scope: 14 (11 + JE, MenA and Yellow fever being added)

- Uses a **framework developed by WHO**, first used for IA2030 analysis
  - Models reporting to VIMC (8)
    - JE, Hib, Hep B, MenA, Pneumococcal disease, Rotavirus, Rubella, Yellow fever
  - External modelling (2)
    - Polio, measles*
  - In-house models (4)
    - Diphtheria, tetanus, pertussis, TB (BCG)

- The goal:
  - A strong **statement piece** built on **solid scientific analysis** to inform **advocacy**

- <u>Notes:</u>
  - No reporting at the country level
  - No reporting of number of cases

* Measles modeling groups (LSHTM, PSU) report to VIMC but we have run this model directly

IA2030 vaccine impact estimates (IG 1.1) vs. EPI@50 analysis

Contents lists available at ScienceDirect

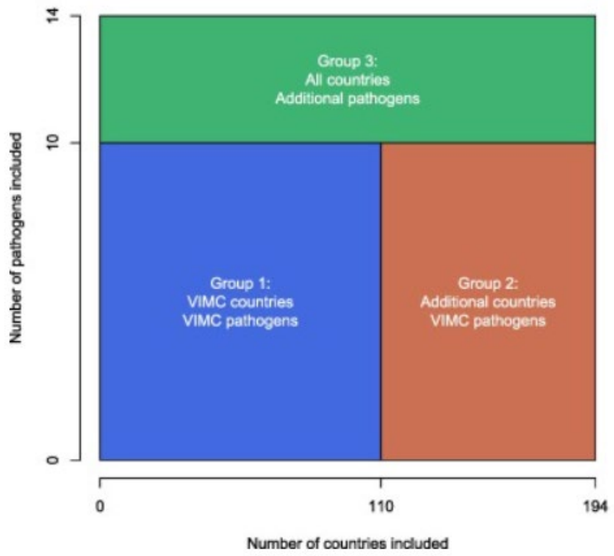
Vaccine

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

Modeling the impact of vaccination for the immunization Agenda 2030: Deaths averted due to vaccination against 14 pathogens in 194 countries from 2021 to 2030

Austin Carter [a,c,*], William Msemburi [b], So Yoon Sim [c,*], Katy A.M. Gaythorpe [d], Philipp Lambach [c], Ann Lindstrand [c], Raymond Hutubessy [c]

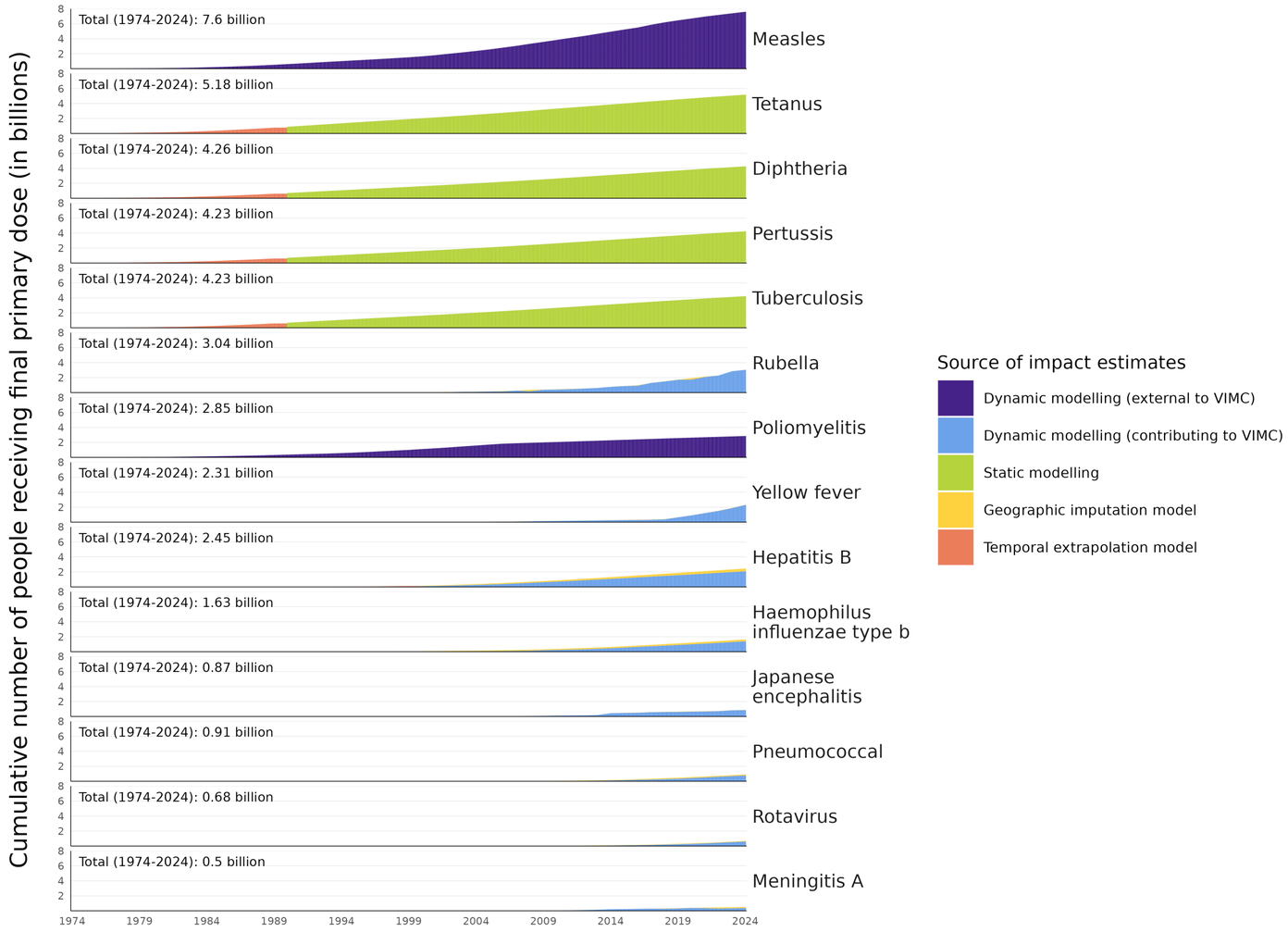
[a] University of Washington, Seattle, WA, USA
[b] World Health Organization, Division of Data, Analytics and Delivery for Impact (DDI), Geneva, Switzerland
[c] World Health Organization, Department of Immunization, Vaccines and Biologicals (IVB), Geneva, Switzerland
[d] Imperial College London, London, United Kingdom



- EPI50 analysis broadly based on IA2030 framework
- EPI50 upgrades:
  - Improved analytical approach for DTP & TB
  - Inclusion of morbidity impact measure (DALYs)
  - Inclusion of SIA data
  - Move away from constant death averted per vaccinated person assumption
- Differences

	EPI@50 framework	IA2030 framework
Timeframe	Historical analysis (1974- present)	Future projection based on aspirational IA2030 coverage scenario (2021-30)
Units	Calendar year impact ** Impact X in year Y from vaccines delivered up to and including year Y (no future projections required)*	Year of Vaccination method ** Vaccines administered in year Y have impact X when measured over the next 70 years (requires long term future projection)*

EPI50 framework



- Visual: Cumulative number of people receiving final primary dose (in million) by source of impact estimates
- Impact of the majority of vaccines are being quantified by dynamic models
- Geographic imputation model is necessary but doesn’t contribute substantially

Questions for IVIR-AC

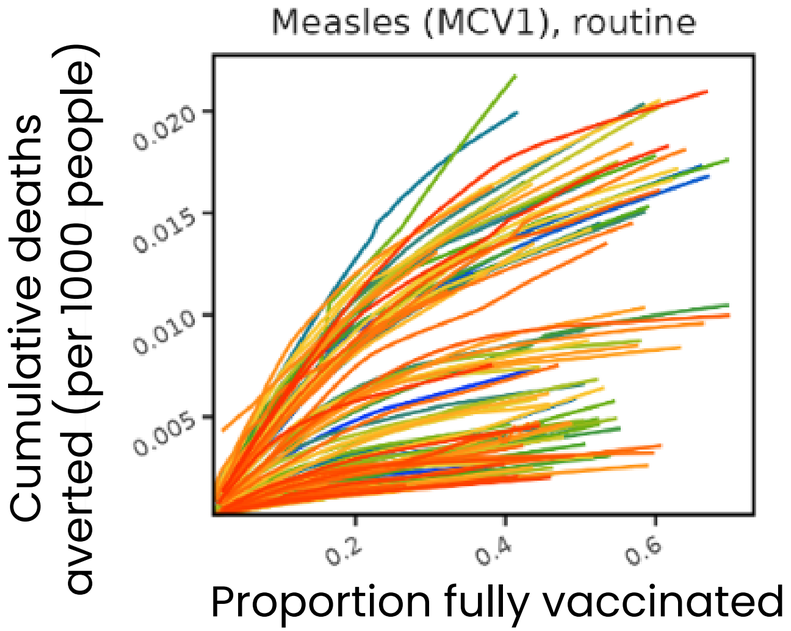
- **Question 1:** We invite advice on the methodological advancements made on the IA2030 analytical framework. We are also interested in how the IVIR-AC committee views their potential extension to ensure maximal insight, applicability and value of communication.

- **Question 2:** Do IVIR-AC members have any additional points of caution or advice around the messaging of the EPI@50 analysis, within or beyond those communicated in the presentation?

- **Question 3:** What potential do IVIR-AC members see in applying the methodological advancements of the EPI@50 analysis to the ongoing work of IA2030?

Technical presentation

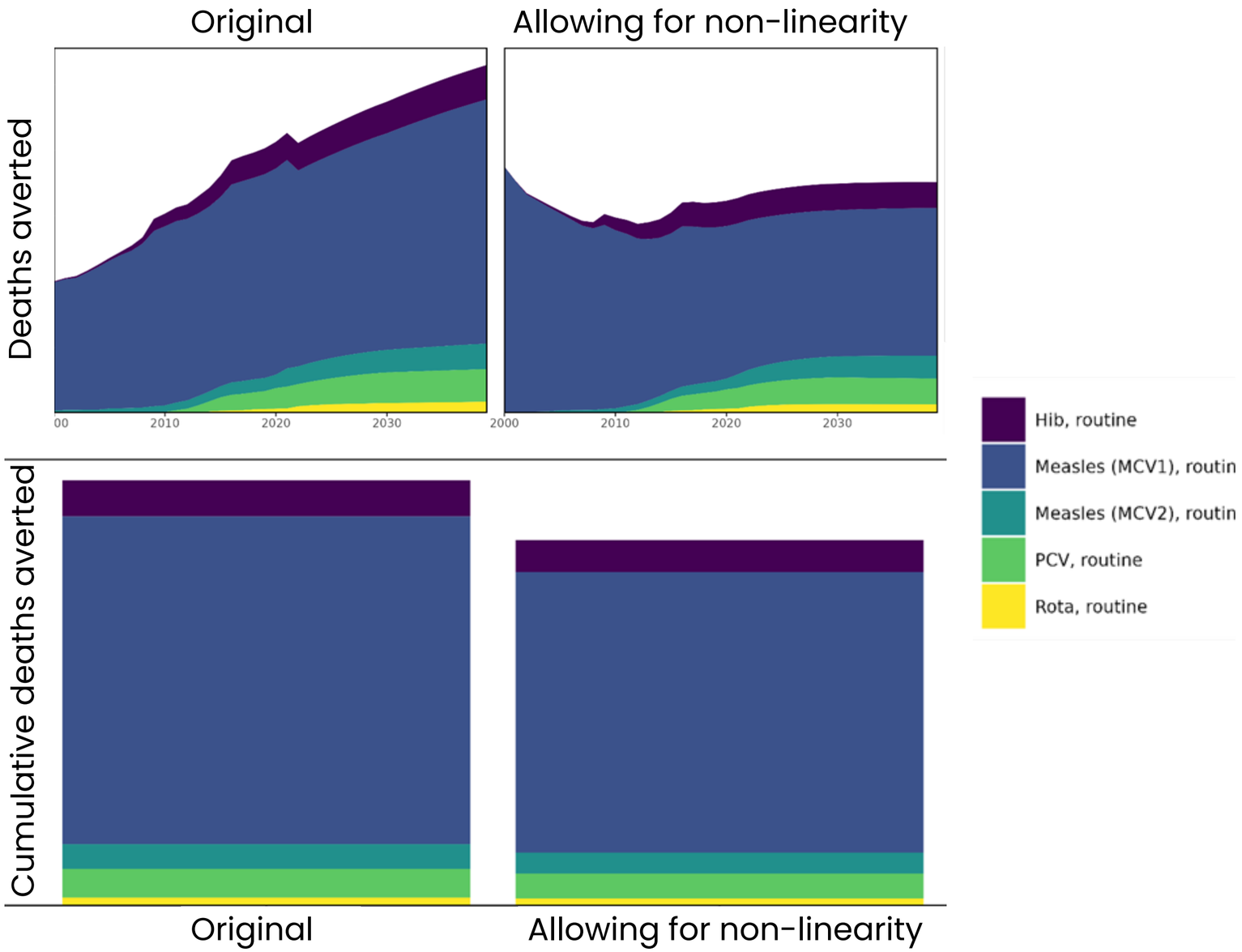
Accounting for non-linear impact



- To account for non-linearity in vaccine impact with increasing coverage, a model selection approach was employed
- For each country and disease-vaccine-activity, three functions were evaluated: linear, basic logistic and flexible logistic
- Corrected Akaike Information Criterion was used to select the most appropriate choice

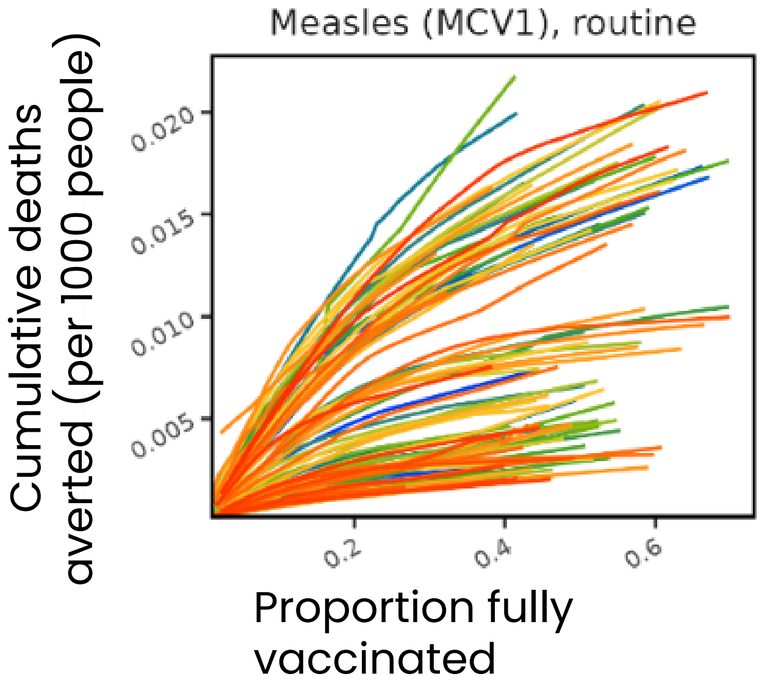
Function name	Functional form	Number of parameters	Description
Gradient function	$y = ax$	1	Straight line through the origin with the gradient representing an 'impact factor'
Basic logistic function	$y = \frac{b}{1 + e^{-ax}}$	2	Logistic function with inflection (or 'mid') point at the origin.
Flexible logistic function	$y = \frac{b}{1 + e^{-a(x-c)}}$	3	Logistic function with variable mid point, can be convex and/or concave.

Accounting for non-linear impact



- As anticipated, the impact of measles vaccination was particularly sensitive to assumptions of linearity
- Originally, impact was underestimated earlier in the programme and overestimated later
- Including non-linearity of impact reduced the cumulative number of deaths averted by ~ 5million

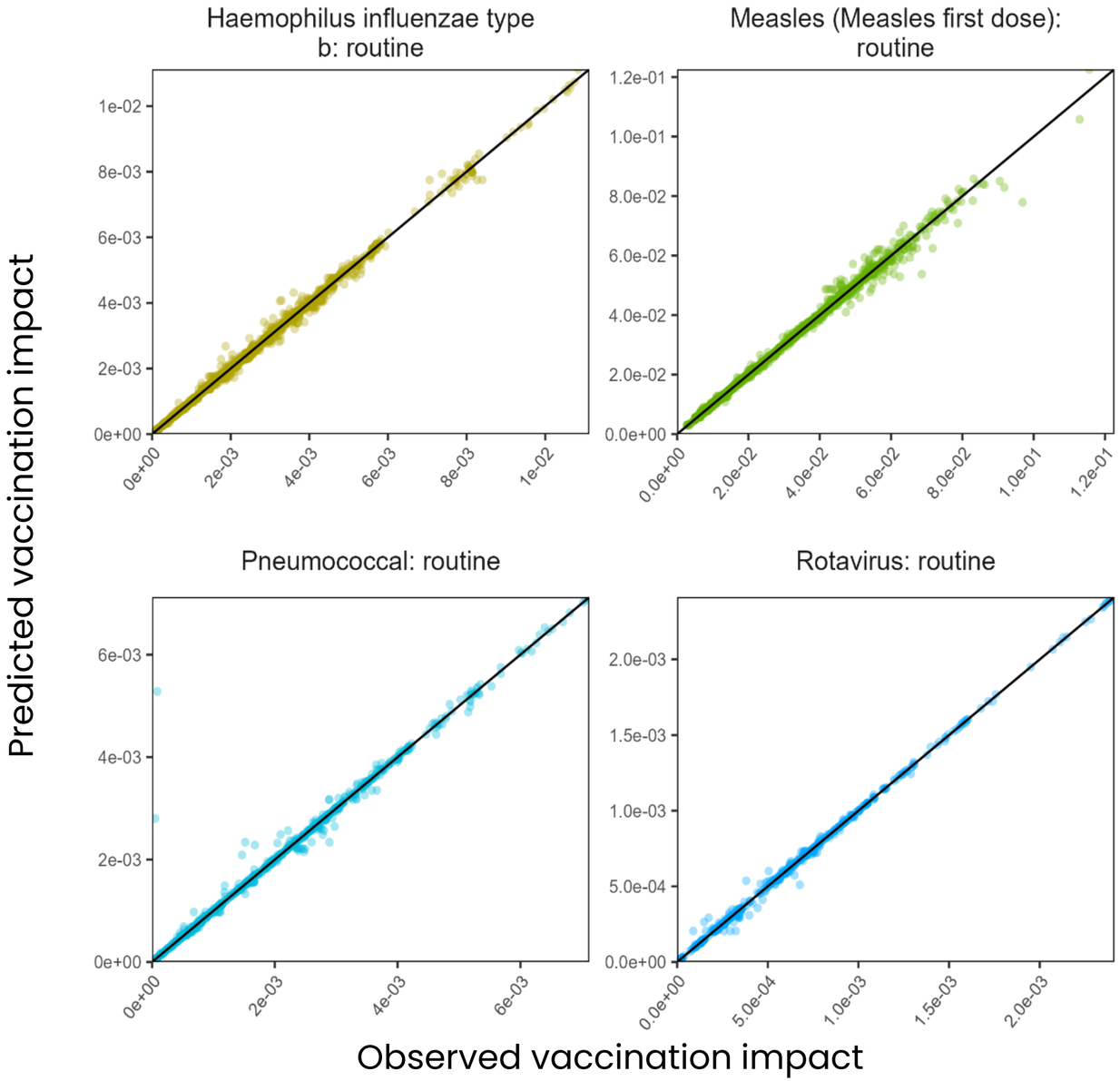
Accounting for non-linear impact



Key Messages

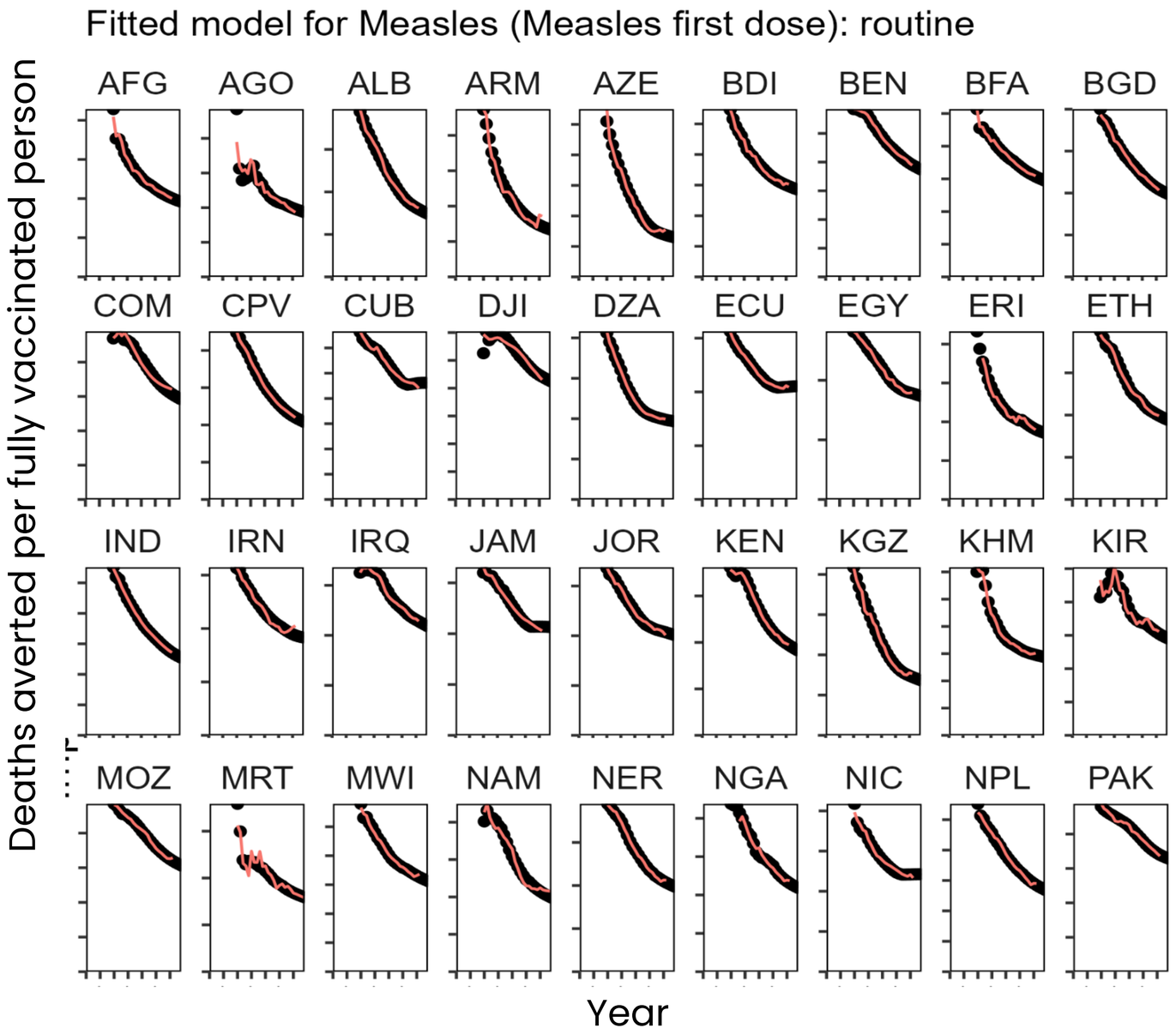
- Past success vs future potential: In a retrospective, celebratory analysis, must also communicate the message that sustained effort is essential
- Decreasing coverage levels undermine the impact of the program more and more rapidly
- Importance of universal coverage: In established programs, the impact of each dose lessens over time. However, many people are still dying of these diseases
- Innovation is required to find and protect those are missed (SDG 3)

Geographical imputation



- To impute impact in countries for which we had no results, we estimated the impact of predictors that give rise to differences between countries
- Time series regression models were fitted each country, for each vaccine activity, using an AICc model selection approach
- Predictor variables included:
  - Vaccination coverage, up to 4 years lag
  - Gini coefficient (inequality)
  - Health spending
  - Malnutrition
  - Maternal mortality
  - Access to clean water and sanitation
  - Etc.

Geographical imputation

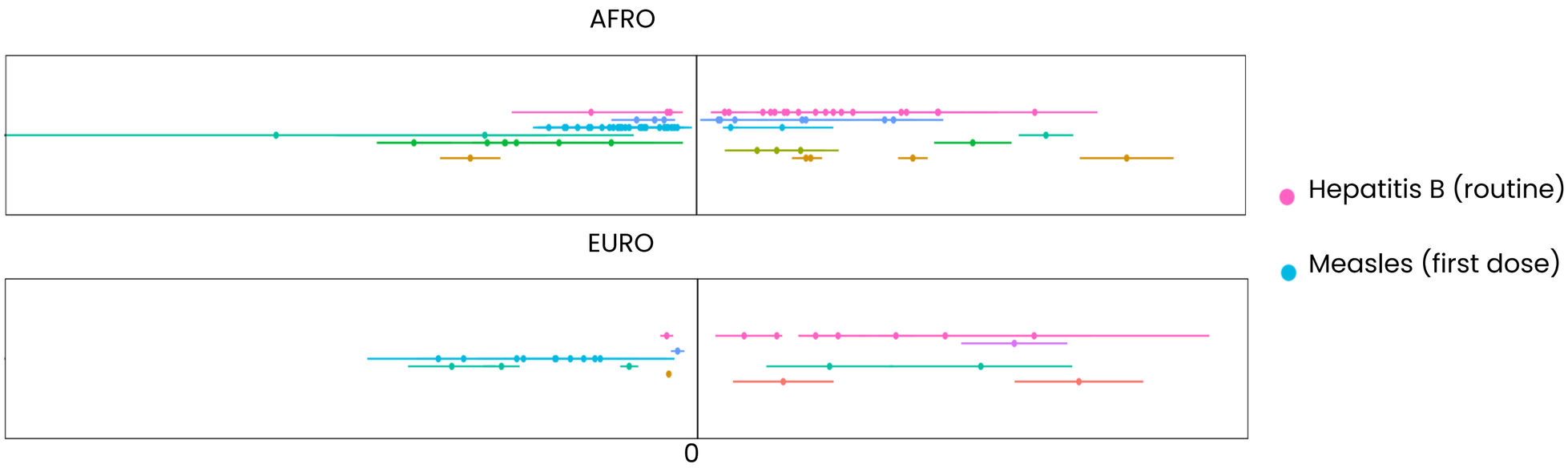


- The fitted time series regression models were used to impute vaccination impact in countries for which we did not have estimates
- Coefficients of correlation were sampled for selected predictors from the fitted distributions of 'similar' countries
- Sensitivity approach for 'similarity':
  - Same WHO region
  - Geographical proximity
  - Proximity in developmental indices

Observed impact

Modelled impact

Geographical imputation



Correlation coefficient for human development index (HDI)

- Further analysis of predictors gives valuable insights into the drivers of high program impact
- For example, high impact of vaccination with primary dose of measles-containing vaccine is associated with a lower development index, associated with high measles prevalence
- However, high impact of routine Hepatitis B vaccination is associated with higher development index, may be due to challenges with program implementation

Preliminary results

CONFIDENTIAL:
Preliminary results shared with IVIR-AC

Communication strategy

- Framing the number: The number of deaths and the disease averted by vaccines over 50 years is large (although remember the global population is now more than twice what it was in 1974):
    - Impact per person
    - Comparison with other health / non-health risks
    - Ranking of communicable disease as cause of death
- Who benefits from vaccination?: Improved survival of children to their 1st birthday, 5th birthday…
- Past success vs future potential: In a retrospective, celebratory analysis, must also communicate the message that sustained effort is essential
- Absolute vs. relative gains: How best to present results by region?
- When do vaccination programs work best?: EPI@50 analysis shows factors associated with high impact (death and disease reduction). These change over time: at first vaccination coverage is most important, then levels of inequality become more important
- Importance of universal coverage: In established programs, the impact of each dose lessens over time. But many people are still dying of these diseases. Use positive language of inclusion -> finding and protecting those who are missed (SDG3)

Questions for IVIR-AC

Questions for IVIR-AC

- **Question 1:** We invite advice on the methodological advancements made on the IA2030 analytical framework. We are also interested in how the IVIR-AC committee views their potential extension to ensure maximal insight, applicability and value of communication.

- **Question 2:** Do IVIR-AC members have any additional points of caution or advice around the messaging of the EPI@50 analysis, within or beyond those communicated in the presentation?

- **Question 3:** What potential do IVIR-AC members see in applying the methodological advancements of the EPI@50 analysis to the ongoing work of IA2030?

Appendix

Previous IVIR-AC recommendations (specific to IA2030 vaccine impact estimates)

In addition to acknowledging the response to previous recommendations and revised methods, IVIR-AC recommended clarifying the terminology used by, and the online dissemination strategy of the project code base, including the following:

- Some of the terms used, such as “future deaths” or “observed deaths averted”, could be liable to misinterpretation. IVIR-AC suggested clearly defining various terms and using them consistently.

- Regarding the inclusion of DALYs in target metrics, IVIR-AC found the proposed approach sound, and encouraged systematic identification of key drivers of heterogeneity in case fatality and basing the stratification of estimates on identified drivers.

- IVIR-AC noted that the uncertainty in estimates of both deaths and case fatality ratios need to be propagated in the estimates of DALYs.

- IVIR-AC commended the open-source sharing of project code, recommends additional documentation and communication on use of the code, and advises considering the merit of developing a supplementary online tool or dashboard to allow user-friendly data exploration.

IA2030 vaccine impact estimates: Stakeholder Committee

	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	Sheetal Silal*	Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC)	Cape Town, SA
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	Mike Lynch	US Centers for Disease Prevention and Control (US CDC)	Atlanta, USA
8	Haidong Wang	WHO Division of Data, Analytics and Delivery for Impact (DDI)	Geneva, Switzerland
9	Naor Bar-Zeev Unit head, IAI	WHO Department of Immunization, Vaccines and Biologicals (IVB)	Geneva, Switzerland
10	Raymond Hutubessy* Team Lead, VoV	WHO Department of Immunization, Vaccines and Biologicals (IVB)	Geneva, Switzerland

Notes:.

- Pesentations, meeting minutes, and background materials from previous meetings are available in the shared folder.

IA2030 vaccine impact estimates: project team

Function	Name	Affiliation	Location/time zone
Analytics	Andrew Shattock	Independent consultant for WHO IVB Swiss Tropical and Public Health Institute University of Basel Telethon Kids Institute University of Western Australia	Basel, Switzerland Perth, Australia
Analytics	Helen Johnson	Independent consultant for WHO IVB Safinea Ltd.	London,
Analytics	Austin Carter *(Contract break)*	Independent consultant for WHO IVB; University of Washington	Portland, USA
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	Raymond Hutubessy	WHO Department of Immunization, Vaccines and Biologicals (IVB)	Geneva, Switzerland

Modelling analysis in support of EPI@50

Background

In support of the advocacy efforts for the 50th anniversary of the Expanded Program on Immunization (EPI), the IA2030 team is estimating the deaths and DALYS averted by vaccination globally in the period 1974-2024. The analytical framework of IA2030 has been extended by i) the inclusion of non-linear vaccine impact estimates and ii) improvements to imputation for countries not modelled by the Vaccine Impact Modelling Consortium (VIMC). The team is working closely with communications stakeholders from both WHO and partner organisations in anticipation of the publication of the results during World Immunization week (24 – 30 April). Advice is sought on both the methodological advancements and the communication strategy.

Methodological updates

Since the last presentation of IA2030 modelling analysis to IVIR-AC in September 2023, the methodology has been extended. We shall present the inclusion of non-linear models for vaccine impact, acknowledging the diminishing marginal return associated with established programs. Furthermore, a report will be given on advancements to the approach for imputing impact for non-VIMC countries. Time series regression models are fitted for each country where impact estimates are available, estimating the contribution of not only vaccination coverage but also socio-economic and demographic factors. In each case, a model selection approach is conducted to identify the appropriate degree of complexity and imputation for the missing countries is made by sampling from the regression coefficients of neighbouring countries. This approach is now being further extended to estimate the drivers of high impact by region and decade of the EPI program.

Q1. We invite advice on the methodological advancements. We are also interested in how the IVIR-AC committee views their potential extension to ensure maximal insight, applicability and value of communication.

Communication

The team is cognisant that the results of the EPI@50 analysis are powerful for advocacy but will come under close scrutiny. In collaboration with communications stakeholders from WHO, GAVI, Bill and Melinda Gates Foundation and UNICEF, a number of points have been identified for discussion in advance of the release:

- The number of deaths and the disease averted by vaccines over 50 years is large and will require **careful framing** to ensure comprehensibility. Suggested approaches include reporting impact per X people, comparisons with other health / non-health risks and reporting the shift in ranking of communicable disease as cause of death
- An important message is who benefits from vaccination. Rather than reporting the rather arcane metric of ‘years of life lost’, we propose to present the **improved survival rates of children** to their 5th birthday
- By its nature, this analysis is retrospective and somewhat celebratory. However, we are aware that it should **reinforce the need for sustained efforts** and encourage, not detract
- The updated analysis allows the elucidation of **factors associated with high impact of vaccination**. We see potential for this work in the targeting of resources to improve the effectiveness and efficiency of vaccination programs.
- In established programs, the impact of each dose lessens over time (as illustrated by the inclusion of the non-linear impact functions). This should not lead to complacency. We

proposed using the positive language of inclusion, **finding and protecting those who have been missed**.

Q2. Do IVIR-AC members have any additional points of caution or advice around the messaging of the EPI@50 analysis?

Q3. What potential do IVIR-AC members see in applying the methodological advancements of the EPI@50 analysis to the ongoing work of IA2030?

Summary of methodological updates in EPI@50 analysis

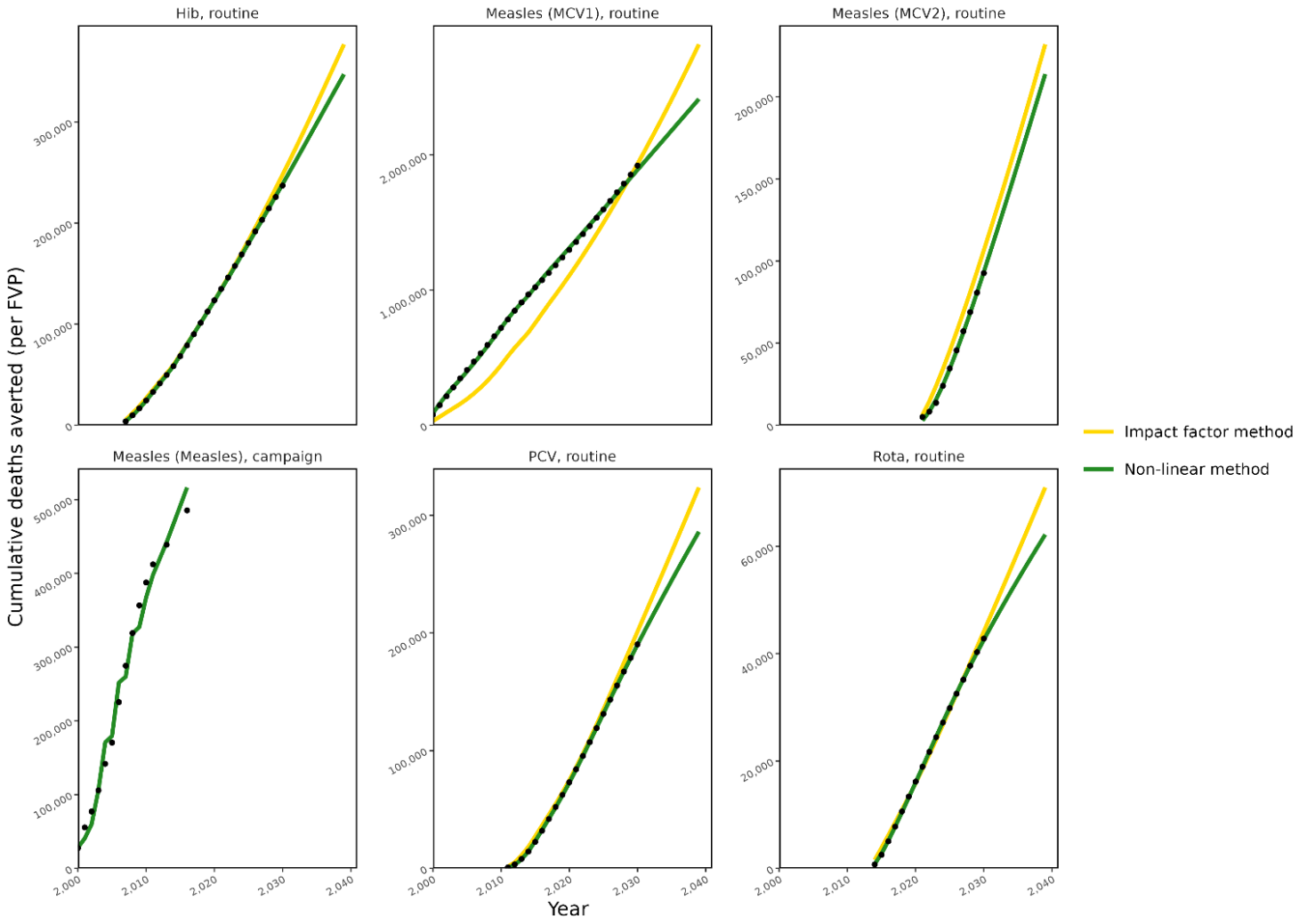
Updates for EPI@50: Non-linear vaccination impact

- In some cases e.g. Measles, vaccination impact diminishes significantly at higher coverage
- We evaluated 3 alternative functions to represent impact

Function name	Functional form	Number of parameters	Description
Gradient function	$y = ax$	1	Straight line through the origin with the gradient representing an 'impact factor'
Basic logistic growth	$y = \frac{b}{1 + e^{-ax}}$	2	Logistic growth with saturation effect.
Flexible logistic function	$y = \frac{b}{1 + e^{-a(x-c)}}$	3	Logistic function with variable mid point, can be convex and/or concave.

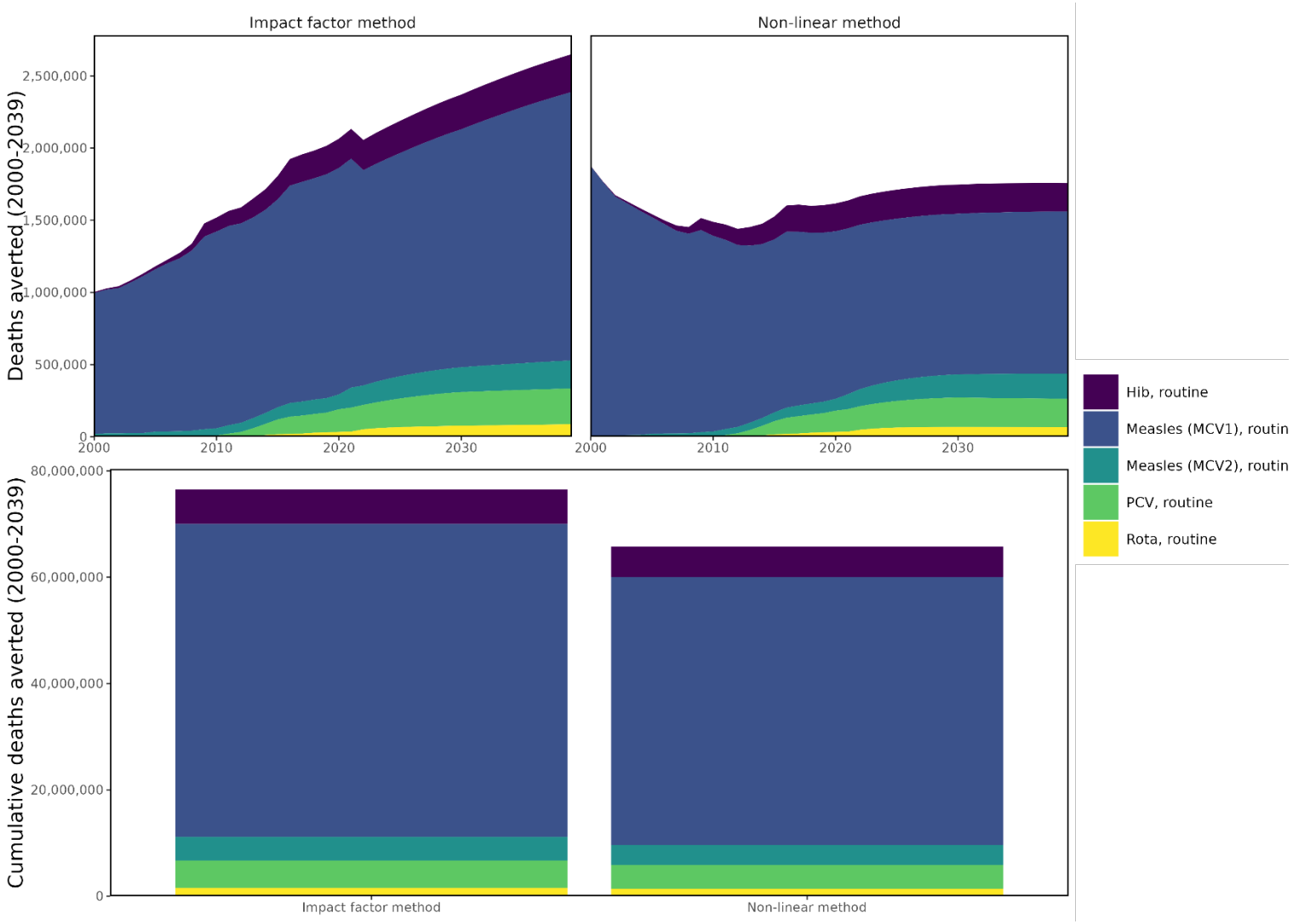
- Each function was fitted to cumulative deaths averted per fully vaccinated person using maximum likelihood estimation
- The corrected Akaike information criterion (AICc) was calculated: a quality of fit measure that punishes additional parameters
- The highest AICc was selected -> balance between complexity and parsimony

Updates for EPI@50: Non-linear vaccination impact



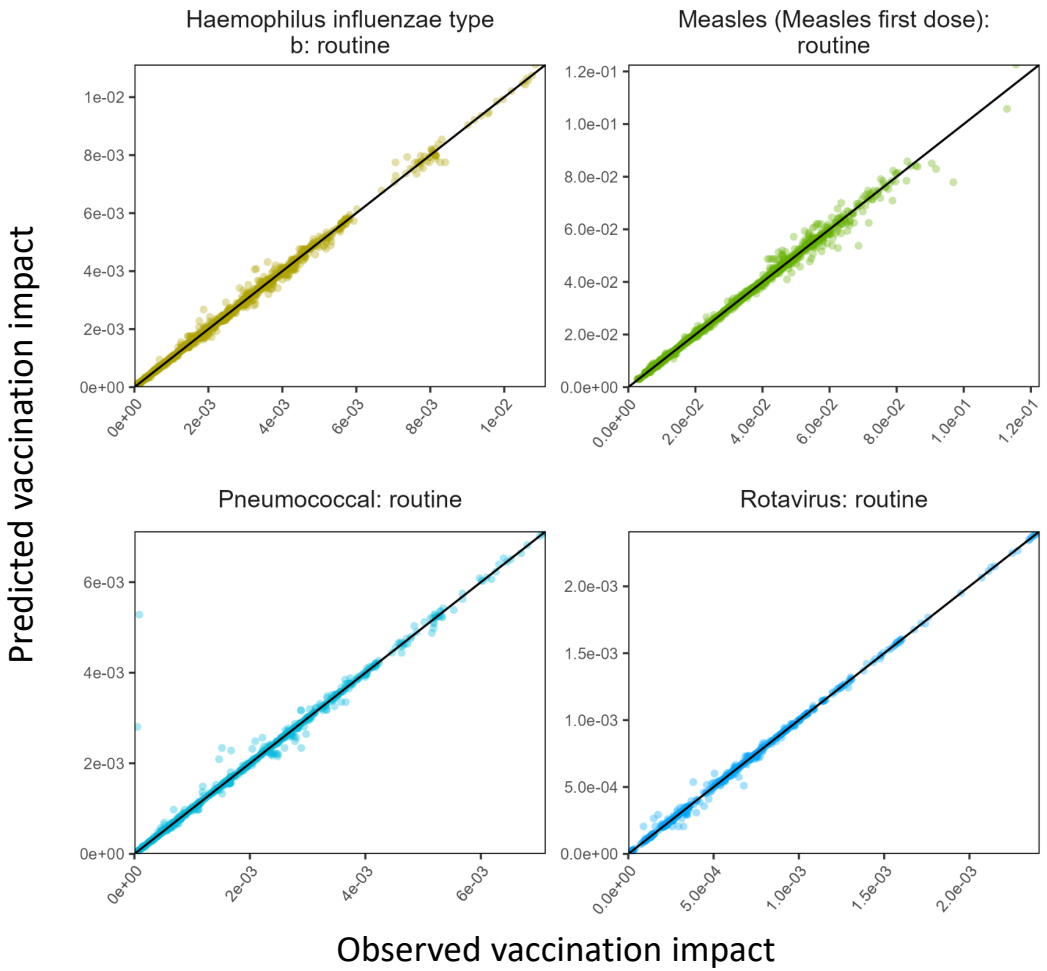
- The model selection approach highlighted the improved fit of the non-linear functions
- The original approach overestimated impact in later years of the vaccination program
- Divergence increased over time, due to indirect impact of vaccination and reduced transmission

Updates for EPI@50: Non-linear vaccination impact



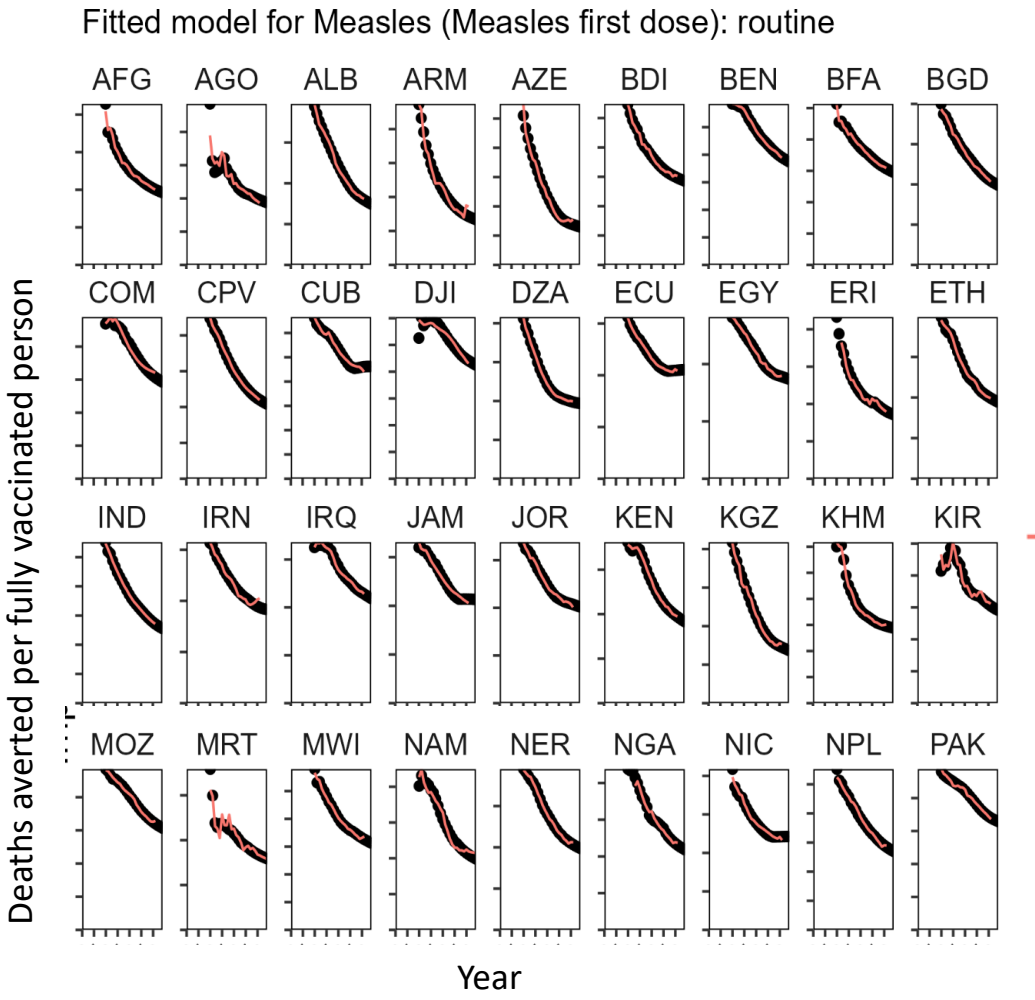
- The model selection approach highlighted the improved fit of the non-linear functions
- The original approach overestimated impact in later years of the vaccination program
- Divergence increased over time, due to indirect impact of vaccination and reduced transmission
- The non-linear approach reduced overestimation of deaths averted

Updates for EPI@50: Imputation for non-VIMC countries



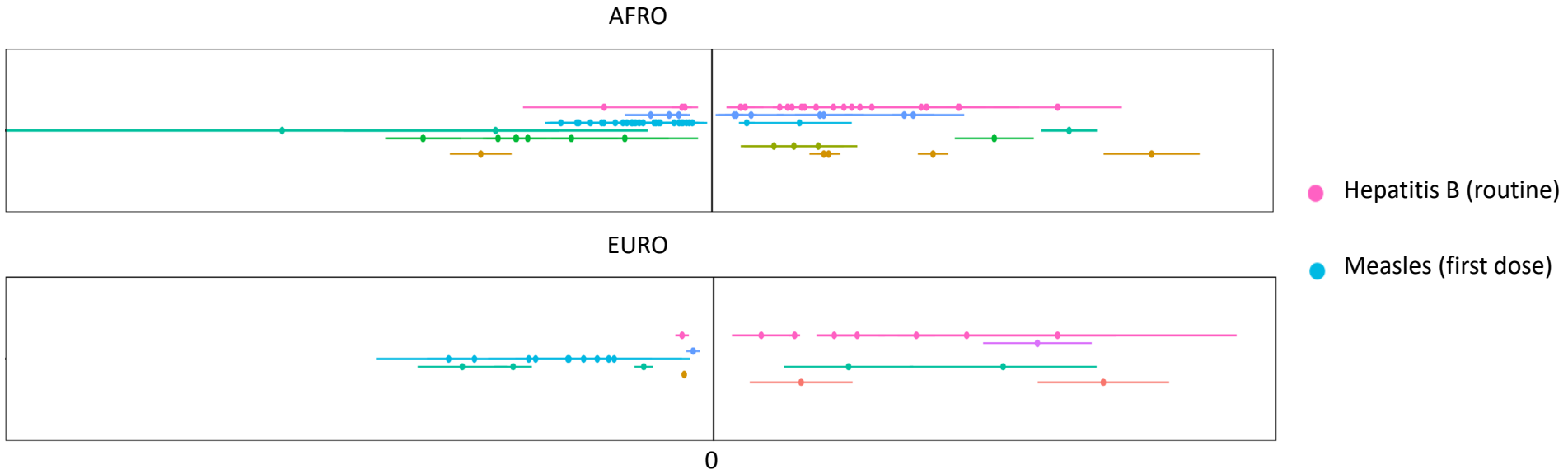
- Following the Sept. 2023 advice of IVIR-AC, we have evaluated the predictors of heterogeneity in vaccination impact between countries
- We fitted time series regression models to each country, for each vaccine activity using an AICc model selection approach
- Predictor variables included:
  - Vaccination coverage, up to 4 years lag
  - Gini coefficient (inequality)
  - Health spending
  - Malnutrition
  - Maternal mortality
  - Access to clean water and sanitation
  - Etc.

Updates for EPI@50: Imputation for non-VIMC countries



- The fitted time series regression models were used to impute vaccination impact in countries for which we did not have estimates
- Coefficients of correlation were sampled for selected predictors from the fitted distributions of neighboring countries

Updates for EPI@50: Imputation for non-VIMC countries



Correlation coefficient for human development index (HDI)

- Further analysis of predictors gives valuable insights into the drivers of high program impact
- For example, high impact of vaccination with primary dose of measles-containing vaccine is associated with a lower development index, associated with high measles prevalence
- However, high impact of routine Hepatitis B vaccination is associated with higher development index, possibly associated with program implementation

World Health Organization

Session 4
Modelling the impact of different dose schedules for RTS,S malaria vaccine

Modeling the impact of different dose schedules for RTS,S malaria vaccine

Mary J Hamel, MD

Senior Technical Officer and Team Lead for Malaria Vaccines,
Product and Delivery Research Unit, IVB, WHO

World Health Organization

Credit: WHO/F.Combrink

Agenda

• Background	Dr. Mary Hamel, WHO
• Technical presentation of modelled public health impact of different malaria vaccine dose schedules in perennial settings	Ms. Daniela Figueroa, Swiss TPH Dr. Melissa Penny, Telethon Kids Institute
• Presentation of modelled public health impact of different dose schedules in seasonal settings	Dr. Hayley Thompson, PATH
• Q & A and Discussion (SAGE/MPAG WG members present)	

World Health Organization

Oct 2023, WHO update to recommendation for malaria vaccines

WHO recommends the programmatic use of malaria vaccines for the prevention of *P. falciparum* malaria in children living in malaria endemic areas, prioritizing areas of moderate and high transmission

- The malaria vaccine should be provided in a schedule of 4 doses in children from around 5 months of age[1] for the reduction of malaria disease and burden
- A 5th dose, given one year after dose 4, may be considered in areas where there is a significant malaria risk remaining in children a year after receiving dose 4
- Countries may consider providing the vaccine using an age-based, seasonal, or a hybrid of these approaches in areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks
- Countries should prioritize vaccination in areas of moderate and high transmission, but may also consider providing the vaccine in low transmission settings
- Vaccine introduction should be considered in the context of comprehensive national malaria control plans

This recommendation now includes two malaria vaccines:

- **RTS,S/AS01**
- **R21/Matrix-M**

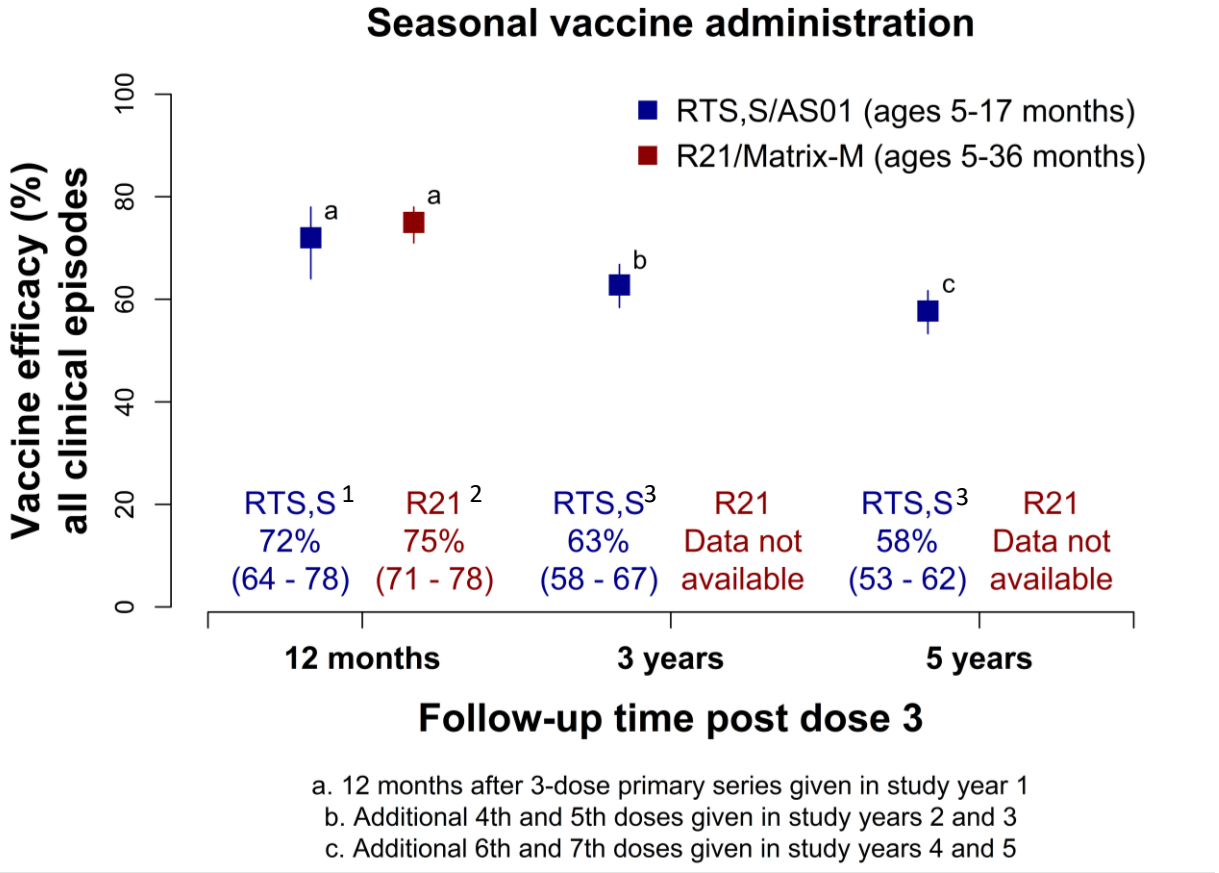
[1] Vaccination programmes may choose to give the first dose at a later or earlier age, based on operational consideration. Studies with RTS,S/AS01 indicated lower efficacy if first dose was given around 6 weeks of age. However, it seems unlikely that efficacy would be substantially reduced if some children received the first dose at 4 rather than 5 months, and providing vaccination at an age younger than 5 months may increase coverage or impact

World Health Organization

High malaria vaccine efficacy when provided seasonally in areas of highly seasonal malaria transmission

Aligns period of highest vaccine efficacy with period of high malaria transmission (little transmission during dry season)

- RTS,S VE when provided seasonally (with SMC)
  - **72% (95% CI: 64, 78)[1]**
  - 12 months after 3-dose series
- R21 VE when provided seasonally (with SMC)
  - **75% (95% CI: 71, 78)[2]**
  - 12 months after 3-dose series
- Due to programmatic considerations, **no country with highly seasonal transmission has opted for seasonal approach**

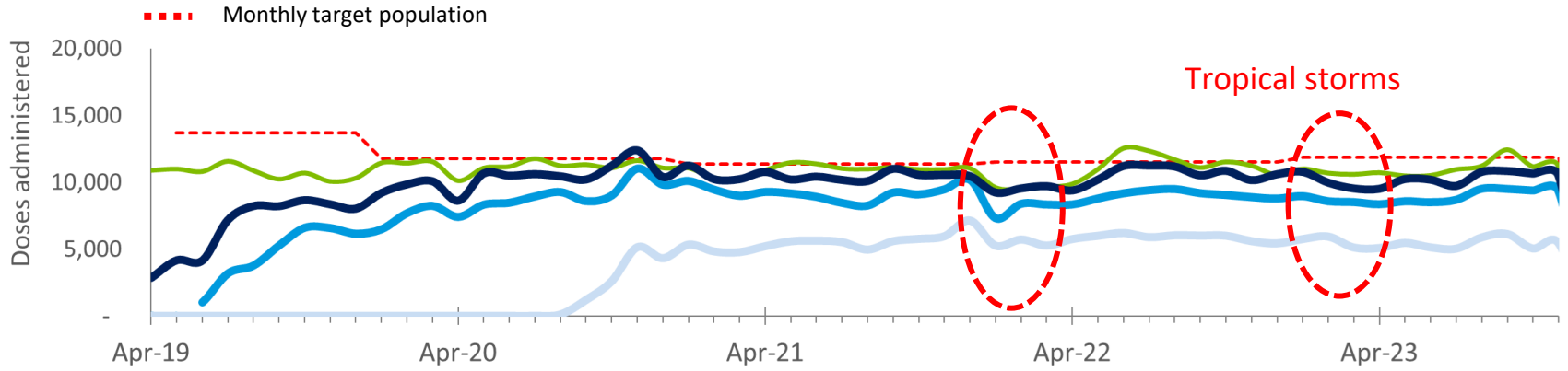


World Health Organization

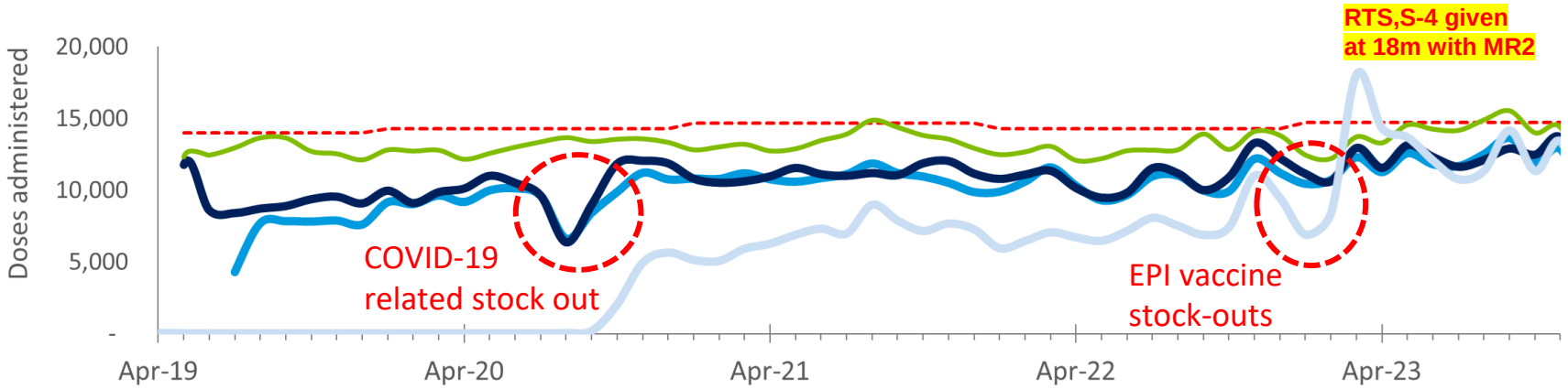
1. Chandramohan N Engl J Med 2021: https://www.nejm.org/doi/pdf/10.1056/NEJMoa2026330?articleTools=true
2. R21 Phase 3 results from R21 Full Evidence Report: https://terrance.who.int/mediacentre/data/sage/SAGE_eYB_Sept2023.pdf
3. Dicko Lancet 2023: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(23)00368-7/fulltext

Immunization coverage during MVIP: monthly administrative data reports (through Nov 2023) showing low dose 4 coverage when provided at 22 or 24 months of age

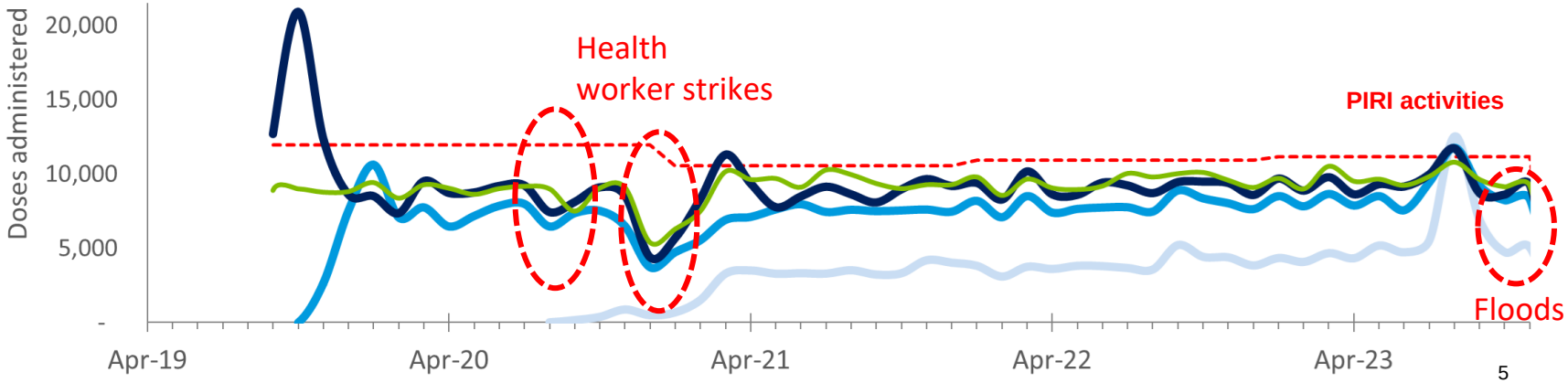
Malawi	2020	2021	2022	Jan-Nov 2023
Penta-3	95%	97%	95%	**93%**
RTS,S-1	88%	93%	90%	**87%**
RTS,S-3	73%	81%	76%	**75%**
RTS,S-4	--	49%	50%	**46%**



Ghana	2020	2021	2022	Jan-Nov 2023
Penta-3	92%	92%	91%	**95%**
RTS,S-1	71%	76%	77%	**83%**
RTS,S-3	66%	74%	74%	**81%**
RTS,S-4		47%	53%	**83%**



Kenya	2020	2021	2022	Jan-Nov 2023
Penta-3	72%	87%	87%	**90%**
RTS,S-1	69%	82%	83%	**84%**
RTS,S-3	60%	67%	72%	**78%**
RTS,S-4		29%	36%	**50%**



Interval between malaria vaccine dose 3 and 4

- Optimal timing between dose 3 and 4 has not been determined
- Trial data with 12 month or 18 month intervals, both showed prolongation of protection
- Higher effectiveness expected with higher dose 4 uptake
- Evidence from Ghana shows that with **age-based dosing**, aligning vaccination with other second year of life vaccines can result in high uptake
    - Results in variable intervals between dose 3 and 4, depending on primary schedule and timing of dose 4 in second year of life
        - Intervals that vary from 6 to 15 month are planned
- **Hybrid dosing** (primary schedule of 3 doses given from 5 months of age, with 4th and subsequent doses given just prior to high transmission season) results in variable intervals between dose 3 and 4, **ranging from 1 to 12 months**
- SAGE supports flexibility of dosing schedule to fit country context and increase coverage (included in WHO recommendation)
- WHO has asked colleagues from TKI and PATH to model what the optimal intervals between dose 3 and 4 would be in perennial or in seasonal settings for high impact, to guide countries in their decision making about dosing schedules.

World Health Organization

Questions about the added value of 4th dose, given 18 months after 3rd, in preventing *severe malaria*

RTS,S Phase 3 trial (N=15,499) – review of clinical data and mathematical modeling brought into question the added value of dose 4 in preventing *severe malaria*

By chance, difference in study arms. Children randomized to 3-dose arm had higher incidence of *severe malaria* than those in the 4-dose arm *prior to dose 4*

Estimates of *severe malaria* VE were pooled across 3 and 4 dose arms until month 20 (when dose 4 given)

Result- potential appearance of greater rebound than there really was for the 3-dose arm, and higher impact of 4th dose for four-dose arm.

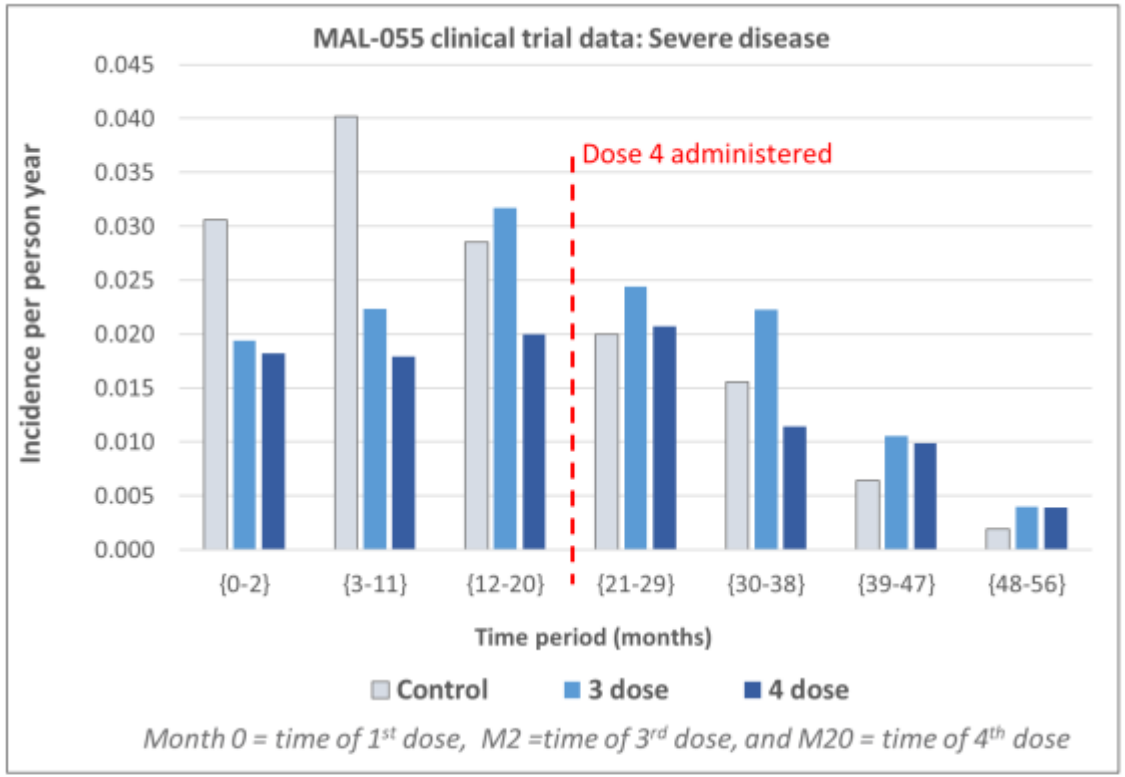


Figure 14: Vaccine impact before and after receiving the 4th dose (intention-to-treat population). Severe disease incidence per person year (MAL 055, aggregated over all clinical trial sites for 5-17 month cohort ITT population) plotted every 8 months after dose 1 is administered. The dotted line represents when dose 4 is given, month 0 indicates time of dose 1, month 2 completion of dose 3 and month 20 administration of dose 4. A difference between the 3-dose and 4-dose groups is apparent before the fourth dose is given (Annex 1).

World Health Organization

Questions to IVIR-AC

1. Given the lack of clinical data to inform different dosing intervals, are the current modelling results sufficient to support a specific policy recommendation on the optimal spacing between dose 3 and 4?
    a. In addition to the modelling, is it recommended that further monitoring be conducted during implementation of different dose schedules to collect on data on the impact of the timing of the 4th dose on vaccine effectiveness?
    b. Is it reasonable to generalise these findings on dose schedules and intervals to R21/Matrix-M? If not, what additional analyses or data would be needed to inform dose schedules for R21?
2. To what extent do the models (or proposed modelling) address potential differences in vaccine impact across transmission intensities and seasonal settings, accounting for variations in the age distribution of severe disease?
    a. For both models, does IVIR-AC have comments on the modelled impact of the timing of dose 4 across transmission intensities?
    b. Is the PATH modelling analysis able to support country decision-making on dose schedules, reflecting differences in impact between age-based, seasonal or hybrid schedules on severe disease in the first year of life vs older ages. Is there benefit to additional sensitivity analysis on vaccine coverage across the dose schedules?
    c. In the absence of clinical data on hybrid schedules in seasonal settings, is the PATH analysis sufficient to support country-decision making, or is additional monitoring during implementation recommended?
3. Does IVIR-AC have feedback on the approach and results of the sensitivity analysis conducted on the assumed efficacies for the timing of the 4th dose? (Telethon Kids model)

World Health Organization

Thank you

World Health Organization

Credit: WHO/Neil Thomas.

Swiss TPH

TIMING AND IMPACT OF A FOURTH DOSE OF RTS,S/AS01 MALARIA VACCINE IN PERENNIAL SETTINGS

February 2024

WHO IVIR-AC: Geneva, Switzerland

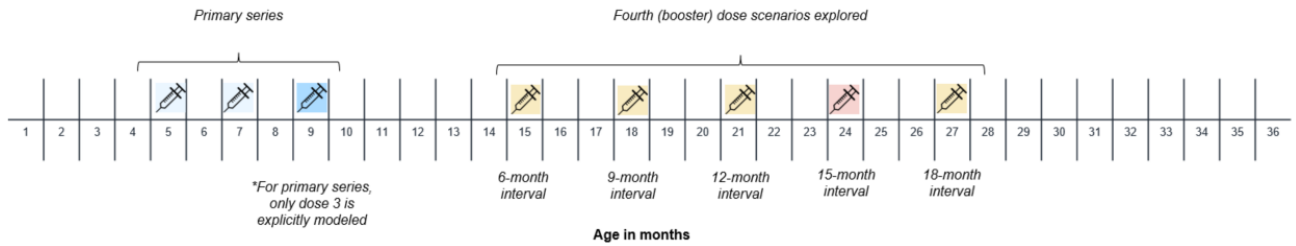
Daniella Figueroa-Downing, Sherrie L. Kelly, Aurelien Cavelan, Melissa Penny, Josephine Malinga
Contact: Melissa.Penny@uwa.edu.au

Executive summary

Objective

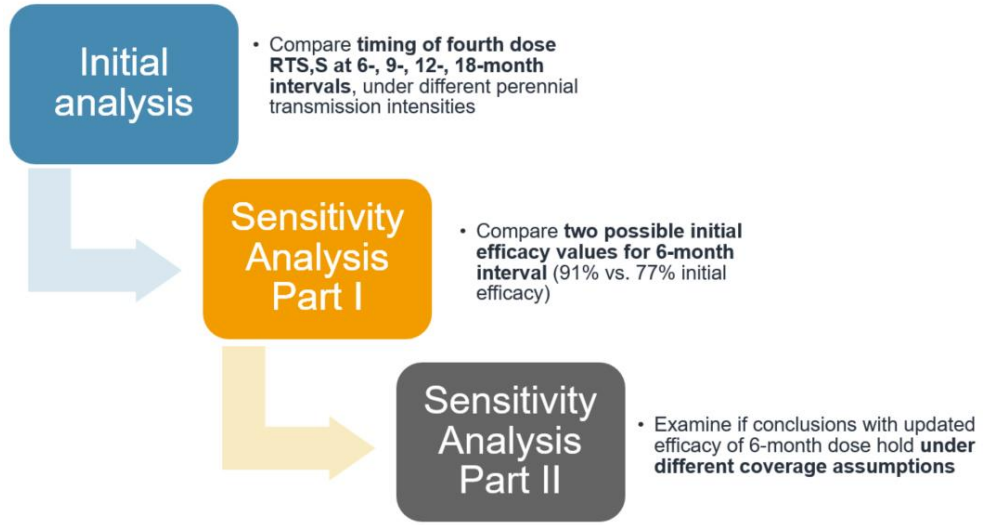
Aim

Address questions around **timing of a fourth dose of RTS,S malaria vaccine in perennial settings** under different transmission intensities and against age patterns of severe disease, considering realistic implementation linked to existing Expanded Programme on Immunisation (EPI) touch points in the second year of life.



Methods

- Modelled potential timing of a fourth dose between 15 and 27 months of age using an individual-based model for malaria transmission (OpenMalaria).
- Explored fourth dose timing different transmission intensities and against age patterns of severe disease, considering realistic implementation linked to existing EPI touch points in second year of life.
- Conducted sensitivity analysis on assumption of initial efficacy of fourth dose at 15 months of age, under different coverage assumptions.



Executive summary

Results of timing of fourth dose

Three-dose primary series substantially reduces the malaria burden

Three dose primary series substantially reduces the malaria burden across transmission settings, regardless of timing of the fourth dose.

Primary series is responsible for 70-90% of the total clinical cases averted around 60-90% of the total severe cases averted, across transmission archetypes.

This suggests that coverage of the primary series should be prioritised in the first instance.

A fourth dose delivered from 6 to 12 months after third dose would add impact

A fourth dose vaccine given 6 to 18 months after dose three could avert additional malaria cases and deaths compared with the primary series alone.

We find potential flexibility in timing the fourth dose from 6 to 12 months after dose three, even at 18 months in lower prevalence settings ($PfPR_{2-10}$ of 10%).

The majority of clinical cases would be averted in children 12 to 36 months of age for all fourth dose timings.

This suggests that a fourth dose given 6 months after primary series may still have an impact (regardless of efficacy).

Vaccine coverage is the most important determinant for impact

In settings where coverage of the primary series is low, the additional impact of a fourth dose would likely be substantially minimized as compared to a scenario with higher primary series coverage.

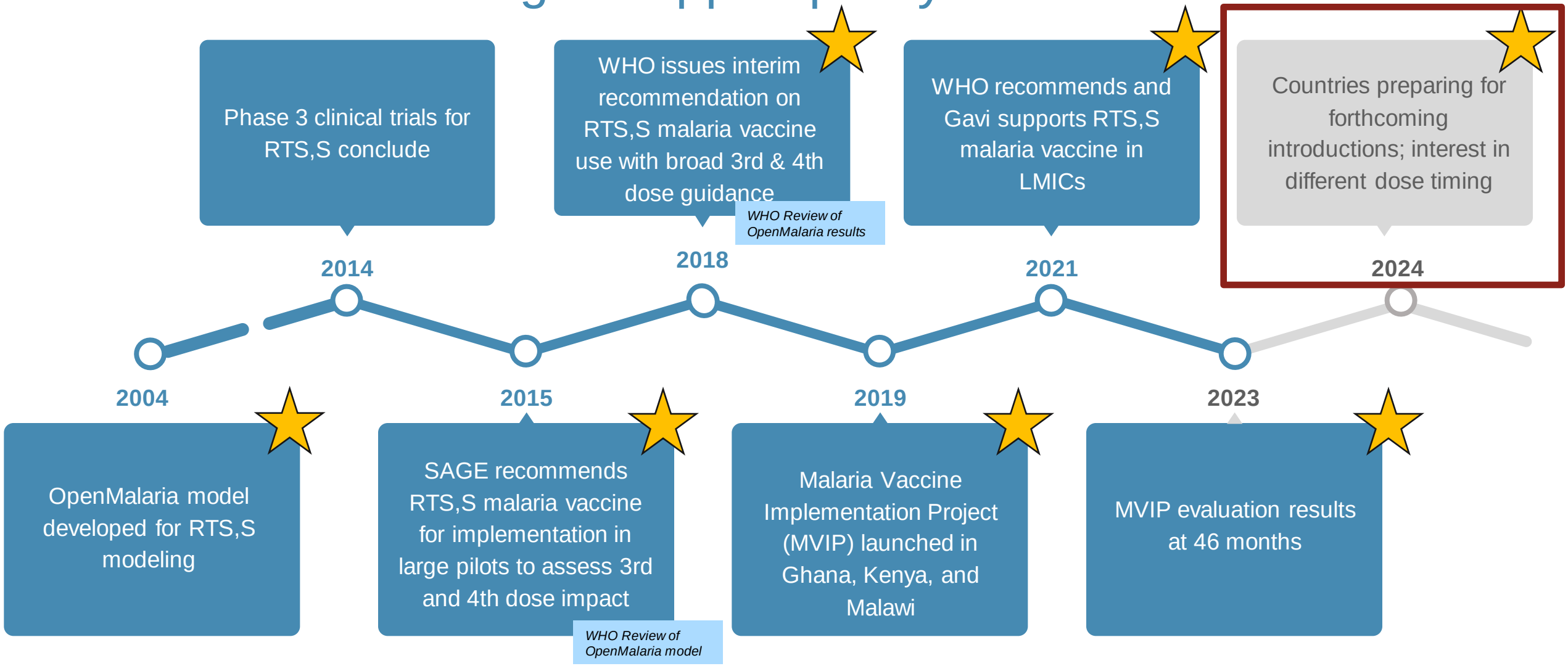
Under high drop out assumptions, a fourth dose would still have minor impact; however, coverage of a fourth dose is a crucial driver for the *added* impact (in addition to the primary series).

This suggests that timing of the fourth dose should prioritise touchpoints that will maximise coverage.

The results support timing the fourth dose in perennial settings to align with an existing immunization touchpoint in the second year of life to increase coverage and optimize the impact on malaria.

BACKGROUND

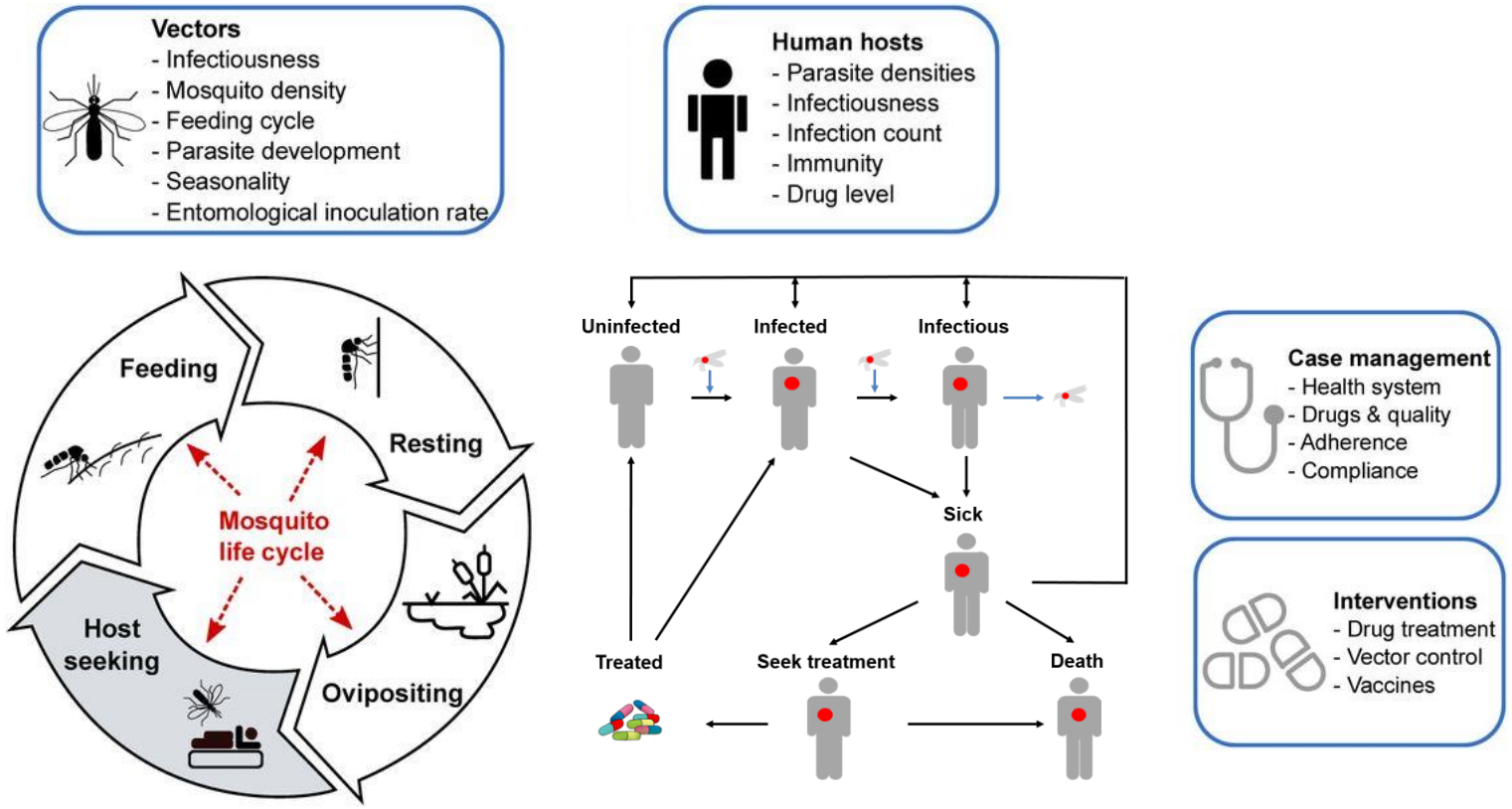
Timeline of modelling to support policy



★ Where modelling with OpenMalaria has and can continue to inform policy decisions

OpenMalaria model

OpenMalaria is an **individual-based, stochastic model of malaria transmission and disease progression** that includes dynamics of mosquito infectiousness, human host infection, blood-stage parasite densities, incidence of severe malaria, hospitalization, and mortality.



Highlight: model functionality

- **Mechanistic acquisition of immunity**

For **RTS,S vaccine**:

- Model was **calibrated to (a) historical characteristics of trial sites** and; **(b) trial implementation characteristics**
- To **match clinical endpoints** of the trial

- OpenMalaria models RTS,S as it functions: **prevention of sporozoites and therefore infection**

Swiss TPH

Modelling and scenario design

Modelling exercise comprising initial deployment scenarios and a two-step sensitivity analysis

Initial analysis

- Compare **timing of fourth dose RTS,S at 6-, 9-, 12-, 18-month intervals**, under different perennial transmission intensities

Sensitivity Analysis Part I

- Compare **two possible initial efficacy values for 6-month interval** (91% vs. 77% initial efficacy)

Sensitivity Analysis Part II

- Examine if conclusions with updated efficacy of 6-month dose hold **under different coverage assumptions**

** Efficacy bounds determined by available data; did not explore all possible parameter values*

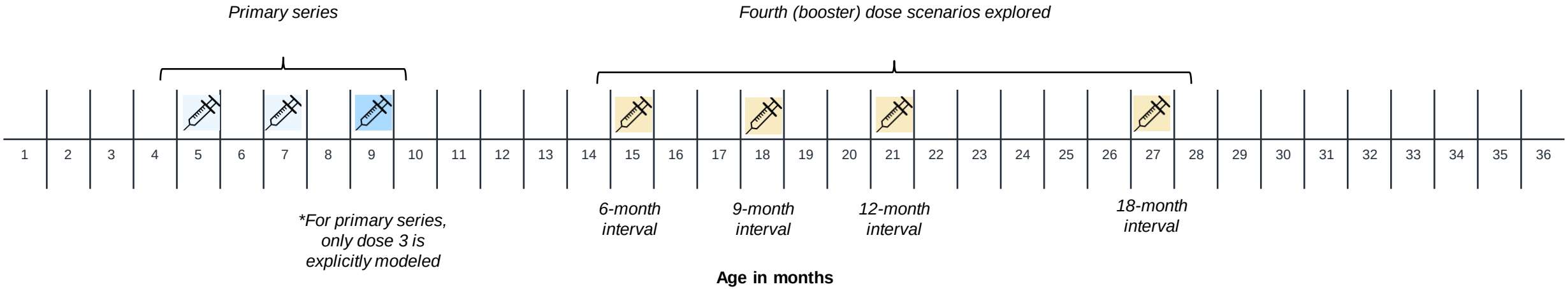
RTS,S scenarios: model and simulation assumptions

Parameter	Scenario
Study period	10 years
Population	100,000 population, with children disaggregated by age in months up to 5 years of age
Baseline transmission	*Pf*PR$_{2-10}$: from 10% to 60%, with **20% as the default reference scenario** in perennial settings
Access to care	Probability of access to uncomplicated case management within 14-days of infection: • Low: 10% • **Medium: 30% (default reference scenario)** • High: 50%
RTS,S assumptions	<u>Primary series efficacy</u> • Dose 3 (given at 9 months of age) with **91%** initial efficacy against infection, half-life 7.32 months[1] <u>Efficacy by timing of dose 4</u> • 6 months (given at 15 months of age) with **77%** initial efficacy assumed (85% efficacy of dose 3) • 9 months (given at 18 months of age) with **77%** initial efficacy assumed (85% efficacy of dose 3) • 12 months (given at 21 months of age) with **77%** initial efficacy assumed (85% efficacy of dose 3) • 18 months (given at 27 months of age) with **49%** initial efficacy (54% efficacy of dose 3)[1] <u>Coverage</u> • Primary series (doses 1-3): **100% (default reference scenario)** or see scenario details • Booster (dose 4): **100% (default reference scenario)** or see scenario details

[1]Modeling was carried out using OpenMalaria, an individual-based, stochastic model of malaria transmission and disease progressing that includes dynamics of mosquito infectiousness, human host infection, blood-stage parasite densities, incidence of severe malaria, hospitalization, and mortality This study builds on previously described work to develop and fit a micro-simulation model for predicting the impact of RTS,S malaria vaccine (Penny 2016).

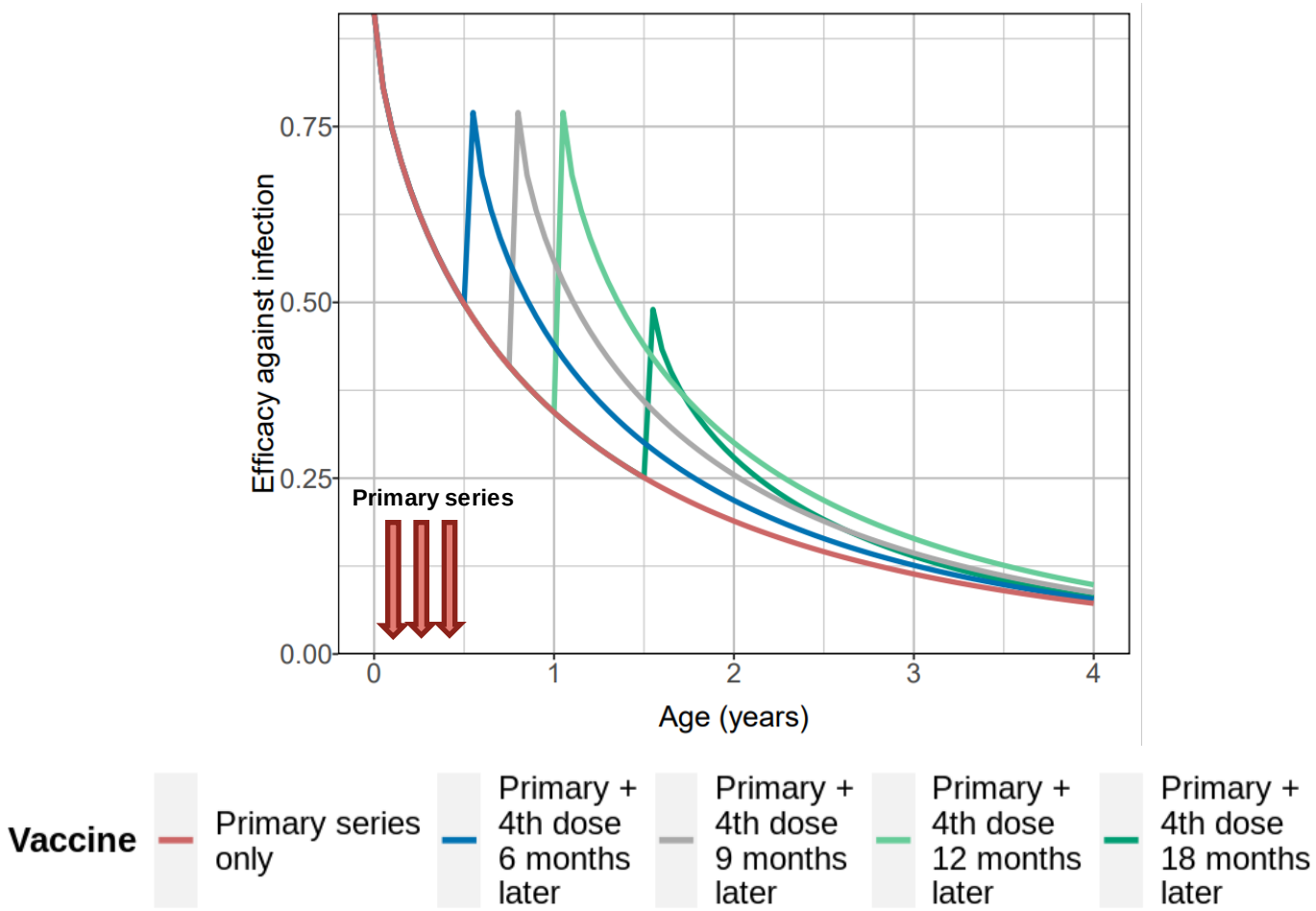
EIR: entomological inoculation rate. *Pf*PR$_{2-10}$: *Plasmodium falciparum* parasite rate standardized to the age group 2-10 years.

Modelled potential timing of a fourth dose of RTS,S vaccine between 15 and 27 months of age in perennial settings



Dose timing	Age of delivery
Dose 3 (primary series)	*Delivered at **9 months of age***
Dose 4, 6-month interval	Delivered at **15 months of age**
Dose 4, 9-month interval	Delivered at **18 months of age**
Dose 4, 12-month interval	Delivered at **21 months of age**
Dose 4, 18-month interval	Delivered at **27 months of age**

RTS,S vaccine deployment and efficacy decay profile for scenarios



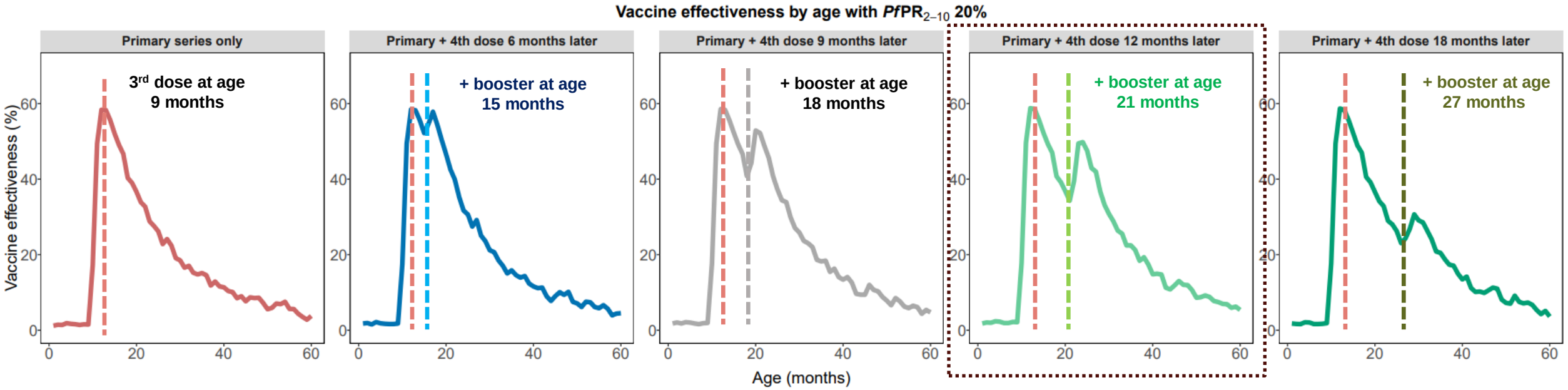
Primary series (doses 1 to 3) is deployed at monthly intervals in children aged 5-9 months[1]
Booster vaccine (dose 4) is deployed at 6, 9, 12, or 18[1] months after dose 3

[1]This study builds on work previously described in Penny 2016

Swiss TPH

Results

Model estimated vaccine effectiveness against clinical cases depending on deployment timings and vaccine booster efficacy profiles



Vaccine effectiveness, defined as the proportion of clinical cases averted (here shown for parasite prevalence of 20%)

RTS,S vaccine timing

- **Primary series** (doses 1 to 3) is deployed at monthly intervals in **children aged 5-9 months** assuming maximum initial efficacy achieved at 9 months of age after dose 3
- **Booster** (dose 4) is deployed 6, 9, 12, or 18 months after dose 3

Overall findings for perennial settings

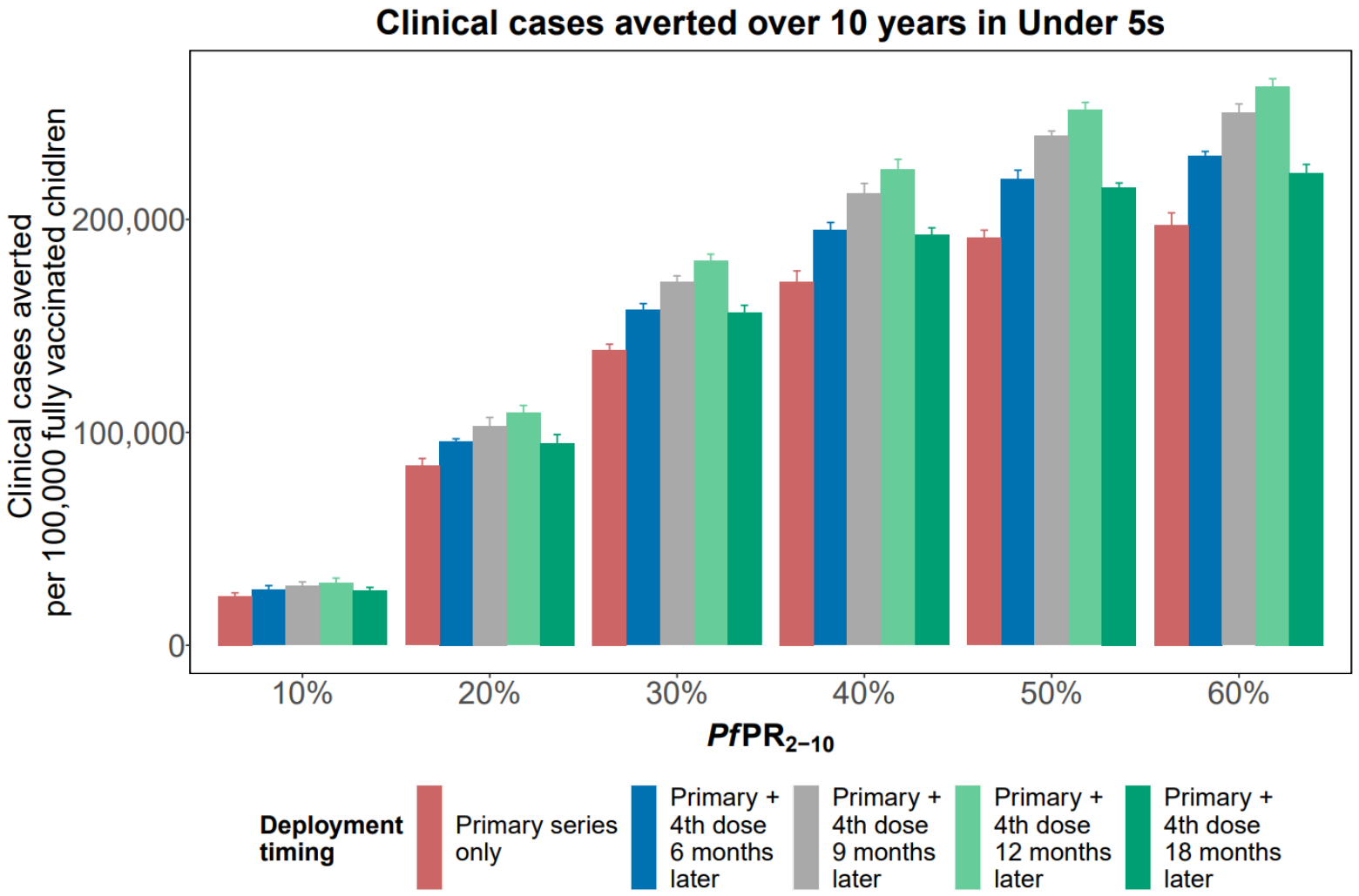
- **Booster impact varied somewhat by 4th dose schedule timing**
- **The highest impact was observed when dose 4 is deployed 12 months after dose 3** (under the assumption that a booster dose 6, 9 and 12 months following primary series to 85% of primary[1], and at 18 months to 54% of primary[2])

*Pf*PR$_{2-10}$: *Plasmodium falciparum* parasite rate standardized to the age group 2–10 years

[1] *Malinga et al. (forthcoming) based additional analyses of Chandramohan et al., 2021*
[2] *Penny, Pemberton-Ross & Smith, 2015*

Swiss TPH

Clinical cases averted by prevalence for children under 5 years



*Pf*PR$_{2-10}$: *Plasmodium falciparum* parasite rate standardized to the age group 2–10 years

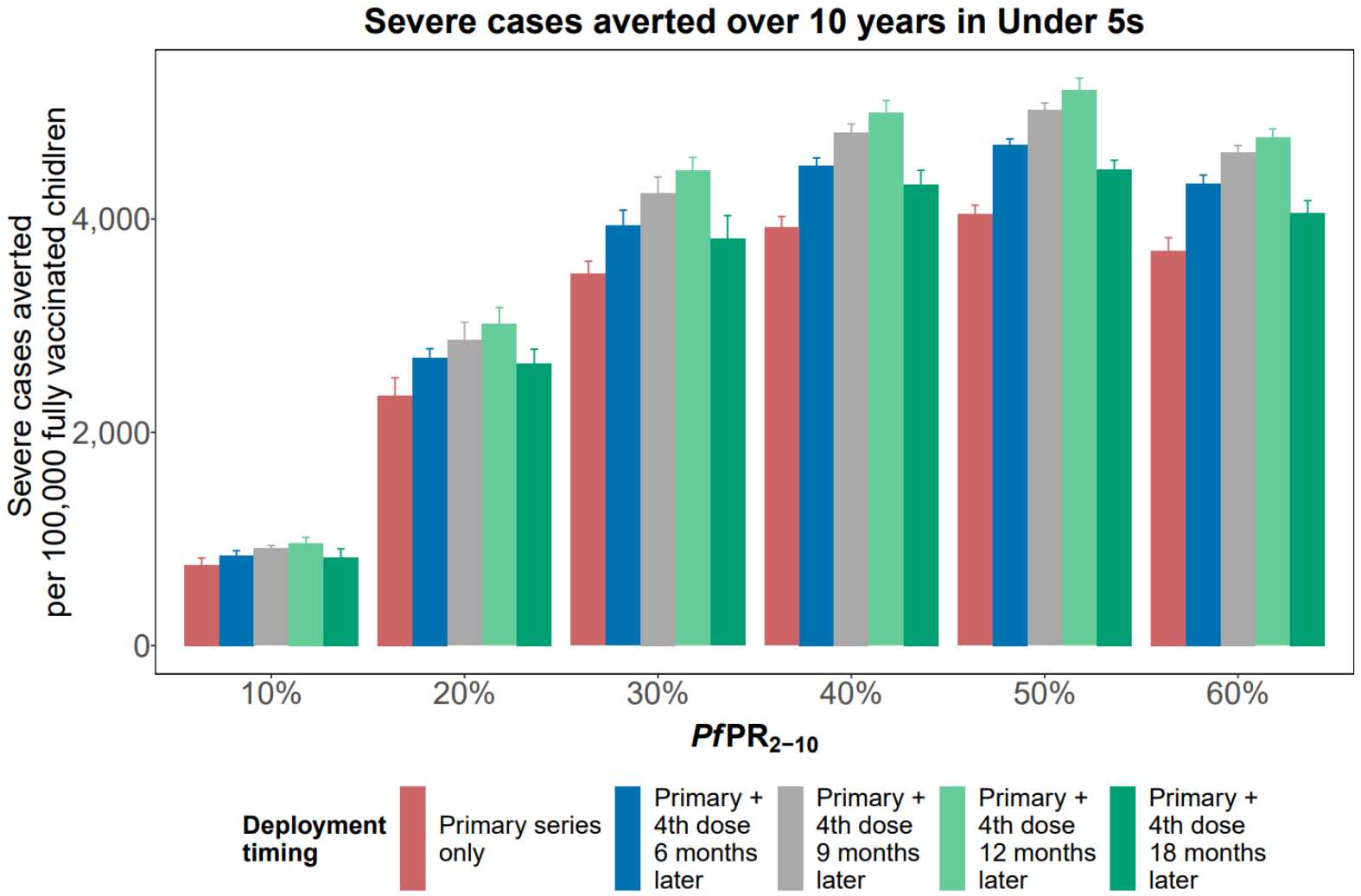
Overall findings for perennial settings

- Events averted **varies by baseline prevalence**
- Primary series (doses 1-3) substantially reduces malaria burden
- Overall, the **booster** (dose 4) shows the largest burden reduction when deployed **12 months** after dose 3 in settings with transmission prevalence (*Pf*PR$_{2-10}$) from 10% to 60%

Recommendations

- Given the timing and efficacy modelled, we suggest there is **potential flexibility in timing the 4th dose between 6 and 12 months** after dose 3, even at 18 months after dose 3 in lower prevalence settings (*Pf*PR$_{2-10}$ 10%)
- Scheduling the **4th dose could be aligned with an existing health routine immunization touchpoint (EPI) in the second year of life**

Severe cases averted by prevalence for children under 5 years



*Pf*PR$_{2-10}$: *Plasmodium falciparum* parasite rate standardized to the age group 2–10 years

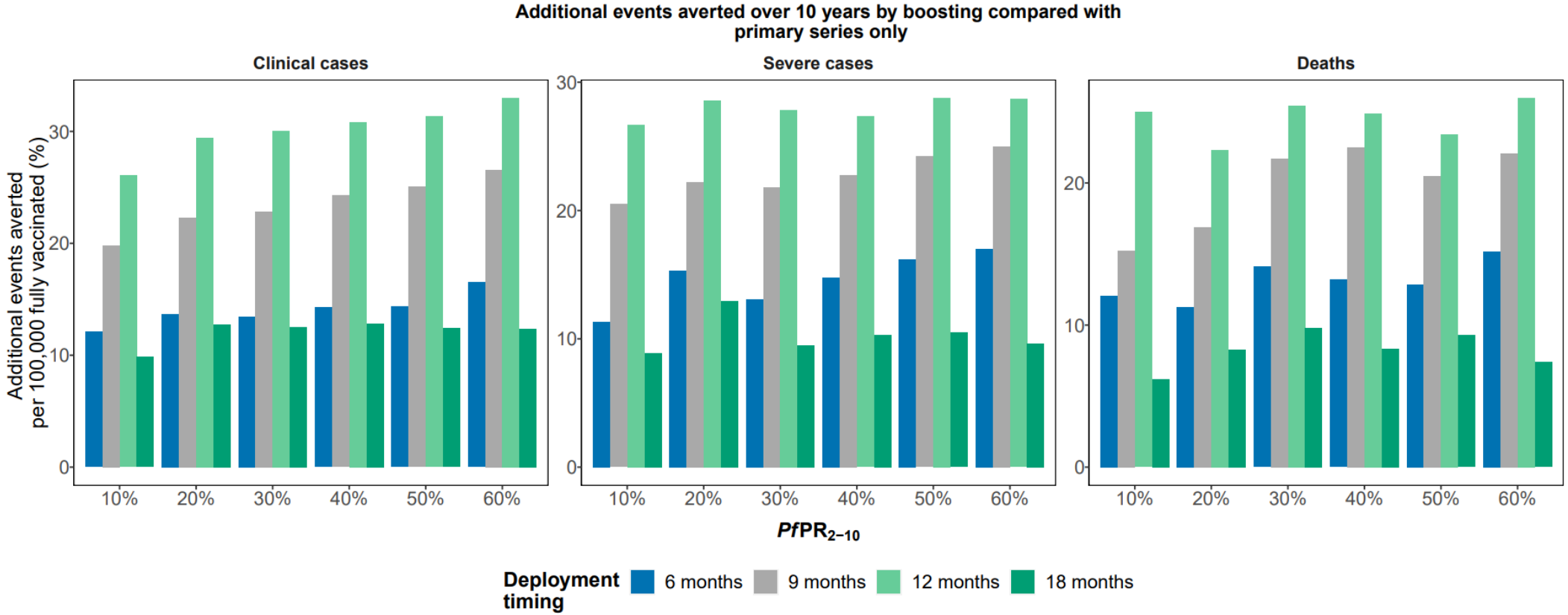
Overall findings for perennial settings

- Events averted **varies by baseline prevalence**
- Primary series (doses 1-3) substantially reduces malaria burden
- Overall, the **booster** (dose 4) shows the largest burden reduction when deployed **12 months** after dose 3 in settings with transmission prevalence (*Pf*PR$_{2-10}$) from 10% to 60%

Recommendations

- Given the timing and efficacy modelled, we suggest there is **potential flexibility in timing the 4th dose between 6 and 12 months** after dose 3, even at 18 months after dose 3 in lower prevalence settings (*Pf*PR$_{2-10}$ 10%)
- Scheduling the **4th dose could be aligned with an existing health routine immunization touchpoint (EPI) in the second year of life**

Proportion of additional benefit of boosting compared with primary series alone

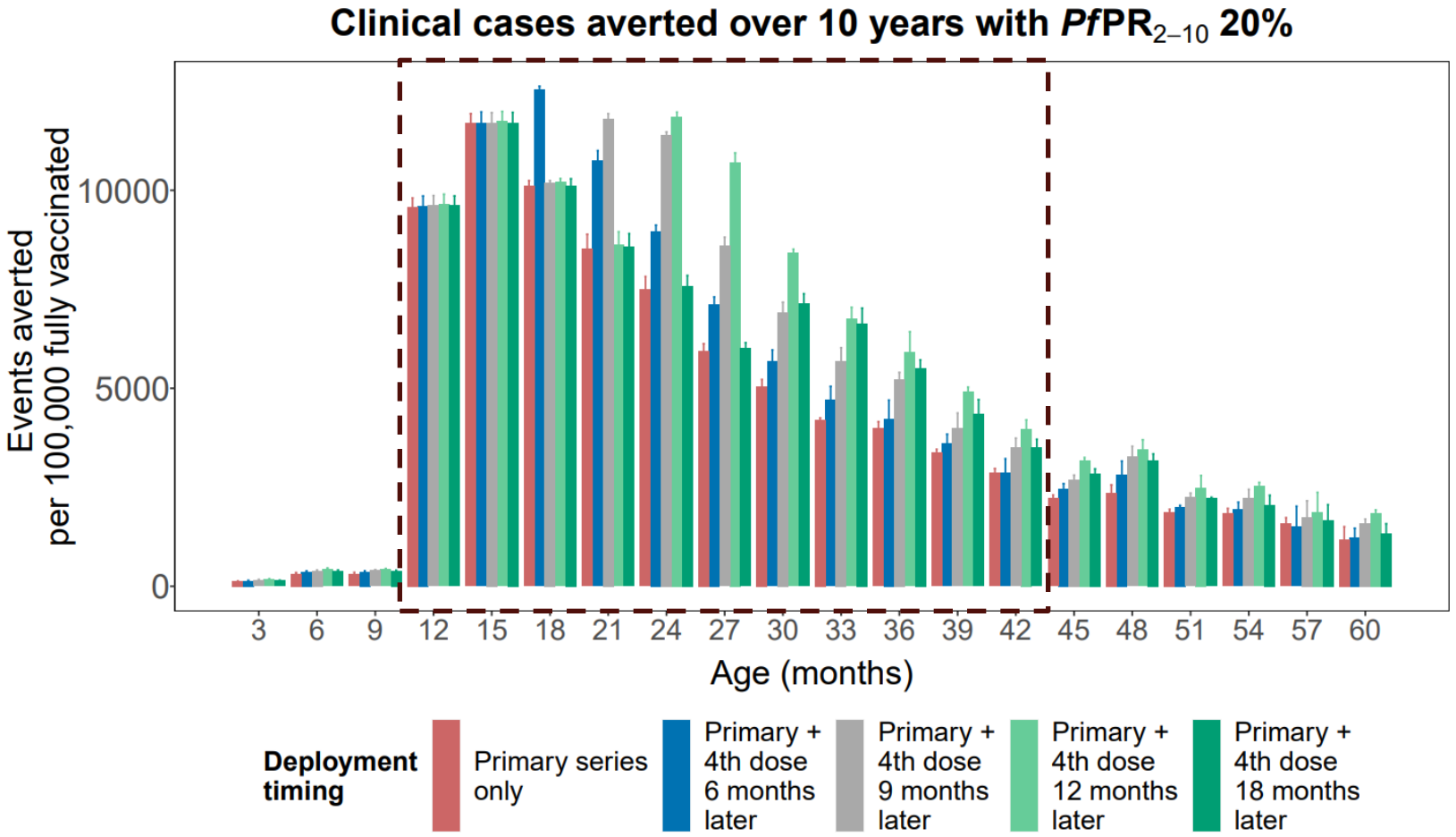


Overall findings for perennial settings

For all health outcomes:

- Between **20%-30% more clinical cases could be averted with a fourth dose** at month 9 or 12 month or 10% more at 6 or 18 month timing compared with primary series alone in settings with transmission prevalence (*Pf*PR_{2-10}) from 20% to 60% less when *Pf*PR_{2-10}<10%.
- Between **15%-30% more severe cases could be averted with a fourth dose** at month 6, 9 or 12 month compared with primary series alone. Less than 10% of additional severe cases would be prevented at 18 month timing across transmission settings.
- Given the timing and efficacy modelled, we find **potential flexibility in timing the 4th dose between 6 and 12 months** after dose 3

Clinical cases averted over 10 years by age for children under 5 years (*Pf*PR$_{2\text{-}10}$ 20%)

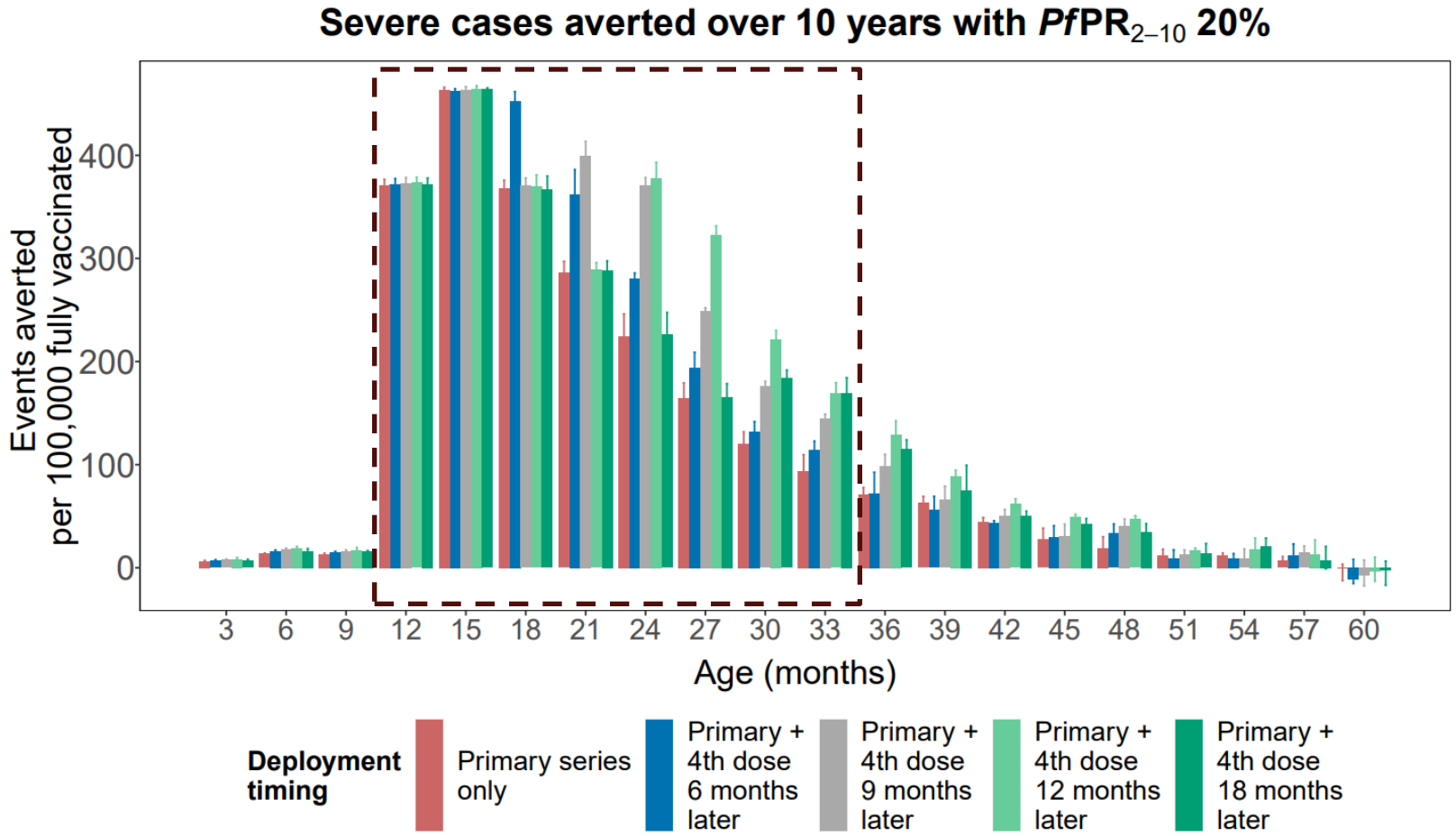


Overall findings for perennial settings

- The primary series (doses 1-3) substantially reduces malaria burden
- The **booster** (dose 4) shows the biggest burden reduction when deployed **12 months** after dose 3 until ~2 years of age
- More clinical events are averted for **children 12 to 40 months of age** for all booster timings

Note, results for severe cases and deaths averted are provided in Additional results

Severe cases averted over 10 years by age for children under 5 years (*Pf*PR$_{2\text{-}10}$ 20%)

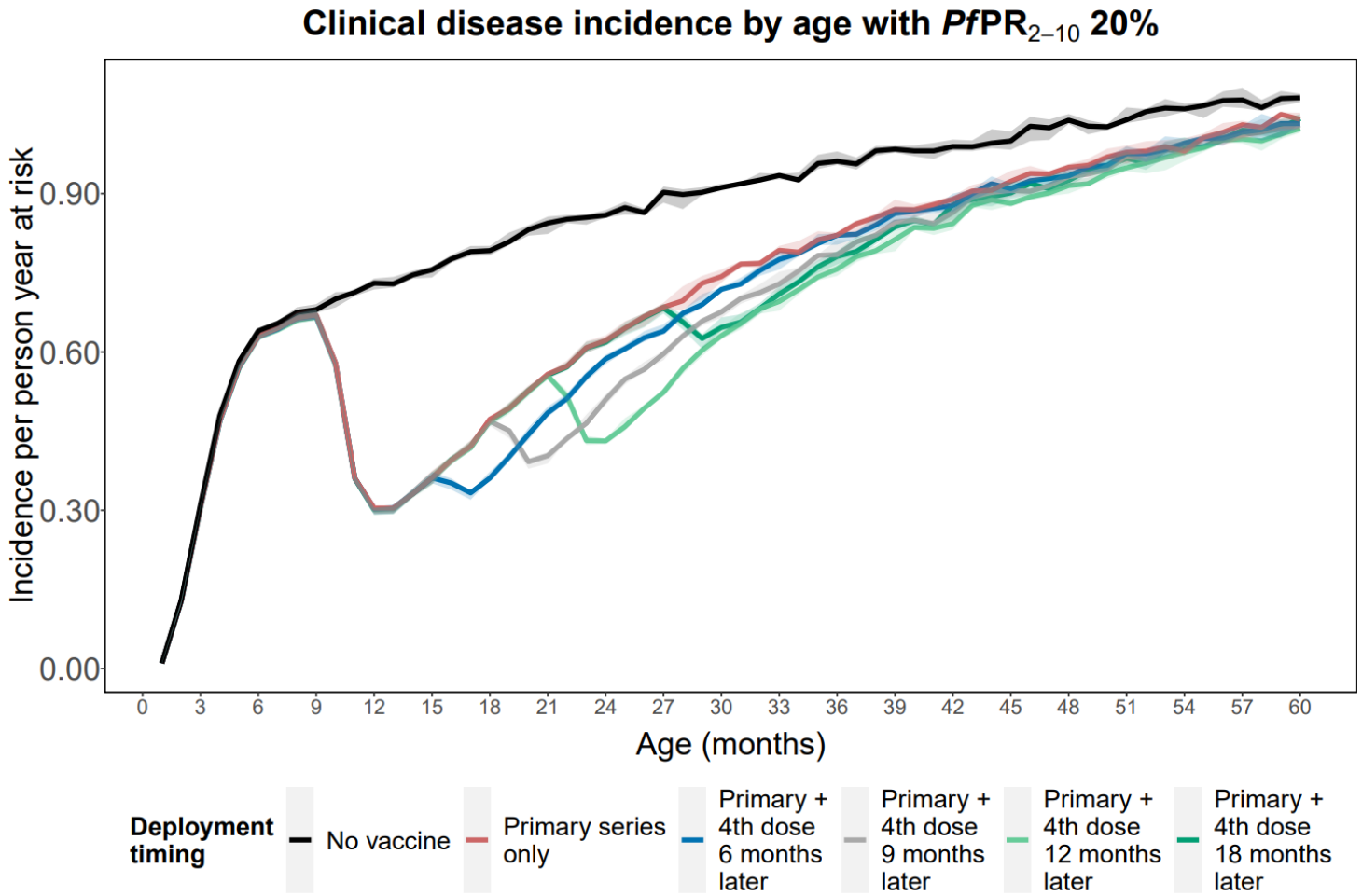


Overall findings for perennial settings

- The primary series (doses 1-3) substantially reduces malaria burden
- The **booster** (dose 4) shows the biggest burden reduction when deployed **12 months** after dose 3 until ~2 years of age
- More severe events are averted for **children 12 to 30 months of age** for all booster timings

Note, results for severe cases and deaths averted are provided in Additional results

Incidence of clinical cases per person year at risk by age for children under 5 years (*Pf*PR$_{2\text{-}10}$ 20%)

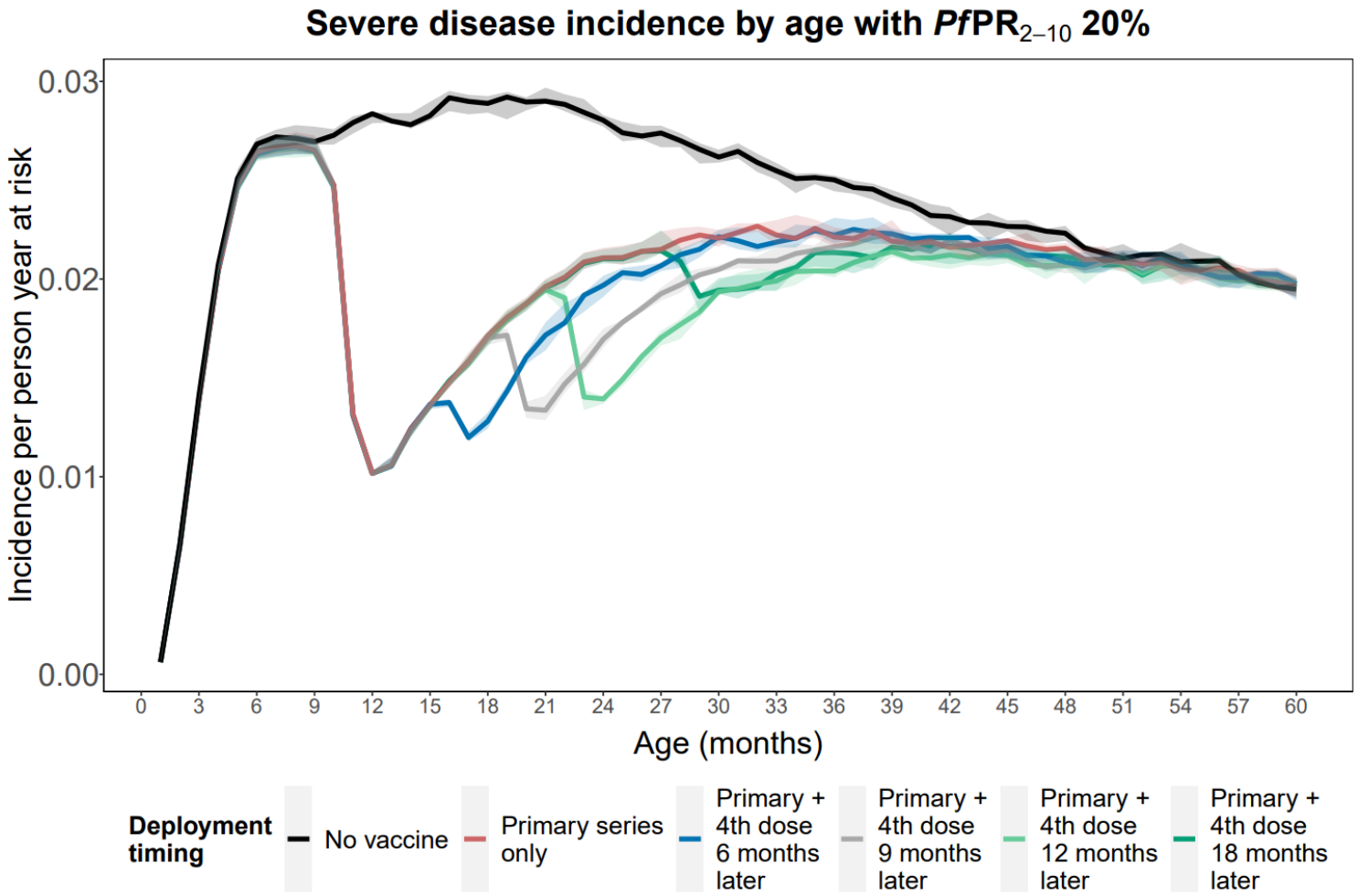


Overall findings for perennial settings

For all health outcomes:

- **Deploying vaccine doses influences the age patterns of disease**
- Incidence declines from 9 months (after the primary series is deployed)
- **Booster timing has an additional effect on the patterns of disease and deaths in all transmission settings**

Incidence of clinical cases per person year at risk by age for children under 5 years (*Pf*PR$_{2\text{-}10}$ 20%)



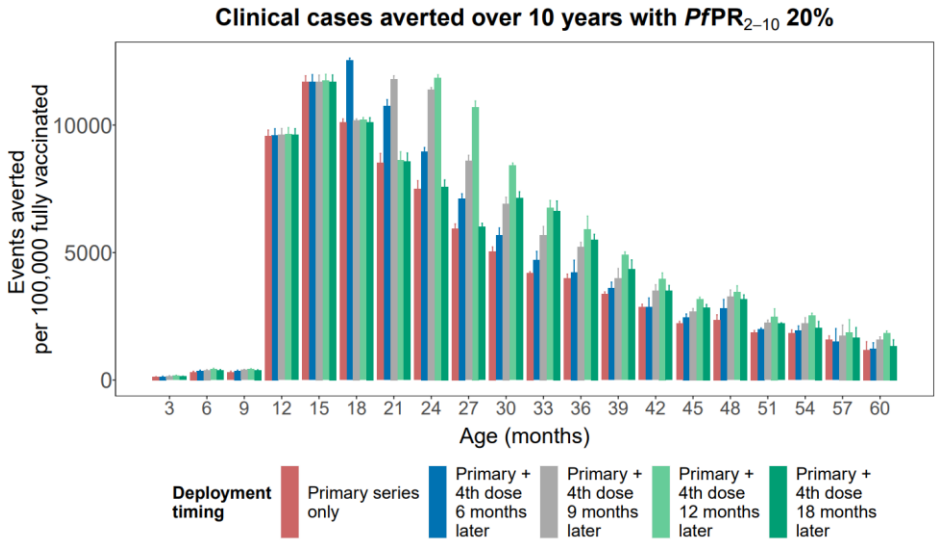
Overall findings for perennial settings

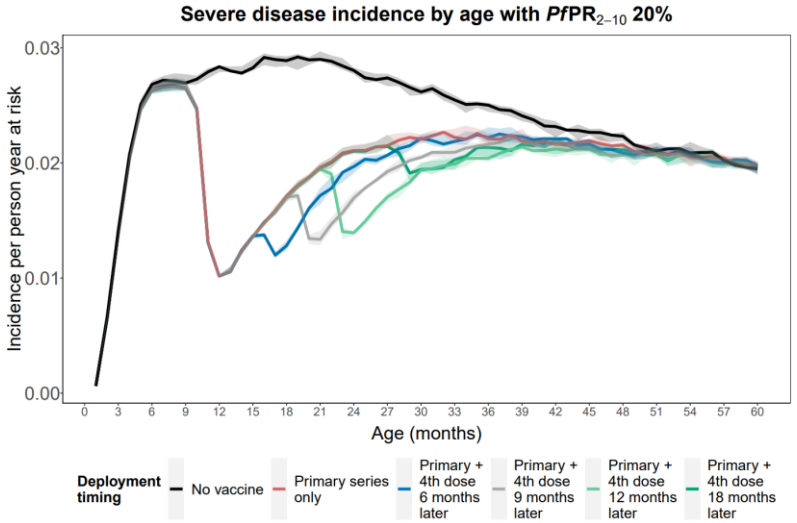
For all health outcomes:

- **Deploying vaccine doses influences the age patterns of disease**
- Incidence declines from 9 months (after the primary series is deployed)
- **Booster timing has an additional effect on the patterns of disease and deaths in all transmission settings**

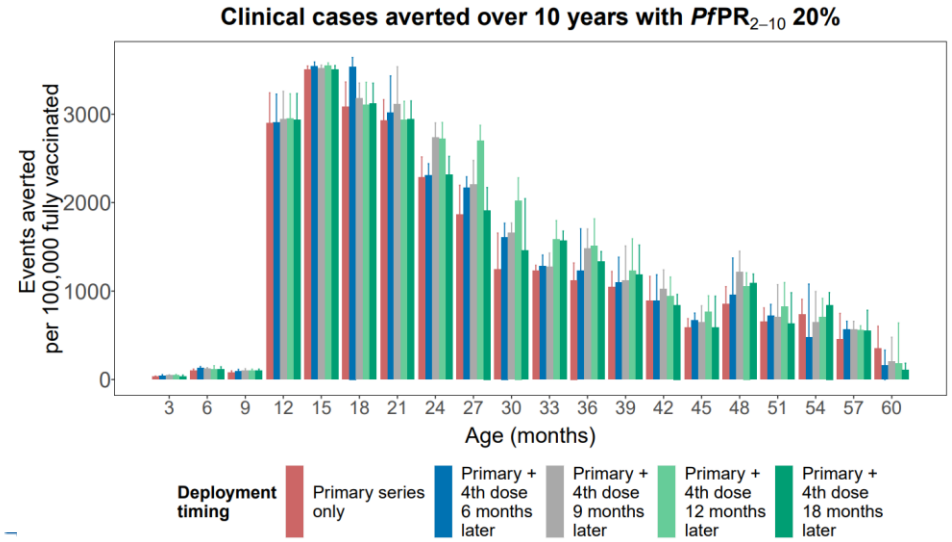
When RTS,S vaccine coverage is low, age patterns of clinical and severe disease are not as impacted (illustrated here in *Pf*PR$_{2-10}$ 20%)

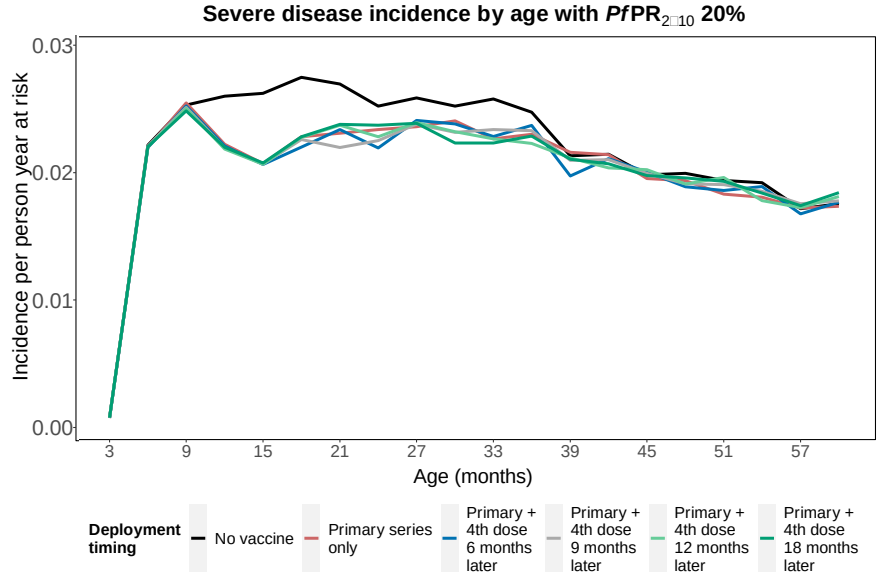
High coverage
Primary series (100%)
Booster (100%)





Low coverage
Primary series (30%)
Booster (15%)





Summary of Results

The results support timing a fourth dose of RTS,S malaria vaccine to align with an existing immunization touchpoint in the second year of life to increase coverage and optimize the impact in perennial settings.

Three-dose primary series substantially reduces the malaria burden

Three dose primary series substantially reduces the malaria burden across transmission settings, regardless of timing of the fourth dose.

Primary series is responsible for 70-90% of the total clinical cases averted around 60-90% of the total severe cases averted, across transmission archetypes.

This suggests that coverage of the primary series should be prioritised in the first instance.

A fourth dose delivered from 6 to 12 months after third dose would add impact

A fourth dose vaccine given 6 to 18 months after dose three could avert additional malaria cases and deaths compared with the primary series alone.

The fourth dose would avert the largest proportion of additional cases if given at a 12- or 9- months interval. A 6-month interval would have a greater impact on severe cases than clinical cases, across transmission intensities.

This suggests that timing of the fourth dose should consider transmission intensity and underlying pattern of disease, as well as the main impact of interest: clinical cases, severe cases, or deaths.

Vaccine coverage is the most important determinant for impact

In settings where coverage of the primary series is low, the additional impact of a fourth dose would likely be substantially minimized as compared to a scenario with higher primary series coverage.

Under high drop out assumptions, a fourth dose would still have minor impact; however, coverage of a fourth dose is a crucial driver for the added impact (in addition to primary series).

This suggests that timing of the fourth dose should prioritise touchpoints that will maximise coverage.

Thank you for your attention!

ACKNOWLEDGEMENTS

SwissTPH: Disease Modelling Unit

Melissa Penny, PhD

Josephine Malinga, PhD

Sherrie L. Kelly, PhD

Aurélien Cavelan, PhD

Additional thanks to:

Lydia Braunack-Mayer

Andrew Shattock

Funder and Collaborators

PATH

World Health Organization

BILL & MELINDA GATES foundation

University of Basel

sciCORE | Center for Scientific Computing

TELETHON KIDS INSTITUTE

Discover. Prevent. Cure.

THE UNIVERSITY OF WESTERN AUSTRALIA

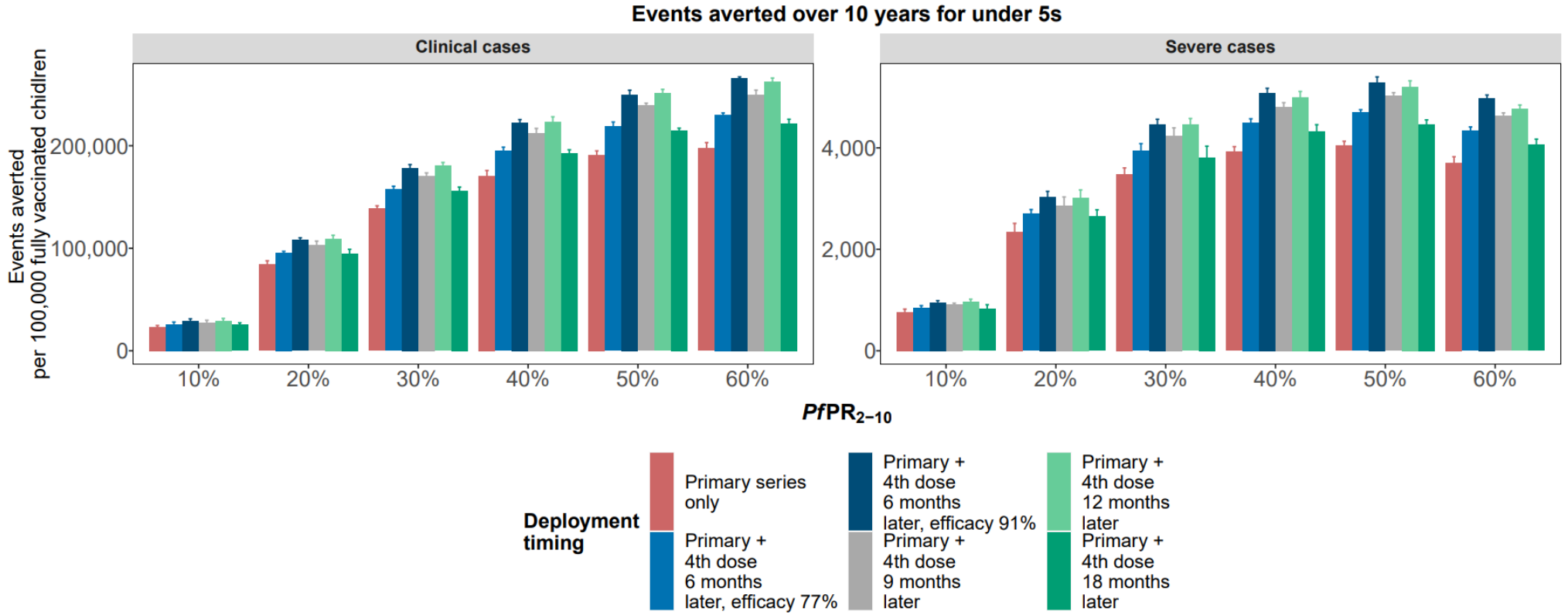
Sensitivity Analysis
Part I: Initial efficacy of 6-month interval

Objective: Compare impact of two possible initial efficacy values for 6-month interval

- Upper and lower efficacy bounds based on available data (did not explore full possible parameter values)

Sensitivity Analysis, Part 1 – efficacy only	
6-month, efficacy	**91%** initial efficacy (original analysis) **77%** initial efficacy (same as 12-month efficacy)

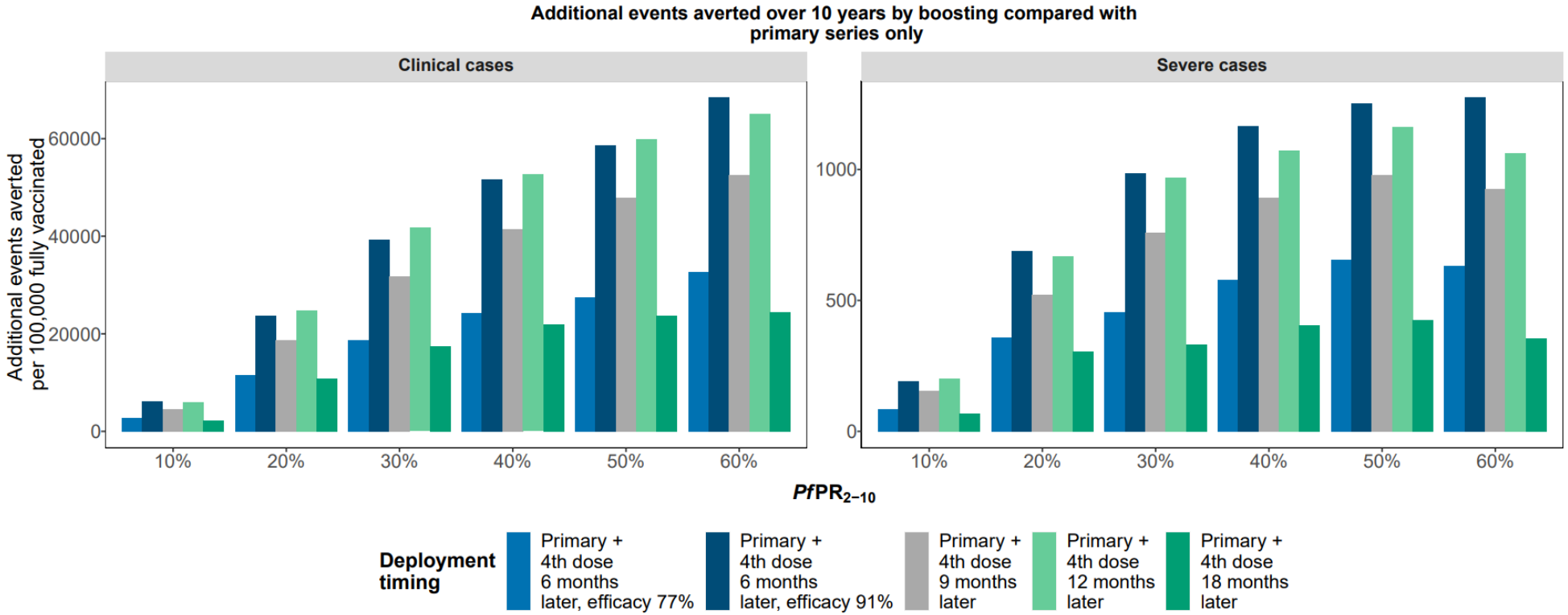
Sensitivity Analysis: initial efficacy for 6-months



Overall findings for perennial settings (sensitivity analysis of initial efficacy)

- Overall, the **booster (dose 4) deployed 6 months** after dose 3 may still **avert additional clinical and severe cases** in all transmission settings.
- A fourth dose deployed at a 6-month interval still provides more burden reduction than a fourth dose deployed at 18-month interval in all transmission settings.
- At higher efficacy assumption of 6-month interval, this dosing schedule would avert the most cases over a 10 year time period.

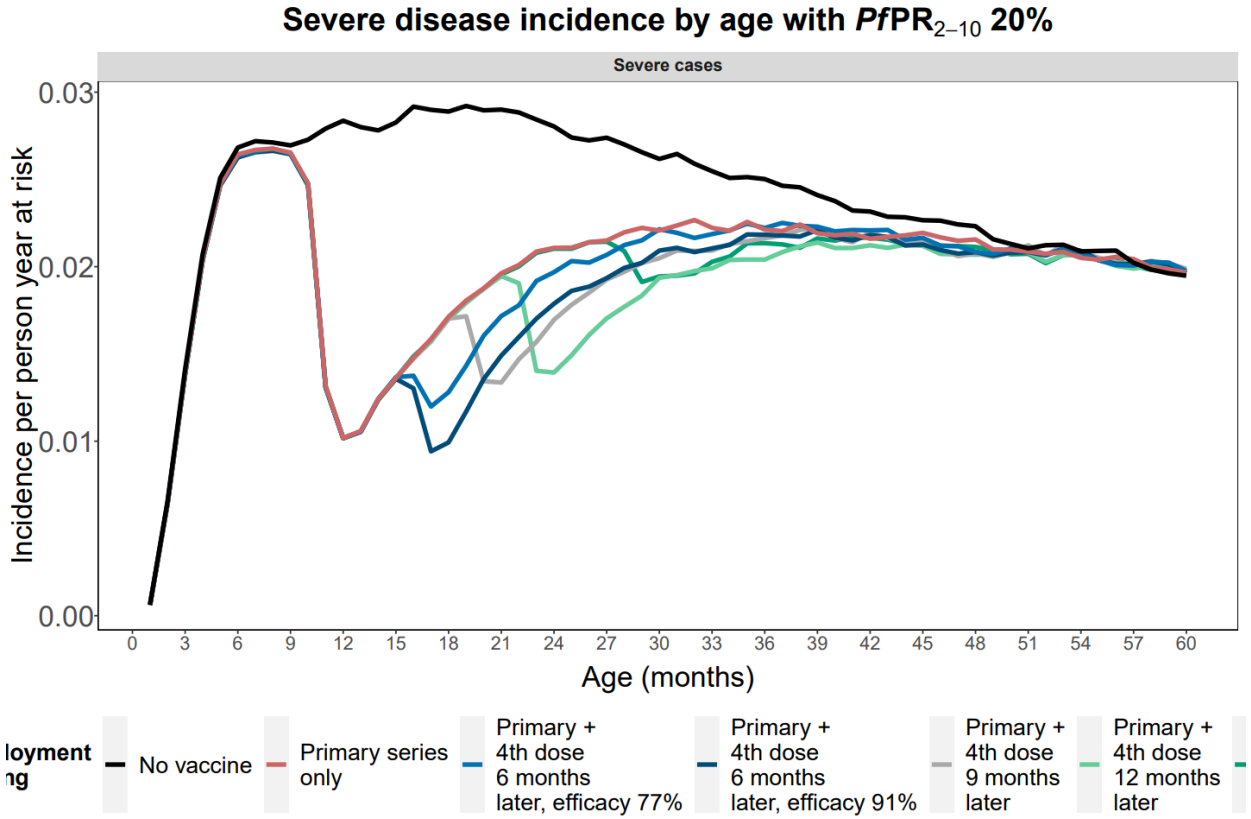
Sensitivity Analysis: initial efficacy for 6-months



Overall findings for perennial settings (sensitivity analysis of initial efficacy)

- Overall, the **booster (dose 4) deployed 6 months** after dose 3 may still **avert additional clinical and severe cases** in all transmission settings.
- A fourth dose deployed at a 6-month interval still provides more burden reduction than a fourth dose deployed at 18-month interval in all transmission settings.
- **At higher efficacy assumption of 6-month interval, this dosing schedule would avert the most cases over a 10 year time period**.

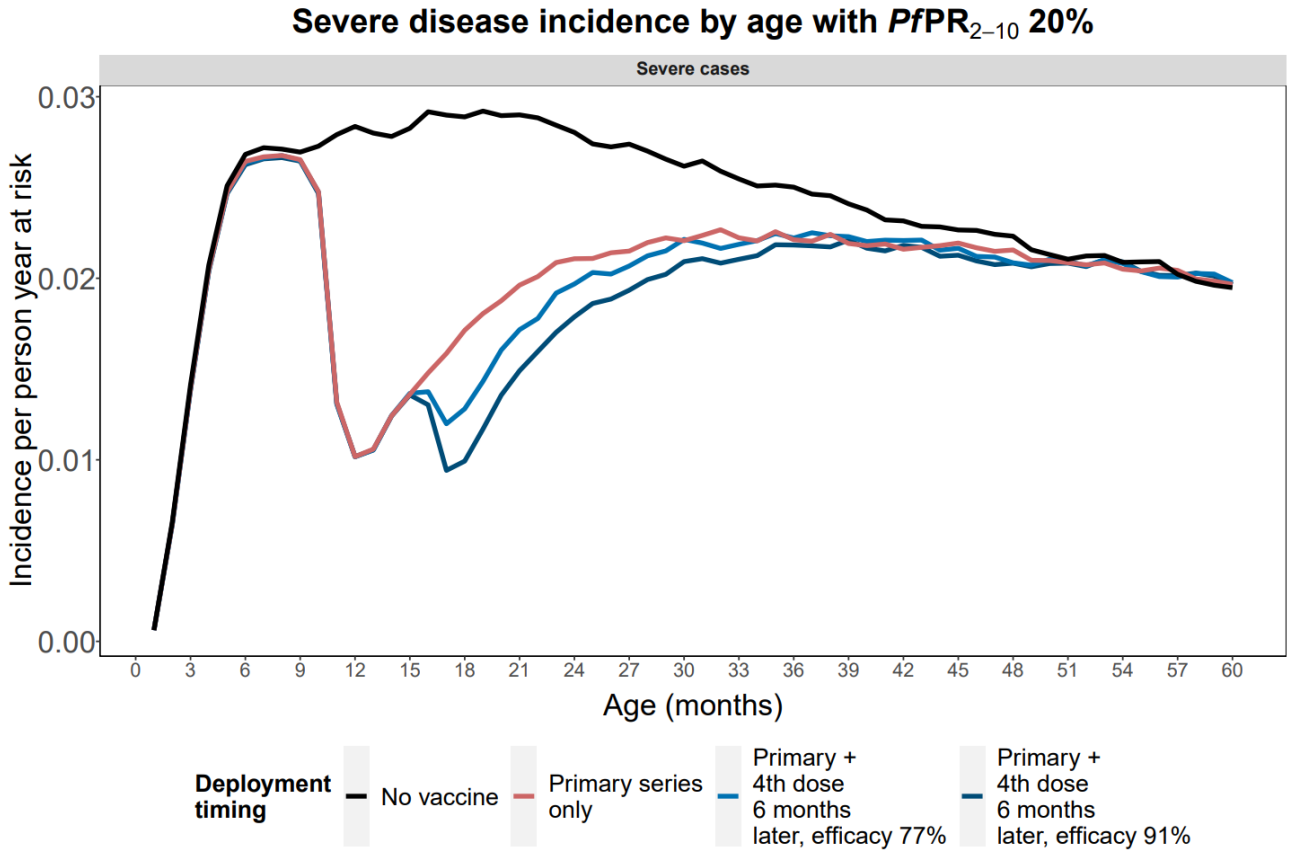
Incidence of cases per person year at risk by age for children under 5 years (*Pf*PR$_{2-10}$ 20%) – comparing 6-month efficacy



Overall findings for perennial settings

- **Deploying vaccine at 6-months, with either lower (light blue) or higher (dark blue) efficacy, has effect on age patterns of disease**
- At 6 months with lower efficacy (light blue), impact is seen in earlier age groups based on deployment age but not as well sustained in later age groups

Focus: Comparison of two 6-month efficacy assumptions and impact on incidence of severe disease



Overall findings for perennial settings

- Deploying vaccine at 6-months, with either lower (light blue) or higher (dark blue) efficacy, has effect on age patterns of disease
- At 6 months with lower efficacy (light blue), impact is seen in earlier age groups based on deployment age but not as well sustained in later age groups

March 2024

Modelling RTS,S delivery strategies in seasonal transmission settings

IVIR-AC Session 4

Hayley Thompson, Hannah Slater, Scott Gordon

hthompson@path.org

PATH

Background

Age-based schedules

Hybrid schedules

Multi-schedule comparisons

Summary

Background

Prior modelling work has been used to understand the potential public health impacts of the RTS,S when delivered at scale in perennial and seasonal settings of malaria transmission[1,2].

Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models

Melissa A Penny, Robert Verity*, Caitlin A Bever*, Christophe Sauboin*, Katya Galactionova, Stefan Flasche, Michael T White, Edward A Wenger, Nicolas Van de Velde, Peter Pemberton-Ross, Jamie T Griffin, Thomas A Smith, Philip A Eckhoff, Farzana Muhib, Mark Jit, Azra C Ghani*

Seasonal use case for the RTS,S/AS01 malaria vaccine: a mathematical modelling study

Hayley A Thompson, Alexandra B Hogan, Patrick G T Walker, Peter Winskill, Issaka Zongo, Issaka Sagara, Halidou Tinto, Jean-Bosco Ouedraogo, Alassane Dicko, Daniel Chandramohan, Brian Greenwood, Matt Cairns, Azra C Ghani

A third vaccine schedule has been proposed in seasonal settings that hasn't previously been evaluated in field trials or modelling scenarios. This schedule referred to as a hybrid schedule proposes to use age-based vaccination for the first three doses of RTS,S followed by subsequent doses timed in line with the peak transmission season

This work uses a well-established and validated model of malaria transmission and a similar analytic framework to prior modelling exercises to compare the potential public health impact of age-based, hybrid, and fully-seasonal RTS,S schedules in settings of seasonal malaria transmission.

1. https://doi.org/10.1016/S0140-6736(15)00725-4
2. https://doi.org/10.1016/S2214-109X(22)00416-8

PATH

Key Questions of interest

Age-based schedules

- What is the public health impact of different **vaccination ages** for the **primary series?**
- What is the public health impact of the **minimum interval** between dose-3 and dose-4?

Hybrid schedules

- What is the public health impact of different **minimum dose spacing intervals** between dose-3 and dose-4?

Multi-schedule comparisons

- **Which RTS,S schedule** provides the **greatest public health impact** in seasonal settings?
- How does the **degree of seasonality** impact schedule comparisons?
- How does the **inclusion of a 5th dose** of RTS,S in fully-seasonal and hybrid schedules impact schedule comparisons?

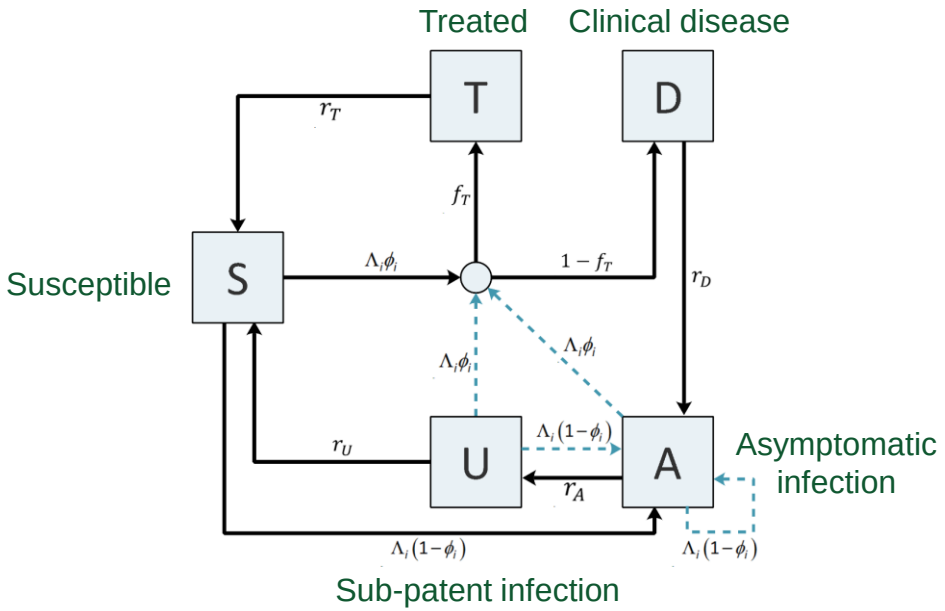
PATH

Mathematical model

Model structure

The Imperial College London Malaria Transmission Model is used for this analysis. the model package and code is publicly available on GitHub (mrc-ide.github.io/malariasimulation) and has been extensively peer-reviewed.

- Age-structured individual-based model of *P. falciparum* transmission
- Consists of human component including immunity acquisition and heterogeneity in biting exposure, and mosquito component including life cycle
- Incorporates current suite of malaria interventions
- Reviewed by previous IVIR-AC committees in RTS,S review processes



https://doi.org/10.1371/journal.pmed.1000324
https://doi.org/10.1038/ncomms4136
https://doi.org/10.1098/rspb.2014.2657
https://doi.org/10.1016/S1473-3099(15)00423-5

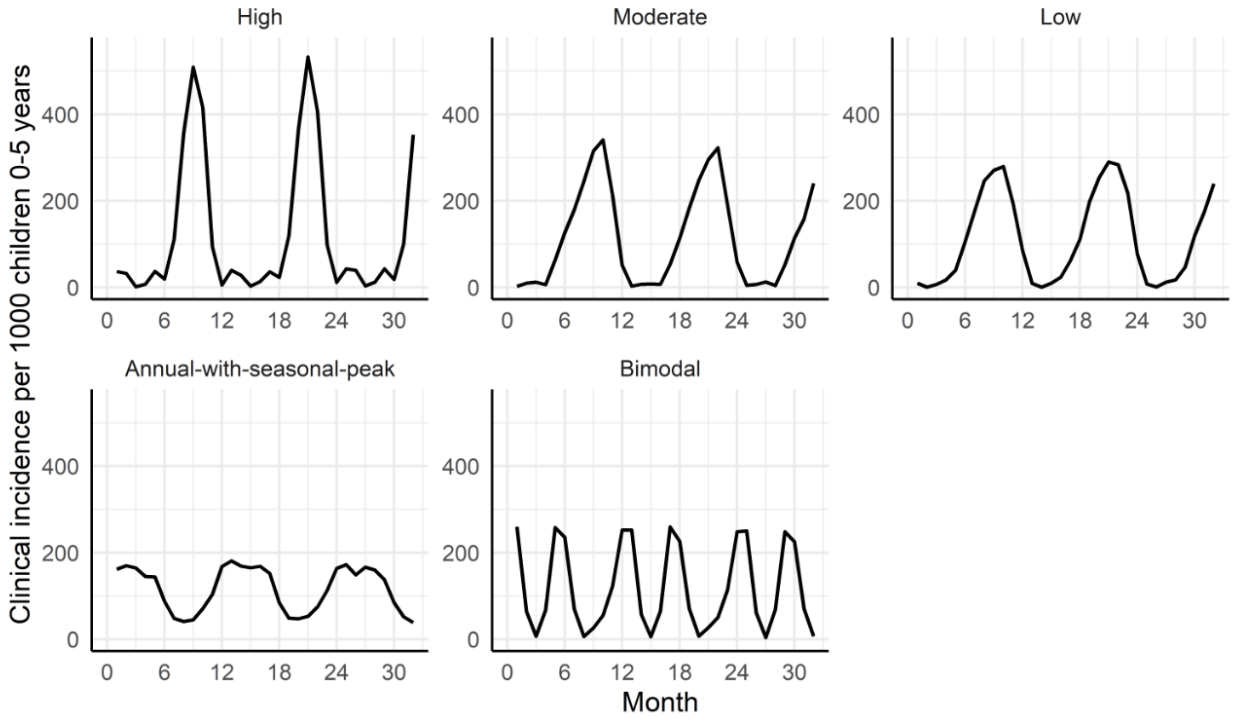
PATH

Mathematical model

The Imperial College London Malaria Transmission Model is used for this analysis and is parameterized as set out below.

Seasonality archetypes

- **High**: >90% of annual rainfall in 4 consecutive months
- **Moderate**: 70-80% of annual rainfall in 4 consecutive months
- **Low**: 60-70% of annual rainfall in 4 consecutive months
- **Bimodal**: 2 seasonal peaks annually
- **Annual transmission with a seasonal peak**



Seasonality in modelled clinical malaria incidence assuming no vaccine introduction. Incidence is shown monthly per 1000 population of children 0-5 years old, assuming a baseline level of transmission intensity of 40% $PfPR_{2-10}$

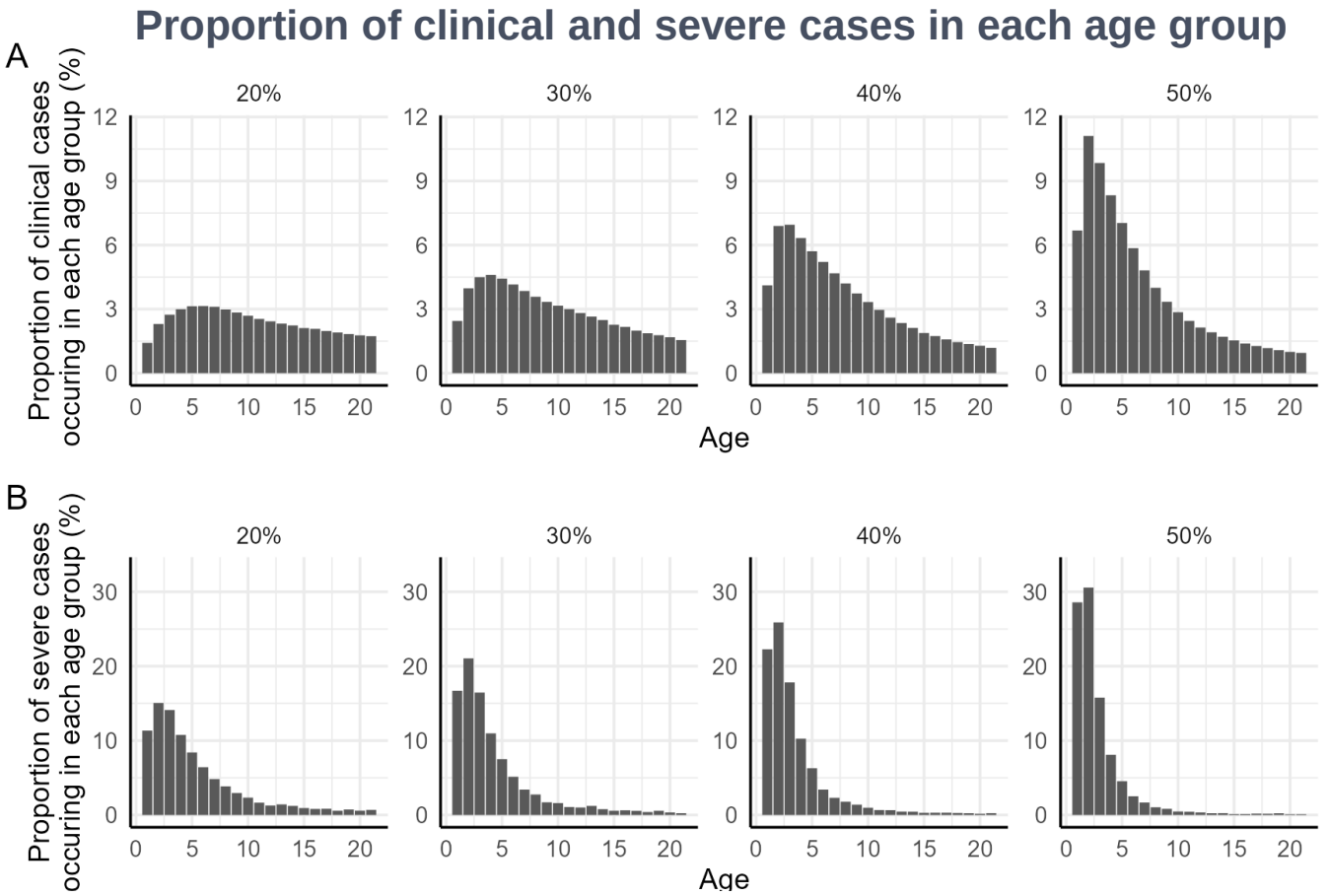
https://mrc-ide.github.io/malariasimulation/

Mathematical model

The Imperial College London Malaria Transmission Model is used for this analysis and is parameterized as set out below.

Transmission intensity

- Defined by starting ***PfPR*$_{2-10}$** of:
- 20%, 30%, 40% and 50%
- Reflect **existing levels** of **vector control** and **access to treatment** (45% ACT coverage)



Baseline distribution of clinical (A) and severe (B) malaria cases across age groups for a given baseline transmission intensity. The proportion of cases over a ten-year period in the absence of vaccination, produced by the individual-based malaria transmission model. This figure illustrates that in higher prevalence settings, the malaria burden shifts to younger age groups.

*Note: **PfPR**$_{2-10}$ = Malaria prevalence in 2-10 year olds by microscopy*

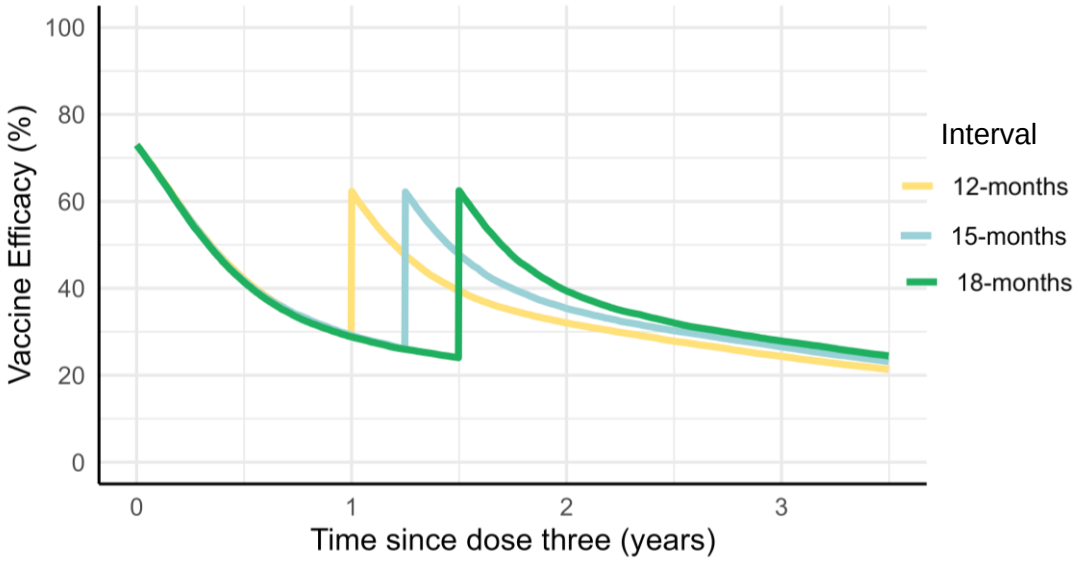
Vaccine efficacy model

The RTS,S vaccine efficacy model is parameterized as set out below

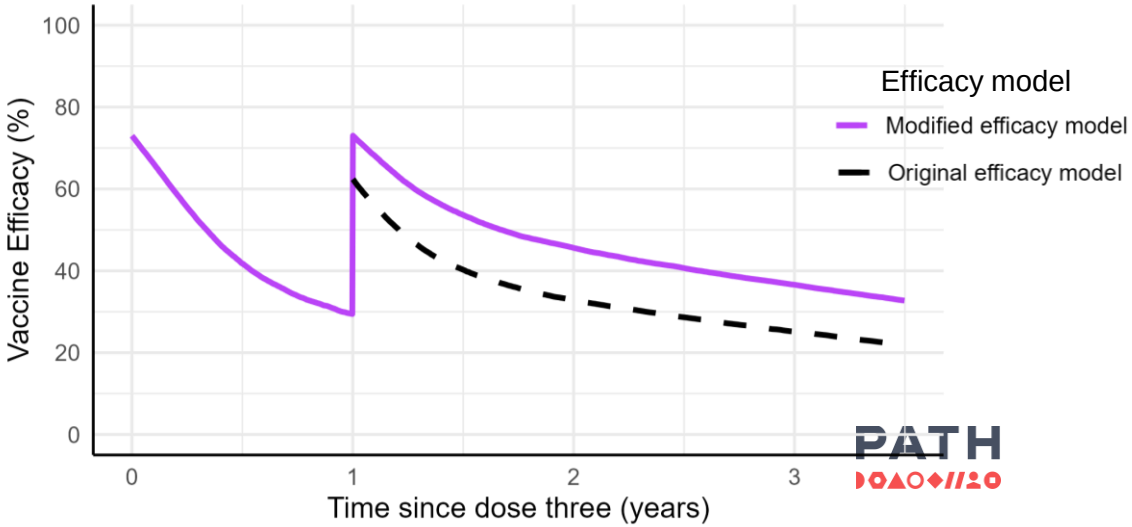
RTS,S model

- RTS,S as a pre-erythrocytic vaccine, is assumed to reduce the **probability of infection** within the model structure.
- We assume that **vaccine efficacy begins following dose-3** and decays over time.
- Parameters to describe these dynamics were fit to individual-level data from the multi-site **Phase 3 RTS,S clinical trial** (*White et al. 2015*).
- A **secondary efficacy parameterization** was considered resulting from earlier validation to the **seasonal RTS,S Phase 3b trial** (*Thompson et al. 2022*). Only considered for schedules with a 12-month interval between dose 3 and dose 4.

Vaccine efficacy and interval between dose 3 and 4



Vaccine efficacy assumptions



Background

Age-based schedules

Hybrid schedules

Multi-schedule comparisons

Summary

Age-based RTS,S delivery

Questions of interest

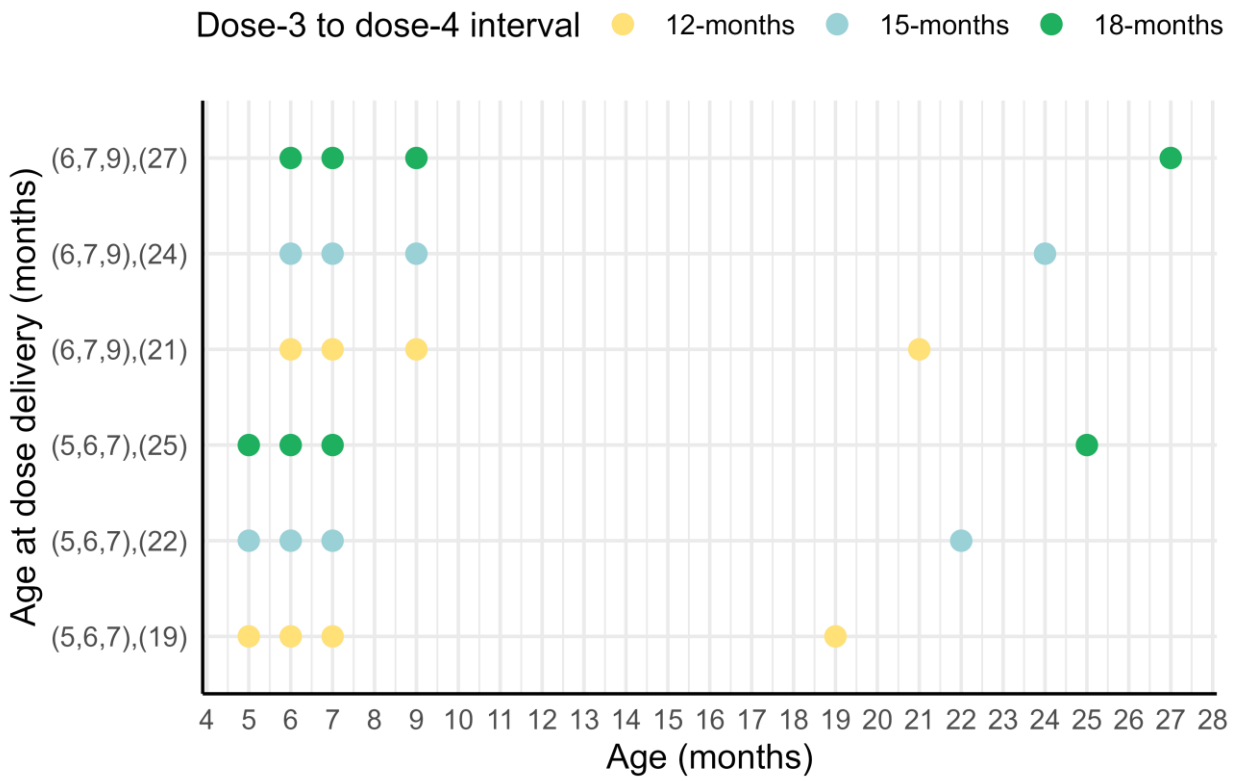
- What is the public health impact of different **vaccination ages** for the **primary series (**5,6,7-months of age or 6,7,9-months**)**?
- What is the public health impact of the **minimum interval** between dose-3 and dose-4 (12, 15, 18 months)?

PATH

Age-Based RTS,S delivery in seasonal settings

- Age-based delivery occurs **independently of seasonality** in malaria transmission.
- Explored 6 scenarios: 2 assumptions for the primary series x 3 assumptions for the dose 4 timing
    - 5-,6-,7- or 6-,7-,9-month primary series
    - 12-, 15-, 18-month interval between dose-3 and dose-4
- Assume 100% coverage of all doses

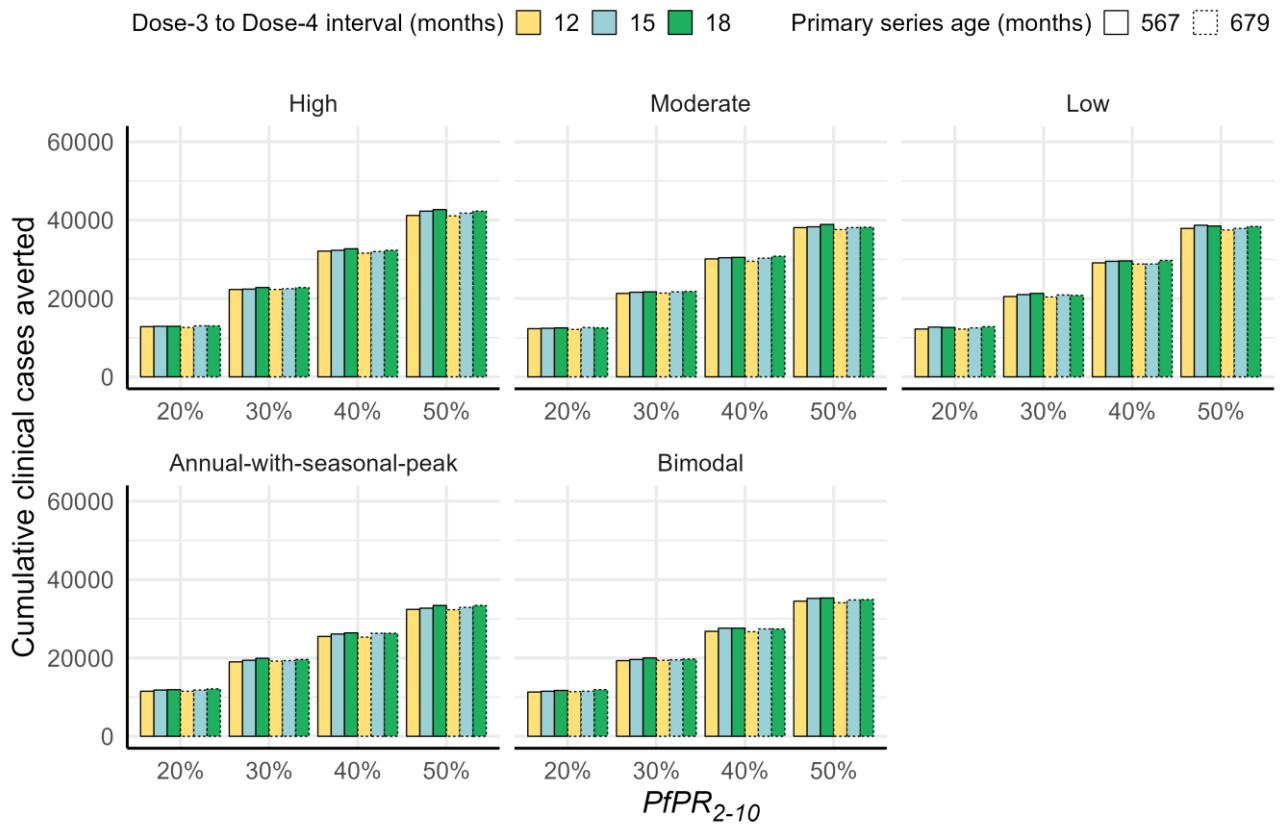
Six age-based RTS,S delivery scenarios considered



Age-based results: Clinical cases averted in children 0-5 years

- We find there to be **minimal difference** in the modelled impact of RTS,S under different primary series and dose spacing intervals
- Slightly more cases averted when the **first dose is given at a younger age** and with a **longer dose-spacing** interval
- **Margin of difference in vaccine effectiveness of +/- 1.1 percentage points** for **clinical** malaria and **severe malaria** at the population level.

Cumulative clinical cases averted under 5 age-based scenarios

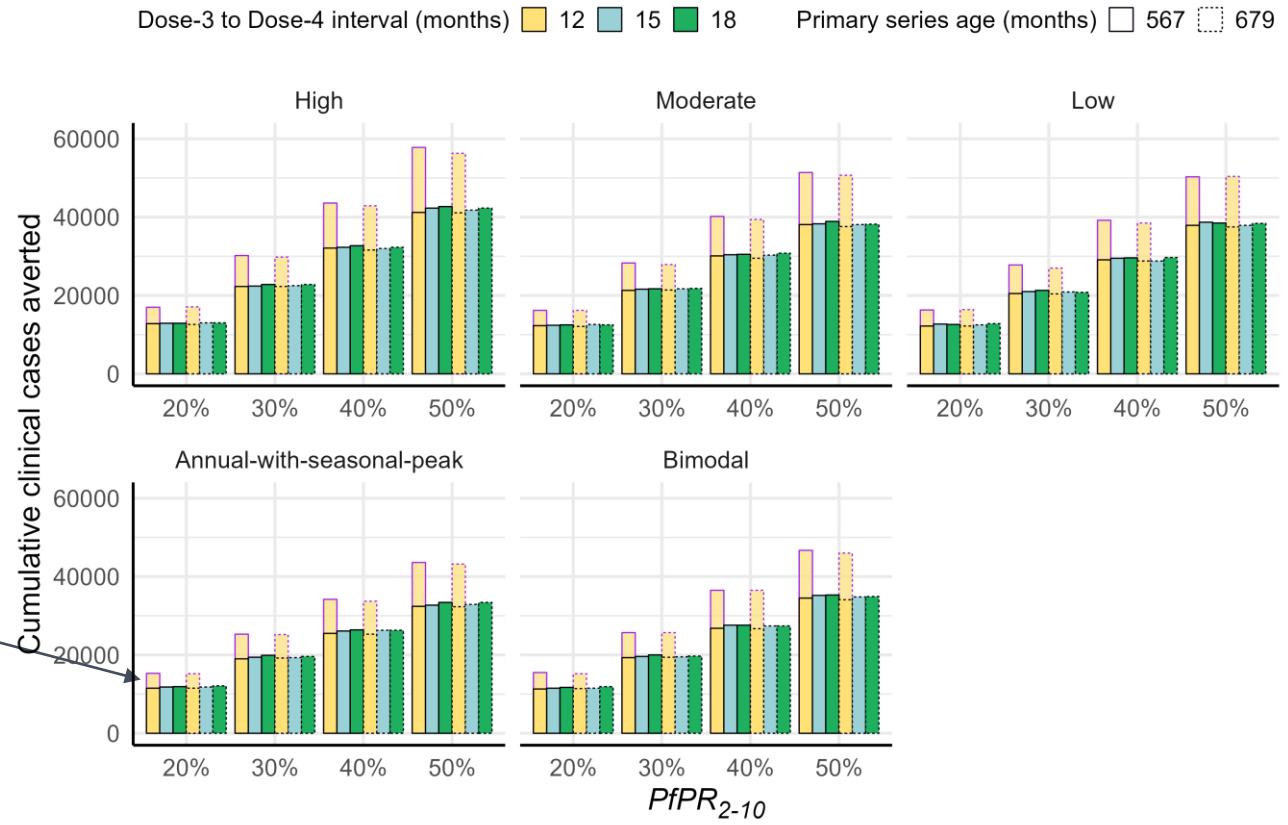


Measuring cumulative reductions in clinical malaria in children aged 0-5 years old over 10 years

Age-based results: Clinical cases averted in children 0-5 years

- We find there to be **minimal difference** in the modelled impact of RTS,S under different primary series and dose spacing intervals
- Slightly more cases averted when the **first dose is given at a younger age** and with a **longer dose-spacing** interval
- **Margin of difference in vaccine effectiveness of +/- 1.1 percentage points** for **clinical** malaria and **severe malaria** at the population level.
- Inclusion of an **improved efficacy** model shows **34% incremental benefit** on average in cumulative reductions for clinical and severe malaria. **Maximum margin of difference** in effectiveness **increases to 7%**

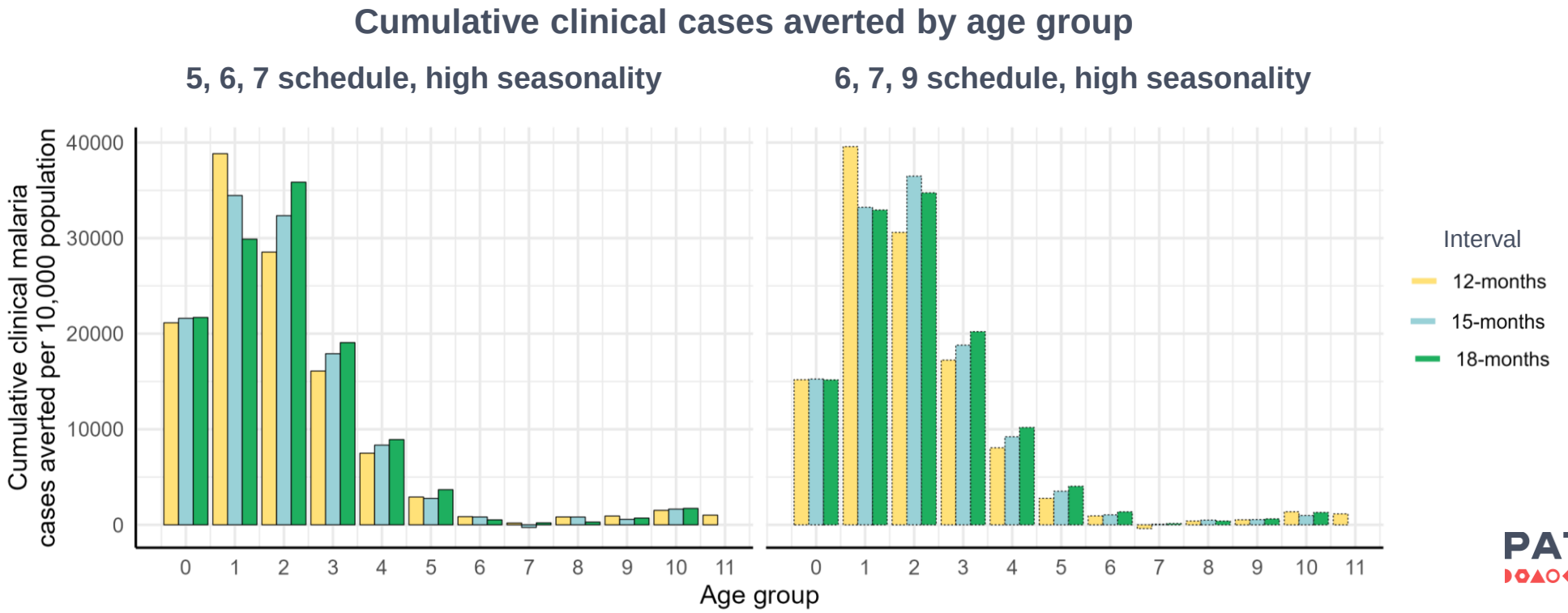
Cumulative clinical cases averted under 5 age-based scenarios



Measuring cumulative reductions in clinical malaria in children aged 0-5 years old over 10 years

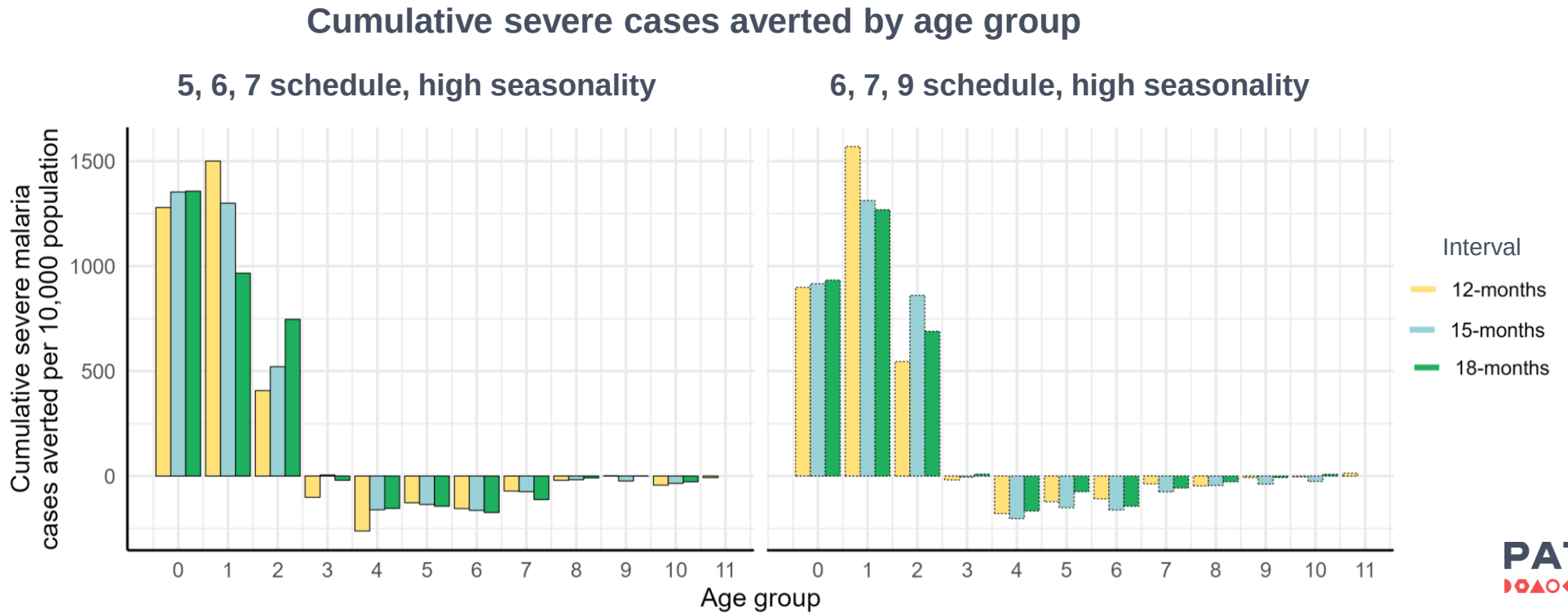
Age-based results: Cases averted by age group

- Measuring cumulative reductions in clinical and severe malaria in children over 10 years by age-group, figure shown for a High seasonality setting with a starting $PfPR_{2-10}$ of 30%
- For clinical malaria, a shorter interval (12-months) between doses 3 and 4 results in impact being more concentrated in younger age groups, whereas the longer interval (18-months) resulted in slightly more cases averted in older age-groups



Age-based results: Cases averted by age group

- Measuring cumulative reductions in clinical and severe malaria in children over 10 years by age-group, figure shown for a High seasonality setting with a starting $PfPR_{2-10}$ of 30%
- For clinical malaria, a shorter interval (12-months) between doses 3 and 4 results in impact being more concentrated in younger age groups, whereas the longer interval (18-months) resulted in slightly more cases averted in older age-groups
- For severe malaria, primary series drives significant proportion of impact, with a younger age at first vaccination resulting in greater reductions in the first year of life. Dose spacing interval determines at what age dose-4 impact is felt with a 12-month interval having greater impact in the second year of life compared to longer intervals



Background

Age-based schedules

Hybrid schedules

Multi-schedule comparisons

Summary

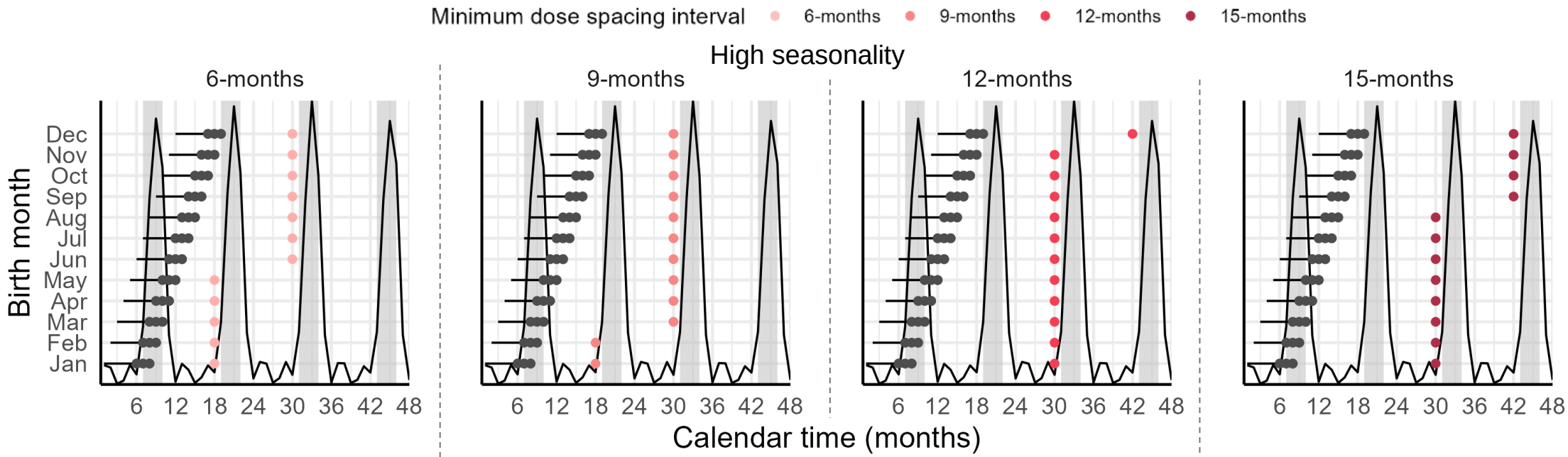
Hybrid RTS,S delivery

Questions of interest

- What is the public health impact of different **minimum dose spacing intervals** between dose-3 and dose-4 (6, 9, 12, 15-months)?

Hybrid RTS,S delivery in seasonal settings

Hybrid delivery utilizes an **age-based primary series** (5-,6-,7-months modelled here) combined with a **pre-transmission season fourth dose**. Model a ***minimum dose spacing interval*** between dose-3 and dose-4 of **6-, 9-, 12- or 15-months.** Assume 100% coverage of all doses



% of children in the birth cohort who have received 4th dose

Yr 1	Yr 2	Yr 3	Yr 4
-	41%	59%	-

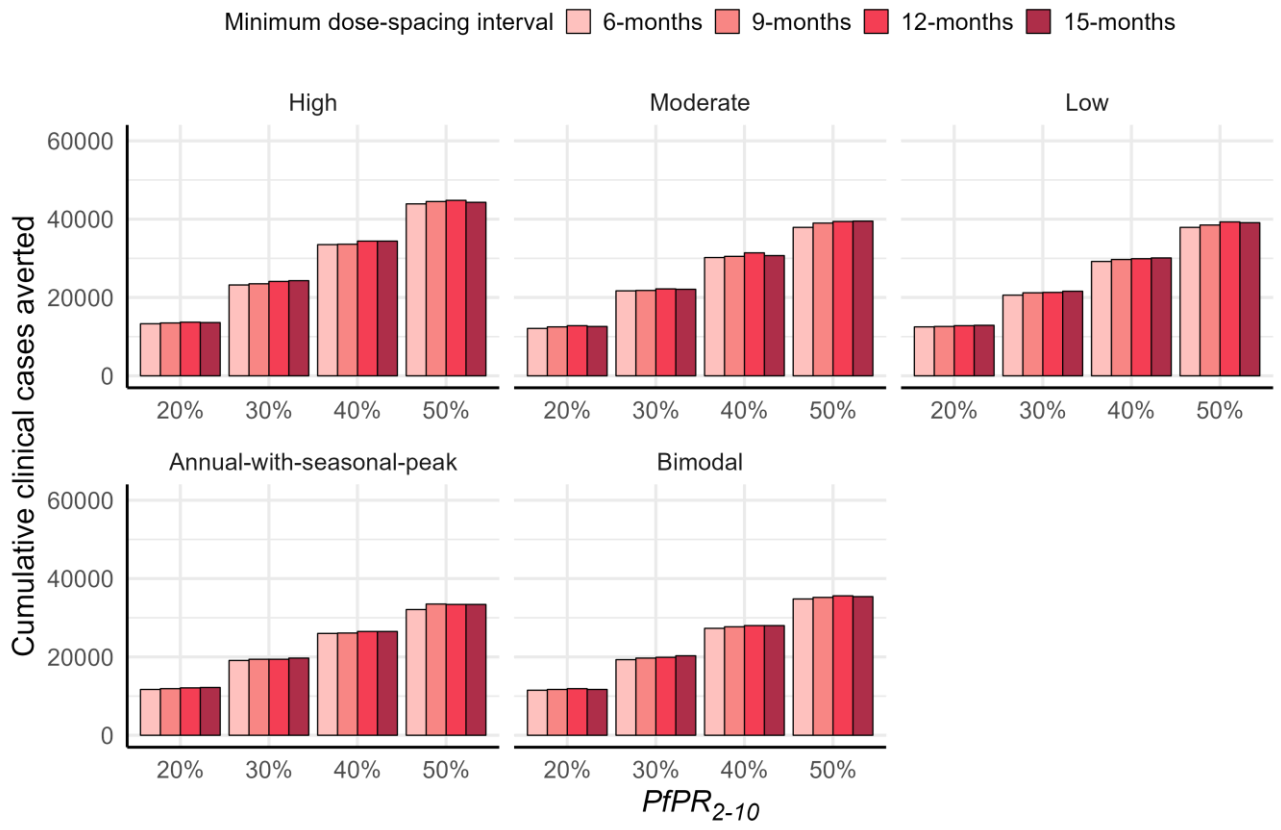
Yr 1	Yr 2	Yr 3	Yr 4
-	16%	84%	-

Yr 1	Yr 2	Yr 3	Yr 4
-	-	92%	8%

Yr 1	Yr 2	Yr 3	Yr 4
-	-	67%	33%

Hybrid schedule results: Clinical cases averted in children 0-5 years

- We find there to be **minimal difference** in the modelled impact of RTS,S under different minimal dose spacing intervals
- Slight trend for **12-month minimum interval** to result in **marginal improvements** in the number of cases averted
- **Margin of difference in vaccine effectiveness of +/- 1.2 percentage points** for **clinical** malaria and **severe malaria** at the population level.

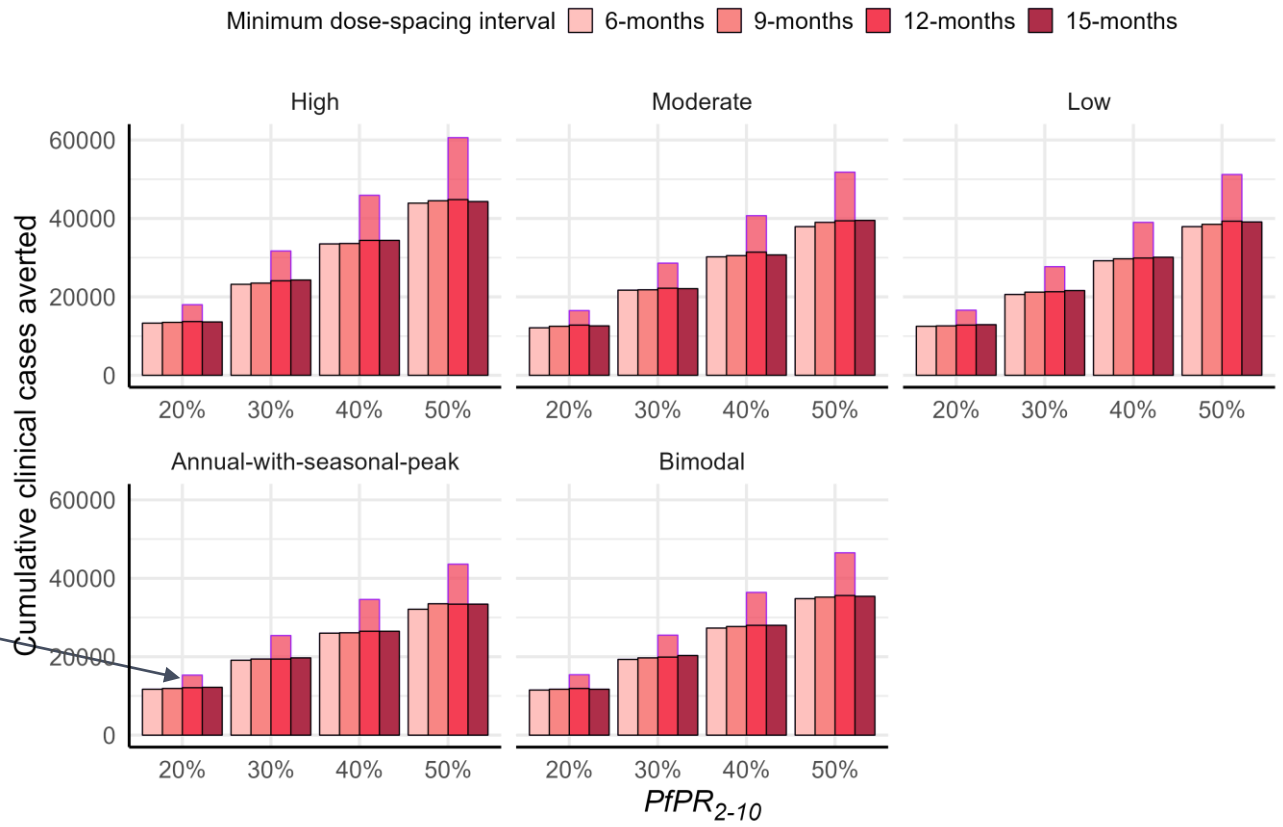


Measuring cumulative reductions in clinical malaria in children aged 0-5 years old over 10 years

PATH

Hybrid schedule results: Clinical cases averted in children 0-5 years

- We find there to be **minimal difference** in the modelled impact of RTS,S under different minimal dose spacing intervals
- Slight trend for **12-month minimum interval** to result in **marginal improvements** in the number of cases averted
- **Margin of difference in vaccine effectiveness of +/- 1.2 percentage points** for **clinical** malaria and **severe malaria** at the population level.
- Inclusion of an **improved efficacy** model shows **30% incremental benefit** on average in cumulative reductions for clinical and severe malaria. **Maximum margin of difference** in effectiveness **increases to 7%**

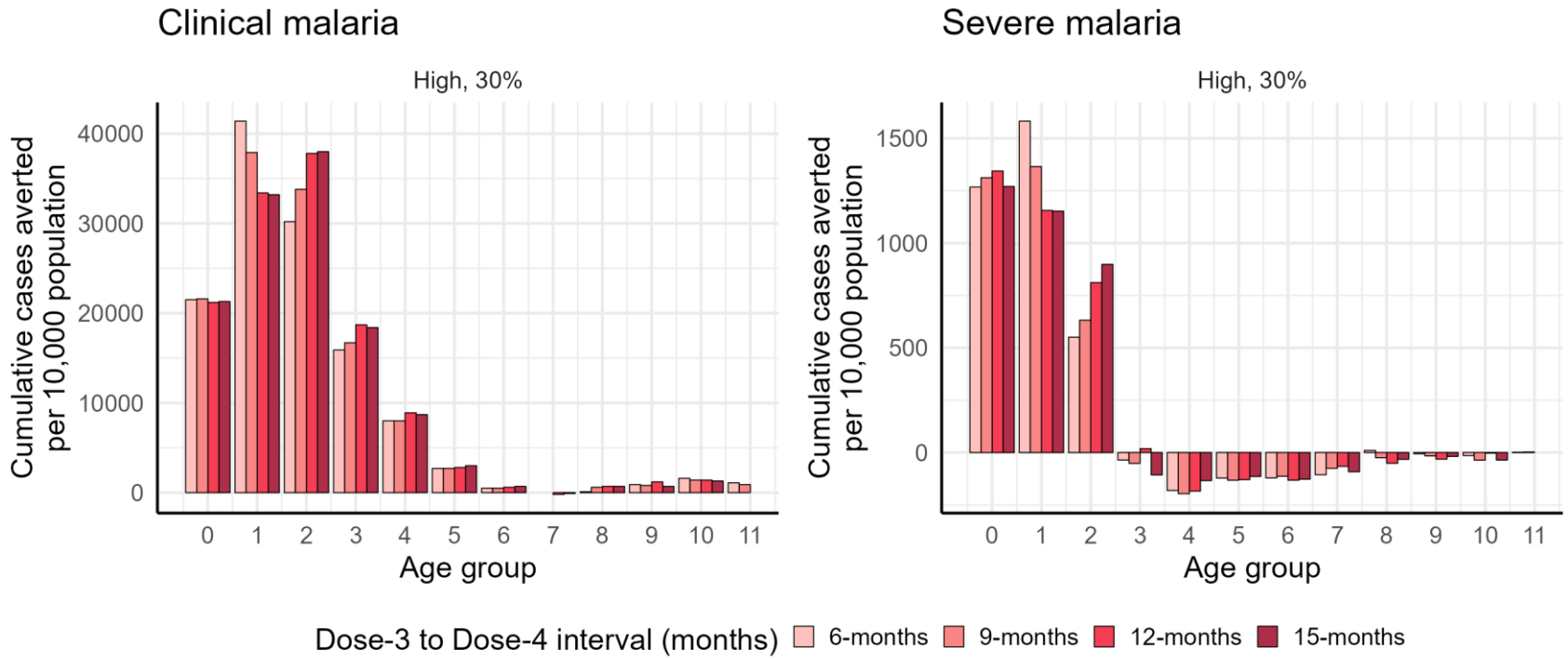


Measuring cumulative reductions in clinical malaria in children aged 0-5 years old over 10 years

Hybrid schedule results: Impact of minimum dose spacing on cases averted by age-group

- For clinical malaria outcomes, minimum dose spacing interval changes the age group where dose-4 impact is highest, with a smaller interval (6 or 9 months) maximizing reductions in 1 year old children compared with a slightly longer interval (12 or 15 months) maximizing reductions in children older than 2 which are then sustained in older ages.

- For severe malaria outcomes, the primary series drives a significant proportion of impact, with dose-4 driven impacts maximized under a 6-month and 9-month minimum interval in children aged 1 years old with longer intervals showing higher cases averted in older ages where the drop off in impact of the 6 and 9 month schedules is quite significant.



Measuring cumulative reductions in clinical and severe malaria in children over 10 years by age-group, figure shown for a High seasonality setting with a starting $PfPR_{2-10}$ of 30%

Background

Age-based schedules

Hybrid schedules

Multi-schedule comparisons

Summary

Multi-schedule comparisons

Multi-schedule comparisons

- **Which RTS,S schedule** provides the **greatest public health impact** in seasonal settings?
- How does the **degree of seasonality** impact schedule comparisons?
- How does the inclusion of a **5th dose** of RTS,S in fully-seasonal and hybrid schedules impact schedule comparisons?

PATH

RTS,S delivery schedules

Delivery mode	Primary series	Dose-4
Age-based	5,6,7-months of age	19-months of age (12-month dose spacing)
Hybrid	5,6,7-months of age	Delivered pre-season after a 12-month minimum dose spacing interval
Fully-seasonal	All children 5-17 months of age vaccinated in the 3 months preceding the transmission season	Delivered pre-season,12 months after dose-3

Assume 80% coverage of primary series with a 20% drop out to dose-4

PATH

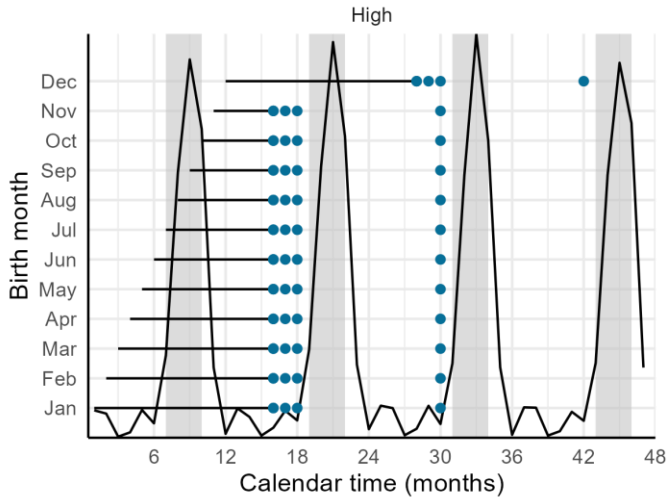
Multi-schedule comparison results: Clinical cases averted in children 0-5 years

- **Fully-seasonal** delivery resulted in **higher reductions**. Except in settings with **annual transmission with a seasonal peak**, where **hybrid vaccination** performs marginally better.
- **Incremental benefit** of **fully-seasonal** vaccination **was highest in High seasonal** archetypes (20%) and decreased with decreasing seasonality.
- Overall **differences in vaccine effectiveness** of a maximum of **2.8 percentage points** for clinical and 1.8 percentage points for severe malaria
- Inclusion of an **improved efficacy** model shows **higher absolute reductions** but **relative relationships** between schedules **remain the same**.
- The addition of a fifth dose resulted **in the highest reductions,** and relative performance of schedules remained the same, with the **incremental benefit of fully-seasonal RTS,S** with 5 doses **increasing to 33%.** Increases the margin of **difference in vaccine effectiveness** to a maximum of **5.2 percentage points**

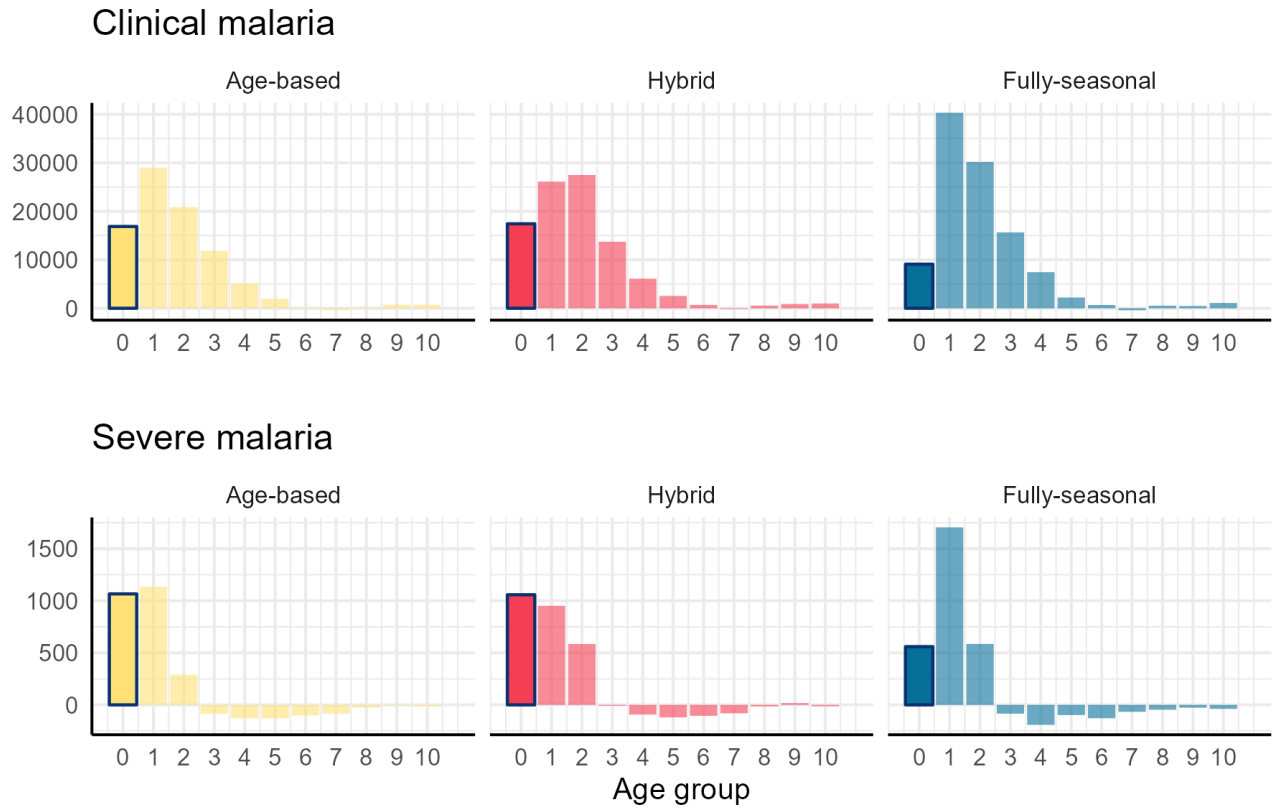
Measuring cumulative reductions in clinical malaria in children aged 0-5 years old over 10 years.

Delivery comparison results: Age disaggregated reductions in malaria cases

- As a result of the potential **delayed time to first vaccination** in **fully seasonal** delivery, **reductions** in **clinical** and **severe malaria** are **smaller** in the **first year of life** compared to **schedule with an age-based primary series**.
- Results are presented for a High seasonality setting with a baseline prevalence of 30% but are consistent across all modelled settings



Schematic of RTS,S dose timing in relation to calendar time and seasonality for an annual birth cohort of children under full-seasonal delivery



Background

Age-based schedules

Hybrid schedules

Multi-schedule comparisons

Summary

Summary

- Overall, results suggest that all age-based and hybrid RTS,S schedules provided **largely similar protection** against clinical and severe malaria in seasonal settings, when modelled under the **same coverage and dose number** and **efficacy assumptions**.
- Where **impact differs** particularly is in the **age** that sees the **highest reductions** in clinical and severe cases and when considering the **potential for improved efficacy** of a **12-month dose spacing interval** where the model predicts substantial gains in the potential reductions of malaria.
- In settings of **high seasonality**, a **fully seasonal schedule can maximize case reductions**, especially if a five-dose schedule is considered with incremental benefit over age-based and hybrid approaches reducing with decreasing seasonality.
- Key considerations for vaccine schedules in areas of seasonal transmission will be the delivery system that is able to **achieve the highest coverage**, **the age-specific burden of disease** in that area, **other malaria interventions** in use, and the **degree of seasonality in a setting**.
- Overall, these results suggest there may be **flexibility for programs to select vaccination schedules that are operationally the most feasible** to deliver in their specific contexts and that will **maximise coverage levels in order to maximum impact**.
- The outputs of this exercise, however, should be considered in the context of **understanding overall patterns** rather than as directly guiding country-specific prioritisation. Modelling alongside local data should also be used where available and may be particularly important to inform sub-national introductions of RTS,S moving forwards.

PATH

Acknowledgements

PATH team

Dr Hannah Slater

Dr Scott Gordon

MNTDs team

WHO

Dr Mary Hamel

Imperial College London

Prof Azra Ghani

Dr Peter Winskill

Dr Hillary Topazian

Wider malaria group and malariasim development team

PATH

Modelling the impact of different dose schedules for RTS,S malaria vaccine

IVIR-AC meeting, Thursday 29 February 2024

Background summary

The RTS,S/AS01 and R21/Matrix-M malaria vaccines are recommended for children from around 5 months of age to reduce *P. falciparum* malaria in children living in areas of endemic malaria transmission, prioritizing areas of moderate to high transmission. The vaccine is provided in a 4-dose schedule, with a primary series of 3 monthly doses and a 4th dose given to prolong protection. Clinical trials have shown that in areas of highly seasonal malaria transmission, vaccine efficacy can be optimized by delivering the vaccine seasonally, with the primary series and annual boosters provided just prior to high transmission seasons. A 5th dose, given one year after dose 4, may be considered in areas where there is a significant malaria risk remaining in children a year after receiving dose 4.

Prior modelling of RTS,S/AS01 malaria vaccine has explored the potential public health impact when delivered at scale according to an age-based[1] or seasonal schedule[2]. However, questions remain regarding schedules for optimal effectiveness, including the optimal interval between dose 3 and 4 for impact, and the added benefit of seasonal or hybrid schedules over age-based vaccine schedules.

WHO is interested in the use of mathematical models to explore the predicted impact of different intervals between dose 3 and 4, in particular to align dose 4 with existing second year of life vaccines to optimize dose 4 uptake, and to explore the added benefit of different delivery strategies (age-based, seasonal, hybrid) in different transmission settings. The questions are timely, as countries are planning for malaria vaccine introductions and developing their vaccine schedules and delivery approaches.

The WHO recommendation for malaria vaccines states that there can be flexibility in schedule to optimize uptake of dose 4 and acknowledges that the optimal interval between dose 3 and 4 is not yet known. Clinical trials have included dosing intervals between dose-3 and 4 of 12 or 18 months, while countries that participated in the Malaria Vaccine Implementation Programme (MVIP) adopted a 15-month interval, providing dose 4 at around 24 months of age. Noting that dose 4 reached less than half of the target population, Ghana recently aligned dose 4 with dose 2 of measles-containing vaccine (MCV2) at 18 months of age – a 9-month interval between dose 3 and 4 – and recorded substantial sustained increase in dose 4 coverage.

Country proposals for new vaccine introduction include intervals between dose 3 and 4, from as short as 6 months and to as wide as 17 months. There is currently a lack of clinical data to inform decision making on dose schedules and intervals. Additionally, malaria vaccines provide waning protection, while the risk of clinical and severe malaria and associated death are also age-dependent, and the dynamics between these factors may influence the impact that dose schedule and intervals have on malaria outcomes. For example, would a 6-month interval between dose 3 and dose 4 lead to waning of protection too early at an age when malaria risk remains high? Mathematical modeling could help guide country decision making on vaccine schedule in different transmission settings.

Despite the higher vaccine efficacy shown in clinical trials when malaria vaccines are provided seasonally, thus far most countries are adopting age-based delivery strategies in all settings due to the extra burden (financial and human resource) of campaign-style vaccine delivery. Mathematical modeling can inform decision making when ministries of health are considering the tradeoffs between the different approaches.

[1] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00725-4/fulltext#seccestitle80

[2] https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(22)00416-8/fulltext

In this session, Telethon Kids Institute (formerly Swiss TPH) will present a summary of their modelling of the public health impact of the timing of the 4th dose in perennial settings, and PATH will present their modelling of the public health impact of different vaccination schedules.

Mathematical modeling to estimate the optimal interval between dose 3 and 4 in perennial transmission settings

Modelling conducted by Swiss TPH/Telethon Kids Institute has aimed to address questions around the timing of the 4th dose in perennial settings, which includes:

- What is the benefit of delivering RTS,S using the originally recommended schedule, with primary schedule given from 5 months of age and a minimum of 4 weeks between doses, and 4th dose given 12-18 months after dose 3 vs. timing the 4th dose to existing EPI touchpoints to increase coverage?
- How and to what extent is the ideal 4th dose timing depending on transmission intensities for impact on severe disease? How is this informed by underlying age patterns of severe disease?
- Should settings with different transmission intensities consider different schedules for the 4th dose? How is this informed by underlying age patterns of severe disease?

The Swiss TPH/Telethon Kids Institute analysis used OpenMalaria, an individual-based, stochastic model of malaria transmission and disease progression, to assess the impact of different vaccination timing schedules and coverage on uncomplicated malaria cases, severe malaria cases, malaria hospitalizations, and malaria-related deaths across different transmission settings. **The modelling results suggest there are minimal differences in impact between delivering the 4th dose at 6, 9 and 12 months after the primary series**, supporting flexibility in the timing of the 4th dose to align with existing EPI touchpoints to optimize coverage and minimize burden. While the 3-dose primary series is responsible for most of the vaccine impact, a 4th dose given between 15 and 21 months of age (6-12 months after dose 3) after can still avert additional malaria cases and deaths compared to the primary series alone. While there was some additional benefit of providing the 4th dose 18 months after dose 3, primarily in higher transmission settings of 20-60% $PfPR_{2-10}$, the impact on cases and deaths averted was lower compared to delivering the 4th dose from 6-12 months. This lower relative impact of the 18-month interval is driven by assumptions of lower efficacy at later vaccine delivery and a pattern of higher severe disease burden in younger children.

Mathematical modeling to estimate the impact of different delivery strategies (age-based, seasonal, hybrid) in different transmission settings and the optimal interval between dose 3 and 4

PATH has conducted modelling to compare the potential public health impact of age-based, seasonal, and hybrid schedules (for which there is no clinical data) for RTS,S, while also assessing different intervals between dose 3 and 4 and the age schedule of the primary series. The key questions addressed in this analysis include:

1. In an age-based schedule, what is the public health impact of different ages of vaccination for the primary series (5,6,7-months of age compared to a 6,7,9-months of age delivery schedule)?
    - What is the impact of different minimum dose spacing intervals (12, 15 or 18-months) between dose 3 and 4?
2. In a hybrid schedule, what is the public health impact of different minimum dose spacing intervals (6, 9, 12, 15-months) between dose 3 and dose 4?

3. Which RTS,S dose schedule (age-based, hybrid or fully-seasonal) provides the greatest public health impact in seasonal settings?
    - How does the degree of seasonality impact schedule comparisons?
    - How does the inclusion of a 5th dose of RTS,S in seasonal and hybrid schedules impact schedule comparisons?

The analysis by PATH uses the Imperial College London model of malaria transmission to estimate the impact of RTS,S vaccination schedules on clinical and severe malaria incidence across a range of 5 seasonality archetypes (low, moderate, high seasonality based on rainfall patterns, as well as bi-modal seasonal peaks or annual transmission with seasonal peak) and transmission intensities (20-50% $PfPR_{2-10}$). Results are presented at the population level (cumulative reductions in clinical and severe malaria in children aged 0-5 years old over a period of 10-years) and are also explored in an annual birth cohort of children modelled for a period of five years. Modelling results suggest there are **minimal differences in public health impact as a result of different age of vaccination of the primary series or the dose spacing interval between dose 3 and dose 4 when considering age-based and hybrid vaccination schedules**. Seasonal delivery led to slightly higher reductions in malaria burden, particularly in highly seasonal settings, with the hybrid schedule favored in setting with annual transmission with a seasonal peak. Through including a cohort perspective in this work, results showed differences in impact between the schedules especially in the first year of life, because of the potential delayed time to first vaccination in fully seasonal delivery, reductions in clinical and severe malaria are smaller compared to schedules with an age-based primary series. These results are important for countries to understand the potential differences in disaggregated age-based impacts of different schedules. Overall results suggest that flexibility in scheduling can allow for selection of schedules to maximize coverage and thus impact in seasonal settings.

Technical presentations:

1. Presentation of modelled public health impact of the interval between dose 3 and dose 4 in perennial settings (STPH/Telethon Kids Institute)
2. Presentation of modelled public health impact of different dose schedules (age-based, seasonal and hybrid) in seasonal settings (PATH), including estimated impact at a population-level and by birth cohort.

Questions to IVIR-AC:

1. Given the lack of clinical data to inform different dosing intervals, are the current modelling results sufficient to support a specific policy recommendation on the optimal spacing between dose 3 and 4?
    a. In addition to the modelling, is it recommended that further monitoring be conducted during implementation of different dose schedules to collect on data on the impact of the timing of the 4th dose on vaccine effectiveness?
    b. Is it reasonable to generalise these findings on dose schedules and intervals to R21/Matrix-M? If not, what additional analyses or data would be needed to inform dose schedules for R21?
2. To what extent do the models (or proposed modelling) address potential differences in vaccine impact across transmission intensities and seasonal settings, accounting for variations in the age distribution of severe disease?

a. For both models, does IVIR-AC have comments on the modelled impact of the timing of dose 4 across transmission intensities?
b. Is the PATH modelling analysis able to support country decision-making on dose schedules, reflecting differences in impact between age-based, seasonal or hybrid schedules on severe disease in the first year of life vs older ages. Is there benefit to additional sensitivity analysis on vaccine coverage across the dose schedules?
c. In the absence of clinical data on hybrid schedules in seasonal settings, is the PATH analysis sufficient to support country-decision making, or is additional monitoring during implementation recommended?

3. Does IVIR-AC have feedback on the approach and results of the sensitivity analysis conducted on the assumed efficacies for the timing of the 4th dose? (Telethon Kids model)

Background published articles for Session 4

Thompson, H. A., Hogan, A. B., Walker, P. G. T., Winskill, P., Zongo, I., Sagara, I., Tinto, H., Ouedraogo, J. B., Dicko, A., Chandramohan, D., Greenwood, B., Cairns, M., & Ghani, A. C. (2022). Seasonal use case for the RTS,S/AS01 malaria vaccine: a mathematical modelling study. *The Lancet. Global health*, *10*(12), e1782–e1792. https://doi.org/10.1016/S2214-109X(22)00416-8