



World Health Organization

**Department of Immunization, Vaccines
and Biologicals (IVB)**

IVIR-AC - September 2020

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

MICROSOFT TEAMS - VIRTUAL MEETING

WHO HEADQUARTERS, GENEVA, SWITZERLAND

21 to 25 September 2020

IVIR-AC - September 2020

This booklet contains key background documents for the meeting of the Advisory Committee on Immunization and Vaccines-related Implementation Research (IVIR-AC)
21 to 25 September 2020

This booklet is published after the IVIR-AC meeting at the following link:

https://www.who.int/immunization/research/committees/ivir_ac/en/index4.html

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IVIR-AC Terms of References

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

https://www.who.int/immunization/research/committees/ivir_ac/en/

DECLARATION OF INTERESTS FOR WHO EXPERTS

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

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

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

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

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

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

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

Name:
Institution:
Email:

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

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

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

EMPLOYMENT AND CONSULTING

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

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

RESEARCH SUPPORT

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

- 2a Research support, including grants, collaborations, sponsorships, and other funding Yes No
- 2b Non-monetary support valued at more than US \$1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.) Yes No

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

INVESTMENT INTERESTS

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

- 3a Stocks, bonds, stock options, other securities (e.g., short sales) Yes No
- 3b Commercial business interests (e.g., proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company) Yes No

INTELLECTUAL PROPERTY

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

- 4a Patents, trademarks, or copyrights (including pending applications) Yes No
- 4b Proprietary know-how in a substance, technology or process Yes No

PUBLIC STATEMENTS AND POSITIONS (during the past 3 years)

- 5a As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of the meeting or work, for a commercial entity or other organization? Yes No
- 5b Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of the meeting or work? Yes No

ADDITIONAL INFORMATION

- 6a If not already disclosed above, have you worked for the competitor of a product that is the subject of the meeting or work, or will your participation in the meeting or work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage? Yes No
- 6b To your knowledge, would the outcome of the meeting or work benefit or adversely affect interests of others with whom you have substantial common personal, professional, financial or business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)? Yes No
- 6c Excluding WHO, has any person or entity paid or contributed towards your travel costs in connection with this WHO meeting or work? Yes No

6d Have you received any payments (other than for travel costs) or honoraria for speaking publicly on the subject of this WHO meeting or work? Yes No

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

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

Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity?

Yes No

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

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

CONSENT TO DISCLOSURE. By completing and signing this form, you consent to the disclosure of any relevant conflicts to other meeting participants and in the resulting report or work product.

DECLARATION. I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge.

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

Date: _____

Signature _____

CONFIDENTIALITY UNDERTAKING

Should be sent with the invitation or appointment letter

1. The World Health Organization (WHO), acting through its Department of _____, has access to certain information relating to _____, which information WHO considers to be proprietary to itself or to parties collaborating with it (hereinafter referred to as "the Information").
2. The Undersigned, as a member of the _____ advisory meeting, group or committee (collectively referred to as the "the Advisory Process"), may have access to the Information in the course of his/her participation in the Advisory Process (whether at or in relation to Advisory Process meetings, internet-based collaborative workspaces, telephone conferences or otherwise).
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4. The Undersigned undertakes to regard the Information as confidential and proprietary to WHO or parties collaborating with WHO and agrees to take all reasonable measures to ensure that the Information is not used, disclosed or copied, in whole or in part, other than as provided in this Undertaking, except that the Undersigned shall not be bound by any such obligations if and to the extent he/she is clearly able to demonstrate that the Information:
 - a) was known to him/her prior to any disclosure by or for WHO to the Undersigned; or
 - b) was in the public domain at the time of disclosure by or for WHO to the Undersigned; or
 - c) becomes part of the public domain through no fault of the Undersigned; or
 - d) becomes available to the Undersigned from a third party not in breach of any legal obligations of confidentiality.
5. The Undersigned also undertakes not to communicate the deliberations and decisions of the Advisory Process to third parties except as agreed by WHO.
6. If requested to do so, the Undersigned agrees to return to WHO any and all copies of the Information.

.../..

Annex C

7. The obligations of the Undersigned shall survive the termination of his/her membership in the Advisory Process.
8. Any dispute relating to the interpretation or application of this Undertaking shall, unless amicably settled, be subject to a 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 UNCITRAL rules of arbitration. The parties shall accept the arbitral award as final.

Name:

Signature:

Date:

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

Microsoft Teams - Virtual Meeting

**WHO Headquarters, Geneva, Switzerland
21 to 25 September 2020**

Draft list of participants

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DAY 1				
Duration	Title	Content and key questions to IVIRAC	Purpose	Proposed speaker
1200 – 1205 5'	Opening of Meeting	<ul style="list-style-type: none"> Update on global strategies and issues of relevance to WHO 	For information	K O Brien, Director, Department of Immunization, Vaccines and Biologicals
1205-1215 10'	Introduction/ Objectives of the meeting	<ul style="list-style-type: none"> Administrative issues Objectives of IVIRAC meeting and outline of the 1st day 		P Lambach W Orenstein
1215 - 1225 10'	Background	<ul style="list-style-type: none"> Secretariat view Technical background/Information needs from WHO SAGE to estimate impact of COVID-19 on immunization programs (for SAGE working group) 		R Hutubessy (WHO) / Y Sim
COVID-19 Session 1: Risk of SARS-CoV-2 transmission with different immunization services				
1225 – 1240 15'	Problem statement	<ul style="list-style-type: none"> Understanding risk-benefit of proceeding with immunization services during COVID outbreaks evoke the need for a better understanding of transmission dynamics Questions to IVIRAC <ul style="list-style-type: none"> Does the model address the key analytic question, i.e., <ul style="list-style-type: none"> What is the risk of SARS-CoV-2 transmission to communities and to health workers: 	For recommendation	Susan Wang

		<ul style="list-style-type: none"> • for settings with various levels of COVID-19 burden, • under different health service delivery conditions (e.g., routine immunization via fixed-site, outreach, and schools; mass vaccination campaigns which are either fixed-site or door-to-door), and • in consideration of the nature and extent of Infection Prevention Control (IPC) measures implemented? <ul style="list-style-type: none"> ○ What is the risk of SARS-CoV-2 transmission to health workers? ○ How robust are the conclusions of the modelling work? <ul style="list-style-type: none"> ▪ Are assumptions about roles of children in transmission justified and sufficiently conservative? ○ How can we extrapolate the results from the six analysed settings to the other countries? Do country 		
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		<p>characteristics translate into different transmission risks for communities and health workers and if so, how?</p> <p>Background reading materials: <i>Full report on risk of SARS-CoV-2 transmission</i></p>		
1240 - 1300 15'	The risk of SARS-CoV-2 transmission to communities and to health workers in LMICs under different health service delivery conditions	<ul style="list-style-type: none"> • Presentation of modelling approach to understand risk of SARS-Cov-2 transmission by varying (i) service delivery (fixed site and house to house campaigns as well as routine outreach), (ii) effectiveness of IPC from 0-95%, (iii) country characteristics (age pyramid, income levels, urban/rural) 		K Frey / B Hagedorn
1300-1330 30'	Q&A and Discussion of recommendations to SAGE	<ul style="list-style-type: none"> • Discussion on conclusions for SAGE (to be continued in closed session) 		V Pitzer and Joseph Wu
COVID-19 Session 2: Frameworks and methods to guide COVID 19 vaccine development				
1400 – 1410 10'	<i>Impact modelling of potential COVID vaccines</i>	<ul style="list-style-type: none"> • Update on SAGE WG deliberations on policy-relevant use case scenarios and modelling needs. • Question to IVIRAC: <ul style="list-style-type: none"> • Are additional epidemiologic and economic model criteria needed? • What is IVIR-AC's advice on strategies to address knowledge gaps? • How could IVIRAC support future review processes and quality of modelling? <p>Background reading materials: <i>Modelling questions</i> https://www.who.int/immunization/policy/sage/SAGE_WG_COVID19_Vaccines_Modelling_Questions_3</p>	For recommendation	A Wilder-Smith

		1July2020.pdf?ua=1 ; Overview table of potential modelling groups, Value framework, CMCC Model Fitness-for-Purpose Assessment Report		
1410 - 1430 20'	<i>What is the best use of a COVID19 vaccine during time of limited supply?</i>	<ul style="list-style-type: none"> Modelling approaches and assumptions to determine the optimal use of a COVID-19 vaccine dependent on vaccine performance and target populations 		N Grassly
1430-1500 30'	Q&A and Discussion of recommendations to SAGE	<ul style="list-style-type: none"> Discussion on conclusions for SAGE (to be continued in closed session) 		W Ndifon and J Leask
1500-1510 10'	Wrap up	<ul style="list-style-type: none"> Summary of day's findings and request any follow up from WHO Secretariat/IVIR-AC FPs for closed session 	For information	W. Orenstein, Chair

DAY 2				
Duration	Title	Content and key questions to IVIRAC	Purpose	Proposed speaker
1200 - 1205 5'	Introduction	<ul style="list-style-type: none"> Recap of previous day and objectives for the day 	For information	W. Orenstein, Chair
WUENIC 2.0				
1205 – 1225 10'	Problem statement	<ul style="list-style-type: none"> Since 2019 WHO and UNICEF are reviewing modelling approaches to estimate national immunization coverage A decision is needed to select a model to replace or complement the currently used rule-based approach to these estimates Questions to IVIRAC : <ul style="list-style-type: none"> In light of use cases for WUENIC and observations from doing simulations, what does IVIR-AC see as the main pros and cons of a modeling approach vis-à-vis the current rule-base method? What model to estimate national immunization coverage for Member States would IVIR-AC recommend to WHO and UNICEF replace and or/complement WUENIC? <p>Background reading materials: <i>report comparing models; summary of stakeholder consultation on WUENIC, shiny app to compare estimates by method by country:</i> https://unicef.shinyapps.io/wuenic-</p>	For recommendation	M Gacic-Dobo

		<i>model-explorer/ and a comparison of coverage estimates for selected countries using different methods</i>		
1225 - 1245 20'	<i>Comparison of models available</i>	<ul style="list-style-type: none"> The models currently available and reviewed by WHO/UNICEF with previous support of IVIRAC will be presented to discuss pros and cons of each method 		M Diallo
1245 - 1255 10'	<i>Optimising WUENIC: improvements to the deterministic methodology and WUENIC 2.0</i>	<ul style="list-style-type: none"> Considerations to inform IVIRAC on the options for managing WUENIC 2.0 and optimizing its processes and outputs 		C Danovaro
1255-1335 40'	Q&A and Discussion	<ul style="list-style-type: none"> IVIR-AC discusses presentation, clarifies on content and acknowledges main issues Decision on discussion items for closed session: advice to WHO and UNICEF on model selection or WUENIC or a combination of approaches 		V Pitzer V Nankabirva W Orenstein
MR-MAPs (Measles-Rubella Microarray Patches)				
1430-1440 10'	Accelerating the clinical development of MR-MAPs (Measles-Rubella Microarray Patches): an introduction to workstreams.	<p>Content:</p> <ul style="list-style-type: none"> High-level summary of activities related to MR-MAP product development Rationale for MR-MAP use case sizing <p>Background material:</p> <ul style="list-style-type: none"> MR-MAP target product profile (MR-MAP TPP) 	For information	B Giersing / M Hasso-Agopsowicz

		<ul style="list-style-type: none"> Executive summary and methodology of the Vaccine Innovation Prioritisation Strategy (VIPS) on MAPs 		
1440-1510 30'	<i>Understanding where and how will MR-MAPs be used: Identification of MR-MAP use cases and approach to size the MR-MAP use cases</i>	<p>Content:</p> <ul style="list-style-type: none"> Identification and validation of use case scenarios to deliver MR-MAPs: overview of methodology and results Methodology to estimate the size of the MR-MAP use cases: anticipated variables Key questions regarding the methodological approach and limitations of sizing of use cases <p>Background material:</p> <ul style="list-style-type: none"> A report to develop and validate the MR-MAP use cases 	For information	C Mantel (MMGH Consulting) M Ko (MMGH Consulting)
1510-1540 30'	Q&A and Discussion	<ul style="list-style-type: none"> Does IVIR-AC agree that the approach to identify and verify the MR-MAPs use cases is appropriate, systematic and scientific? Does IVIR-AC have suggestions to improve the methodologies to calculate the size of each of the use cases? 	For recommendation	J-D Lelièvre and D C Lyimo
1540-1550 10'	Wrap up	<ul style="list-style-type: none"> Summarize day's findings and request any follow up from WHO Secretariat/IVIR-AC FPs for closed session 	For information	W. Orenstein, Chair

DAY 3				
1200 – 1205 5'	Introduction	<ul style="list-style-type: none"> Recap of previous day and objectives for the day 	For recommendation	W. Orenstein, Chair
RTS,S Malaria Vaccine				
1205 - 1215 10'	Background	<ul style="list-style-type: none"> <i>Data from the MVIP will be reviewed for policy consideration in late 2021. An economic analysis, including the incremental cost effectiveness benefit of the RTS,S/AS01 vaccine when included as part of a package of malaria control interventions, will inform the policy decision. Prior economic analyses have used a sequential approach, applying individual malaria control interventions until a threshold is reached, before adding the next intervention.</i> <i>IVIR-AC agreed in 2019 that this is not a real-world scenario and would not adequately inform policy.</i> <p>Background documents: will be made available on 18 Sep (see Sharepoint)</p>	For information	M Hamel
1215 – 1245 15'	CHOICE framework	<ul style="list-style-type: none"> Basic principles of the CHOICE framework/principle Update on recent work on CHOICE and malaria interventions including RTS,S Description of how CHOICE answers questions raised by IVIR-AC 2019 on RTS,S 		M Bertram E Patouillard

1245-1315 30'	Q&A and Discussion	<ul style="list-style-type: none"> IVIR-AC is asked to provide feedback on whether they agree with the CHOICE approach as the analytical framework to inform policy on the RTS,S vaccine and on the role of each of the different methods for decision making at different levels. 		D C Lyimo, V Pitzer, H H Farooqui
Vaccine delivery costing consensus statement				
1345-1355 10'	Background	<ul style="list-style-type: none"> Recap of recommendations and updates by IVIR-AC in 2018 and 2019 	For recommendation	KHT Yeung/R Hutubessy
1355-1415 20'	Consensus statement of vaccine delivery costs	<ul style="list-style-type: none"> Presentation of the consensus statement IVIR-AC is asked to review the process leading to the final draft of the consensus statement, next steps and lessons learnt from the process <p>Background reading materials:</p> <ol style="list-style-type: none"> Draft of consensus statement with annex Recommendations by IVIR-AC in Mar 2018 Recommendations by IVIR-AC in Mar 2019 Summary of updates to IVIR-AC in Sep 2019 		A Levin
1415-1445 20'	Q&A and Discussion	<ul style="list-style-type: none"> IVIR-AC discusses presentation, clarifies on content, finds consensus, and acknowledges main issues 		M Jit and S Verguet
IA 2030 Modelling				
1500-1510 10'	Background	<ul style="list-style-type: none"> Background information for the estimation of global deaths averted/lives saved due to vaccination. Data will inform IA2030 M&E Framework development and in particular one of the impact goals 	For recommendation	A Lindstrand

		<ul style="list-style-type: none"> Given the strategic priority of the IA2030 there is an increased need to estimate the number of deaths averted due to vaccination 		
1510-1530 20'	Analytical framework and methodologies for estimating the number of deaths averted due to vaccination for 194 Member States from 2021-2030	<ul style="list-style-type: none"> Presentation of the analytical framework and methodologies for data collection, extrapolation and projection of global, regional and country-specific estimates Questions to IVIRAC <ul style="list-style-type: none"> How to best include a structure of competing risk (to avoid double counting)? How to best compare health outcomes with a short-term impact vs long term impact (Measles vs HPV vaccine)? How to include different sources of uncertainty? <p>Background information: Analytical framework</p>		W Msemburi
1530-1550 20'	Q&A and Discussion	<ul style="list-style-type: none"> IVIR-AC discusses presentation, clarifies on content and acknowledges main issues 		S Verguet and J Wu
1550-1600 10'	Wrap up	<ul style="list-style-type: none"> Summarize day's findings and request any follow up from WHO Secretariat/IVIR-AC FPs for closed session 	For information	W. Orenstein, Chair

DAY 4

1230 - 1235 5'	Introduction	<ul style="list-style-type: none"> Recap of previous day and objectives for the day 	For information	W. Orenstein, Chair
CAPACITI				
1235 – 1245 10'	Background	<ul style="list-style-type: none"> Overview of CAPACITI goals, 3 frameworks, and project status 	For recommendation	B Giersing
1245 - 1255 10'	Decision-support framework and Excel tool	<ul style="list-style-type: none"> Updates since IVIR-AC 2019 meeting (types of MCDA, balance between best practice and practicality) <p>Background reading materials:</p> <ol style="list-style-type: none"> Decision-support tool (Excel) Draft decision-support framework manuscript 		P Thokala
1255-1310 15'	Country context and innovation frameworks	<ul style="list-style-type: none"> Country context framework: rationale and link to decision-support framework Innovation framework: previous iterations and current conceptualisation <p>Background reading materials:</p> <ol style="list-style-type: none"> Draft CAPACITI manuscript 		S Botwright
1310 - 1345 35'	Q&A and Discussion	<p>Questions to the committee:</p> <ul style="list-style-type: none"> Is the decision-support tool ready to be made available online at the end of 2020? Does the committee have advice on the structure and development of the country context and innovation frameworks? 		J Leask and M Jit
Burden of enteric diseases				
1430-1440 10'	Burden of Enteric Diseases: Background and problem statement	<p>Content:</p> <ul style="list-style-type: none"> Understanding pathogen disease burden is critical to understanding the potential 	For information	G Giersing/M Hasso-Agopsowicz

		<p>impact a vaccine may have, and informs priority setting for vaccine development, introduction and use;</p> <ul style="list-style-type: none"> • U5 mortality estimates for Shigella and ETEC reported by two modelling groups IHME and MCEE have diverged over the years and have impacted investment decisions; • PDVAC recommended to evaluate diarrhoeal burden models in 2018; • BoED WG developed and completed workstreams to address PDVAC's needs. <p>Background material:</p> <ul style="list-style-type: none"> • Report from the first meeting of the BoED WG (https://pubmed.ncbi.nlm.nih.gov/32253097/) • Report from the PDVAC 2020 session on BoED 		
1440-1505 25'	<i>Efforts to assess the differences in mortality estimates for enteric pathogens.</i>	<p>Content:</p> <ul style="list-style-type: none"> • Results from workstreams to assess the mortality estimates for enteric pathogens; • Perspectives from IHME and MCEE and suggested approaches to incorporate methods from the analyses into future mortality estimates <p>Background material:</p> <ul style="list-style-type: none"> • Draft article summarising the results of the CFR analysis • Draft article summarising the results of the ORs analysis 	For information	<p>J Baker</p> <p>V Pitzer</p> <p>M Hasso</p> <p>J Platts-Mills</p>

<p>1505-1525 20'</p>	<p>Q&A and Discussion</p>	<ul style="list-style-type: none"> • Do these workstreams potentially impact the assessment of pathogen mortality, and therefore relative value of vaccines against these pathogens? • Does IVIR-AC agree that results of the mortality workstreams should be included in future enteric mortality modelling estimates? 	<p>For recommendation</p>	
<p>1525-1535 10'</p>	<p><i>The impact of enteric pathogens on morbidity: proposed scope of work.</i></p>	<p>Content:</p> <ul style="list-style-type: none"> • Repeated enteric infection causes intestinal damage resulting in malnutrition, wasting and longer term sequelae including growth faltering, cognitive and mental impairment; • The pathogen specific burden of long term morbidity is currently not captured in global burden of diseases estimates, therefore the 'value' of these vaccines is under-estimated; • WHO proposes workstreams to systematically capture evidence on the impact of enteric pathogens on long-term morbidity; and to assess indicators and methodologies to measure such morbidity. <p>Background material:</p> <ul style="list-style-type: none"> • Rationale for morbidity focus of BoED: MWG • Guerrant RL, DeBoer MD, Moore SR, Scharf RJ, Lima AA. The impoverished gut--a triple burden of diarrhoea, stunting and chronic disease. <i>Nat Rev Gastroenterol Hepatol.</i> 2013;10(4):220-229. doi:10.1038/nrgastro.2012.239 	<p>For information</p>	<p>I Khalil</p>

<p>1535-1555 20'</p>	<p>Q&A and Discussion</p>	<ul style="list-style-type: none"> • Are there other elements/activities that should be included in the proposed scope of work to assess long term morbidity? • Is the proposed scope of work considered appropriate next step for further evaluating the full burden, and ultimately the value, of enteric vaccines? 	<p>For recommendation</p>	<p>S Verguet, P Luz, X Wang</p>
<p>1555-1605 10'</p>	<p>Wrap up and closure</p>	<ul style="list-style-type: none"> • Summarize day's findings and request any follow up from WHO Secretariat/IVIR-AC FPs for closed session 	<p>For information</p>	<p>W. Orenstein, Chair</p>

DAY 5	
Closed session: IVIR-AC members only	
1230 – 1600	IVIR-AC reporting/recommendations

WER summary of last IVIRAC



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Immunization and Vaccine-related Implementation Research Advisory Committee Executive summary, September 2019

1. Total Systems Effectiveness

Introduction

The aim of total systems effectiveness (TSE) is to assist countries in selecting products that are appropriate for their context, in order to promote equitable vaccine coverage and reduce the burden of vaccine-preventable disease. A decision-support tool has been developed to support policy bodies in low- and middle-income countries (LMICs) in evaluating the trade-offs between different vaccine interventions. The tool was pilot-tested in Mali in 2019. The purpose of the session of the Immunization and Vaccine-related Implementation Research

Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins: résumé d'orientation, septembre 2019

1. Efficacité totale des systèmes

Introduction

L'objectif de l'efficacité totale des systèmes (ETS) est d'aider les pays à sélectionner des produits adaptés à leur contexte afin de promouvoir une couverture vaccinale équitable et de réduire la charge des maladies évitables par la vaccination. Un outil d'aide à la décision a été mis au point pour aider les organismes responsables de l'élaboration des politiques dans les pays à revenu faible et intermédiaire à évaluer les compromis entre les différentes interventions en matière de vaccination. Cet outil a fait l'objet d'un essai pilote au Mali en 2019. L'objectif de cette session du Comité consultatif sur la vaccination et la recherche

Advisory Committee (IVIR-AC) was to review the TSE tool and the experience in Mali. Specifically, IVIR-AC was asked to comment on the method and validation of the tool.

Conclusions and recommendations

- IVIR-AC has followed development of TSE since 2018 and expresses appreciation for the way in which the team has accepted advice from IVIR-AC, other experts and country stake-holders on refining the tool. One of its strengths is its iterative development, with continued modification based on country feedback.
- Another valuable aspect of TSE is that it can be aligned with other vaccine decision-making initiatives, such as health technology assessment (HTA) and strengthening of national immunization technical advisory committees. While useful moves have been made in countries, more conceptual thinking is required to ensure that national HTA initiatives fit within the TSE framework, including deliberative processes and use of a cost-effectiveness threshold.
- The tool has been pilot tested for choosing vaccines and products, although it was developed for broader choices, such as strategies for the introduction or delivery of a new vaccine. TSE might also be used for choosing strategies to improve vaccination coverage (e.g. checking vaccination records at school entry or reminder systems in early childhood). It was recommended, however, that the tool first be pilot-tested for this use to ensure that it is suitable, including the feasibility of scoring the criteria.
- The TSE framework should be flexible enough to encompass the different ways in which decisions on vaccines are taken. For example, quantitative multi-criteria decision analyses require technical expertise to choose and weight criteria to avoid overlap or double-counting, and it should be recommended only where such expertise is available.
- The decision to separate cost from non-cost criteria in TSE should be considered carefully and left to country stakeholders, as many quantities without explicit prices (such as cold chains and human resource capacity) may be considered economic costs, and financial criteria are often crucial to decisions.
- TSE should include means to incorporate the views of vaccination providers, communities and individuals (e.g. parents and vaccinees) into the decision tools. The means include having these stakeholders on the prioritization committee, undertaking research or using deliberative methods to set criteria that are important to communities in programme considerations.

sur la mise en œuvre des vaccins (IVIR-AC) était d'examiner l'outil ETS et l'expérience du Mali. Plus précisément, l'IVIR-AC a été invité formuler des commentaires sur la méthode et la validation de cet outil.

Conclusions et recommandations

- L'IVIR-AC suit le développement de l'ETS depuis 2018 et se félicite de la manière dont l'équipe a accepté ses conseils et ceux d'autres experts et parties prenantes nationales pour perfectionner cet outil. L'un de ses points forts est son développement itératif; il est continuellement modifié sur la base du retour d'information des pays.
- Un autre aspect important de l'ETS est qu'elle peut être alignée sur d'autres initiatives de prise de décisions concernant les vaccins, comme l'évaluation des technologies de la santé et le renforcement des comités consultatifs techniques nationaux sur la vaccination. Bien que des mesures utiles aient été prises dans les pays, une réflexion plus conceptuelle est nécessaire pour s'assurer que les initiatives nationales d'évaluation des technologies de la santé s'inscrivent dans le cadre de l'ETS, y compris les processus délibératifs et l'utilisation d'un seuil pour le rapport coût-efficacité.
- Cet outil a fait l'objet d'un essai pilote afin de choisir les vaccins et les produits, bien qu'il ait été conçu pour aider à faire des choix dans d'autres domaines, comme les stratégies d'introduction ou d'administration d'un nouveau vaccin. L'ETS pourrait également être utilisée pour choisir des stratégies visant à améliorer la couverture vaccinale (par exemple, la vérification des registres de vaccination à l'entrée à l'école ou des systèmes de rappel au cours de la petite enfance). Il a toutefois été recommandé de procéder d'abord à un essai pilote pour cette utilisation afin de s'assurer que l'outil est approprié, y compris la faisabilité de la notation des critères.
- Le cadre de l'ETS devrait être suffisamment souple pour englober les différentes manières dont les décisions relatives aux vaccins sont prises. Par exemple, les analyses décisionnelles quantitatives faisant intervenir plusieurs critères nécessitent une expertise technique pour choisir et pondérer ces critères afin d'éviter les chevauchements ou le double comptage, et il ne devrait être recommandé que lorsque cette expertise est disponible.
- La décision de séparer les critères financiers et non-financiers dans l'ETS doit être examinée avec soin et laissée à l'appréciation des parties prenantes dans les pays, car les quantités sans prix explicites (telles que les chaînes du froid et les capacités en termes de ressources humaines) sont nombreuses et peuvent être considérées comme des coûts économiques; or les critères financiers sont souvent cruciaux dans la prise de décisions.
- L'ETS devrait inclure des moyens d'intégrer les points de vue des fournisseurs de vaccins, des communautés et des individus (par exemple, les parents et les personnes vaccinées) dans les outils de prise de décisions. Ces moyens comprennent la participation de ces parties prenantes au comité d'établissement des priorités, la recherche ou l'utilisation de méthodes délibératives pour établir des critères qui sont importants pour les communautés dans l'élaboration des programmes.

- IVIR-AC endorses the proposal to replace “TSE” with “Country Platform for Vaccination Preferences”.

2. Global vaccine acceptance and demand

Introduction

The aim of the WHO expert working group on measuring the Behavioural and Social Drivers of Vaccination is to encourage the development of tools and guidance for use by immunization programmes and partners to measure and address the reasons for under-vaccination and to track consistent, comparable national and global data over time. The tools being developed include quantitative survey questions for caregivers of children under 5 and guidance for qualitative interviews with caregivers, health care workers and others. Details of the plans for testing the tool, including a potential list of countries for field testing, were presented to IVIR-AC, which was requested to comment on the testing proposal, the timeframe and the criteria for selecting countries for testing the tools.

Conclusions and recommendations

- IVIR-AC considers the tool valuable for providing information to programmes and partners about the social and behavioural drivers of vaccination.
- The tool should be used for both routine and periodic data collection. If it is used for routine data collection, care should be taken to minimize the burden on health care staff.
- As guidance will be provided for local adaptation and use, the researchers should ensure that low-, middle- and high-income countries are included in testing. IVIR-AC therefore proposes that at least 1 high-income country be included in testing the tools.
- IVIR-AC recommends that the tool first be tested in English-speaking countries, before it is adapted for other languages. Checking translations into other languages is important but is not the initial priority, as it will be time consuming if done properly. Nevertheless, various global regions should be represented in the testing process.
- IVIR-AC recommends that the tools be tested not only in countries where there are large numbers or large proportions of unvaccinated or under-vaccinated children but also in countries with high coverage but with vaccine hesitancy in subgroups.
- Ideally, cognitive testing should be done in more than 5 countries. This would require an increase in the budget, which should be provided to ensure that the tool is useful in various settings.

- L'IVIR-AC approuve la proposition de remplacer «ETS» par «Plateforme nationale pour les préférences en matière de vaccination».

2. Acceptation et demande de vaccins dans le monde

Introduction

L'objectif du groupe de travail d'experts de l'OMS sur la mesure des facteurs comportementaux et sociaux de la vaccination est d'encourager l'élaboration d'outils et d'orientations à l'usage des programmes de vaccination et des partenaires permettant de comprendre les raisons de la sous-vaccination et d'y remédier, et de suivre dans le temps des données nationales et mondiales pertinentes et comparables. Les outils en cours d'élaboration comprennent des questions d'enquêtes quantitatives à l'intention des personnes qui s'occupent d'enfants âgés de <5 ans et des conseils pour mener des entretiens qualitatifs avec les aidants, les agents de santé et d'autres intervenants. Les détails des plans de mise à l'essai de ces outils, y compris une liste potentielle de pays pour les tester sur le terrain, ont été présentés à l'IVIR-AC, qui a été invité à formuler des observations sur la proposition de mise à l'essai, le calendrier et les critères de sélection des pays envisagés pour tester les outils.

Conclusions et recommandations

- L'IVIR-AC considère que cet outil est précieux pour fournir des informations aux programmes et aux partenaires sur les facteurs sociaux et comportementaux de la vaccination.
- L'outil devrait être utilisé à la fois pour la collecte systématique et pour la collecte périodique des données. S'il est utilisé pour la collecte systématique des données, il faudra veiller à réduire au minimum la charge de travail pour le personnel de santé.
- Comme des orientations seront fournies pour l'adaptation et l'utilisation locales de l'outil, les chercheurs devraient veiller à ce que des pays à revenu faible, intermédiaire et élevé soient inclus dans les essais. L'IVIR-AC propose donc qu'au moins 1 pays à revenu élevé fasse l'objet d'une mise à l'essai de l'outil.
- L'IVIR-AC recommande que l'outil soit d'abord testé dans les pays anglophones, avant d'être adapté pour d'autres langues. La vérification des traductions dans d'autres langues est importante, mais ce n'est pas la priorité initiale, car elle prendra beaucoup de temps si elle est effectuée correctement. Néanmoins, diverses Régions du monde devraient être représentées dans le processus de test.
- L'IVIR-AC recommande de tester l'outil non seulement dans les pays où il y a un grand nombre ou une grande proportion d'enfants non vaccinés ou sous-vaccinés, mais aussi dans les pays où la couverture vaccinale est élevée, mais où il existe des sous-groupes hésitants vis-à-vis des vaccins.
- Dans l'idéal, les tests cognitifs devraient être effectués dans plus de >5 pays. Cela nécessitera une augmentation du budget qu'il faudra prévoir pour s'assurer que l'outil est utile dans divers contextes.

- Within countries, IVIR-AC recommends that representative samples of different attitudes, access (hard to reach, marginalized communities) and geographical areas (urban, rural) be selected. Finding parents of 0-dose children is important for testing the surveys, perhaps by sampling networks to determine connectedness.

3. Comparison of models of Ebola virus disease

Introduction

In July 2019, WHO declared the outbreak of Ebola virus disease (EVD) in the Democratic Republic of the Congo a public health emergency of international concern. Real-time modelling, in which data on actual reported cases are used to adapt estimated projections and impact each week, helps to guide the public health response, including planning the strength, timing and location of interventions. Various model structures, assumptions and fitting may result in different projections and conflicting results for the impact of interventions, creating uncertainty for decision makers. A selection of models will be compared to determine the causes of different projections, and a proposal for this study was presented to IVIR-AC with a request for comments and suggestions.

Conclusions and recommendations

- This excellent initiative will be useful for better understanding the EVD models that are used to inform the WHO leadership and partners for making strategic decisions on the response, including estimates of the number of vaccine doses required.
- We recommend that the authors explicitly indicate how the findings of this comparison could improve control and mitigation of EVD outbreaks, perhaps by documenting how inaccurate or conflicting forecasts in the past have hindered outbreak responses.
- The analysis plan corresponds well to existing guidelines for multi-model comparisons of the impact of infectious disease interventions; however, additional steps should be added to minimize selection bias, including a review of the literature, an open call and inclusion of models according to defined criteria.

Phase 1. Model description

- IVIR-AC recommends that the predictive power of the models is evaluated for small geographical areas (e.g. health zones) first. Models that allow accurate predictions on such small scales can predict the most likely locations of future transmission, to which preventive and reactive interventions should be targeted. Unaffected geographical areas should be used as negative controls during

- Au sein des pays, l'IVIR-AC recommande de sélectionner des échantillons représentatifs des différentes attitudes, difficultés d'accès (communautés marginalisées, difficiles à atteindre) et zones géographiques (urbaines, rurales). Il est important de trouver les parents des enfants qui n'ont reçu aucune dose de vaccin pour tester les enquêtes, peut-être en échantillonnant les réseaux afin de déterminer la connectivité.

3. Comparaison des modèles utilisés pour la maladie à virus Ebola

Introduction

En juillet 2019, l'OMS a déclaré que l'épidémie de maladie à virus Ebola (MVE) en République démocratique du Congo constituait une urgence de santé publique de portée internationale. La modélisation en temps réel, dans laquelle les données sur les cas réels notifiés sont utilisées pour adapter les projections et l'impact estimés chaque semaine, aide à orienter les mesures de santé publique, y compris la planification de l'ampleur, du moment et du lieu des interventions. Les diverses structures, hypothèses et ajustements des modèles peuvent donner lieu à des projections différentes et à des résultats contradictoires en ce qui concerne l'impact des interventions, ce qui crée de l'incertitude chez les décideurs. Des modèles sélectionnés seront comparés pour déterminer les causes des différences entre les projections, et une proposition pour cette étude a été présentée à l'IVIR-AC qui a été invité à formuler des observations et des suggestions.

Conclusions et recommandations

- Cette excellente initiative sera utile pour mieux comprendre les modèles utilisés pour la MVE, conçus pour éclairer les dirigeants et les partenaires de l'OMS dans la prise de décisions stratégiques en matière de riposte, y compris l'estimation du nombre de doses de vaccin nécessaires.
- Nous recommandons aux auteurs d'indiquer explicitement comment les résultats de cette comparaison pourraient améliorer le contrôle et l'atténuation des flambées épidémiques de MVE, peut-être en documentant comment des prévisions inexactes ou contradictoires dans le passé ont entravé les ripostes aux épidémies.
- Le plan d'analyse correspond bien aux lignes directrices existantes pour la comparaison de plusieurs modèles d'impact des interventions contre les maladies infectieuses; toutefois, des étapes supplémentaires devraient être ajoutées pour réduire au minimum le biais de sélection, y compris une revue de la littérature, un appel ouvert et l'inclusion de modèles selon des critères définis.

Phase 1. Description des modèles

- L'IVIR-AC recommande d'évaluer d'abord la puissance prédictive des modèles pour de petites zones géographiques (par exemple, les zones de santé). Les modèles qui permettent de faire des prédictions précises à si petite échelle peuvent prédire les lieux les plus probables de transmission future, qui devront être la cible des interventions préventives et réactives. Les zones géographiques non touchées devraient être utilisées comme témoins

training and testing to improve the predictive power of models.

- The evaluation team should consider using the training and test datasets collected between 1 August 2018 and the present to make new predictions. Use of adjacent time periods to select training and test datasets allows consideration of changes in the strength of the EVD response over time, for example due to changes in the availability of resources or in security.
- A table could be compiled of the assumptions made in each model about the epidemiology of the EVD outbreak, each row corresponding to an epidemiological attribute (e.g. proportion of asymptomatic infections) and each column corresponding to the assumptions about that attribute.
- For models that are found consistently in retrospect to make substantially inaccurate predictions, the aspects responsible for suboptimal performance (e.g. erroneous parameterization, invalid model structure) should be investigated.
- IVIR-AC recommends that the uncertainty of model predictions be evaluated in sensitivity analysis for parametric values and model structure.
- IVIR-AC recommends that measures be defined for the predictive power of the models for planning and for field operations in EVD outbreak control.

Phase 2. New iterations with a standardized set of data and parameters

- It is unclear how the drivers of differences among model predictions will be determined. The goal should be to identify the components that are most useful for producing reliable results, so that they can be used to build better models. Modellers should thus be encouraged to use the lessons learnt to build models that provide more accurate guidance to EVD response teams.
- At the least, comparable values should be assigned to equivalent parameters in the different models to ensure that they are not the main reasons for differences between model predictions; however, structural causes must be assessed. Comparable, standardized datasets should be used.
- The response scenarios for simulations should be based on current practice, i.e. “business as usual”, improved response or weaker response (e.g. due to disruption of a response by violent protests).

4. Measles–rubella eradication investment case

Introduction

The relative impact, cost and cost-effectiveness of various strategies for elimination (and potential eradica-

tion) pendant l'entraînement et le test des modèles afin d'améliorer la puissance prédictive de ces derniers.

- L'équipe d'évaluation devrait envisager d'utiliser les ensembles de données d'entraînement et de test recueillis entre le 1er août 2018 et aujourd'hui pour faire de nouvelles prédictions. L'utilisation de périodes temporelles adjacentes pour sélectionner les ensembles de données d'entraînement et de test permet d'envisager des changements dans l'ampleur de la réponse à la MVE au fil du temps dus, par exemple, à des variations dans la disponibilité des ressources ou dans la sécurité.
- On pourrait compiler un tableau des hypothèses formulées dans chaque modèle pour l'épidémiologie de l'épidémie de MVE, chaque ligne correspondant à un attribut épidémiologique (par exemple, la proportion des infections asymptomatiques) et chaque colonne correspondant aux hypothèses relatives à cet attribut.
- Pour les modèles dont on constate rétrospectivement que les prédictions sont inexactes, il conviendra de rechercher les causes de cette performance sous-optimale (par exemple, erreur de paramétrage, structure de modèle non valide).
- L'IVIR-AC recommande d'évaluer l'incertitude des prédictions des modèles dans l'analyse de sensibilité des valeurs paramétriques et de la structure des modèles.
- L'IVIR-AC recommande de définir des mesures de la puissance prédictive des modèles pour la planification et les opérations sur le terrain dans le cadre de la lutte contre les épidémies de MVE.

Phase 2. Nouvelles itérations avec un ensemble normalisé de données et de paramètres

- On ne sait pas très bien comment l'on déterminera les facteurs qui expliquent les différences de prédictions selon les modèles. L'objectif devrait être d'identifier les composants qui sont les plus utiles pour produire des résultats fiables, afin qu'elles puissent être utilisées pour construire de meilleurs modèles. Les modélisateurs devraient donc être encouragés à utiliser les leçons apprises pour construire des modèles qui fournissent des orientations plus précises aux équipes d'intervention contre la MVE.
- À tout le moins, des valeurs comparables devraient être attribuées aux paramètres équivalents dans les différents modèles pour s'assurer qu'ils ne sont pas les principales causes des différences de prévisions entre les modèles; cependant, les causes structurelles doivent être évaluées. Il conviendrait d'utiliser des ensembles de données comparables et normalisés.
- Les scénarios d'intervention à des fins de simulations devraient être fondés sur la pratique actuelle, c'est-à-dire le statu quo, une réponse accentuée ou une réponse limitée (par exemple, en raison de la perturbation d'une intervention par des manifestations violentes).

4. Argumentaire d'investissement pour l'éradication de la rougeole et de la rubéole

Introduction

Un consortium de spécialistes en modélisation mathématique a modélisé l'impact, le coût et le rapport coût-efficacité relatifs

tion) of measles and rubella have been modelled by a consortium of mathematical modellers in order to better understand the investment, consequences and value for money of initiatives to eliminate measles and rubella transmission globally. The consortium consists of 2 multi-country models for measles (the DynaMICE and Penn State University models) and 2 for rubella (the Public Health England and Johns Hopkins University models). In addition, subnational modelling was done with a single-country measles model in Nigeria (model of the Institute for Disease Modeling). The models projected long-term numbers of cases, deaths and disability-adjusted life years and the number and type of vaccinations given, under 4 vaccination coverage scenarios. The outputs were used in an economic model to estimate the direct costs of vaccination and treatment associated with each scenario to evaluate cost-effectiveness.

Conclusions and recommendations

Impact modelling

- The summary of the modelling should specify that rubella but not measles can be eliminated in the scenarios analysed; however, a substantial reduction in the burden of measles disease and death is a laudable goal, even if it falls short of eradication.
- Presentation of modelling, budget impact and cost-effectiveness by region and/or by income group might allow region-specific recommendations.
- IVIR-AC recommends analysis of the results for each of the 93 countries to determine which factors, such as income level, country size, demography, population density or coverage (with which dose), is the strongest determinant of the time to reach the elimination threshold.
- IVIR-AC recommends that the results of the subnational Nigerian model be compared with those of each of the national models to infer the effect of incorporating spatial heterogeneity; i.e. comparison of national model 1 with national model 2 and then comparison of each of the national model results with the result of the subnational Nigerian model extrapolated to national level.
- In the subnational model, evaluate in a 3x3 format the 3 different ways of distributing and increasing vaccine coverage in the 3 scenarios evaluated to determine whether optimizing vaccine distribution or increasing vaccine coverage is more important. Variation on the y-axis of the plots appears to be greater than the variation among the 3 box plots within each plot, and this should be investigated.
- The intermediate coverage scenarios should be eliminated, and only the base case and the most aggressive coverage scenarios should be presented to SAGE at its meeting in October 2019.

de diverses stratégies d'élimination (et d'éradication potentielle) de la rougeole et de la rubéole afin de mieux comprendre l'investissement, les conséquences et le rapport qualité-prix des initiatives visant à éliminer la transmission de la rougeole et de la rubéole dans le monde. Ce consortium se compose de 2 modèles multi-pays pour la rougeole (les modèles DynaMICE et Penn State University) et de 2 modèles pour la rubéole (les modèles Public Health England et Johns Hopkins University). En outre, une modélisation infranationale a été réalisée à l'aide d'un modèle national de la rougeole au Nigéria (modèle de l'Institute for Disease Modeling). Les modèles ont généré des projections à long terme du nombre de cas, de décès et d'années de vie ajustées sur l'incapacité, ainsi que du nombre et du type de vaccins administrés, selon 4 scénarios de couverture vaccinale. Les résultats ont été utilisés dans un modèle économique pour estimer les coûts directs de la vaccination et du traitement associés à chaque scénario afin d'évaluer le rapport coût-efficacité.

Conclusions et recommandations

Modélisation de l'impact

- Le résumé de la modélisation devrait préciser que la rubéole peut être éliminée dans les scénarios analysés, mais pas la rougeole; toutefois, une réduction substantielle de la charge de morbidité et de mortalité dues à la rougeole est un objectif louable, même s'il ne permet pas l'éradication.
- La présentation de la modélisation, de l'impact budgétaire et du rapport coût-efficacité par Région et/ou par groupe de revenu pourrait permettre de formuler des recommandations spécifiques à chaque Région.
- L'IVIR-AC recommande d'analyser les résultats pour chacun des 93 pays afin de déterminer quels facteurs – niveau de revenu, taille du pays, démographie, densité de population ou couverture (avec quelle dose) – est le déterminant le plus important du délai nécessaire pour atteindre le seuil d'élimination.
- L'IVIR-AC recommande de comparer les résultats du modèle nigérian infranational à ceux de chacun des modèles nationaux afin de déduire l'effet de l'intégration de l'hétérogénéité spatiale; autrement dit, de comparer le modèle national 1 avec le modèle national 2, puis de comparer les résultats de chaque modèle national avec les résultats du modèle infranational du Nigeria extrapolé au niveau national.
- Dans le modèle infranational, il conviendrait d'évaluer dans un format 3x3 les 3 différentes façons de distribuer et d'augmenter la couverture vaccinale dans les 3 scénarios testés afin de déterminer si l'optimisation de la distribution des vaccins est plus importante que l'augmentation de la couverture vaccinale ou inversement. Il conviendrait d'étudier le fait que les variations sur l'axe des y des diagrammes semblent être plus grandes que les variations entre les 3 diagrammes de quartiles à l'intérieur de chaque diagramme.
- Les scénarios de couverture intermédiaire devraient être éliminés et seuls les scénarios de couverture de base et de couverture la plus massive devraient être présentés au SAGE lors de sa réunion qui se tiendra en octobre 2019.

Costing and cost-effectiveness method

- Presentation of average costing and cost-effectiveness for the 93 LMICs was uninformative, as heterogeneity among the countries was not reflected, and almost all the scenarios were cost-effective or cost-saving. A graph or table presenting costing and impact estimates separately by country would facilitate use of the results in decision-making.
- Presentations to decision-makers should include the budget implications and affordability of measles-rubella eradication. The overall costs and benefits in each scenario (but not necessarily the ratio) should be presented to indicate how much eradication will cost and how much will be saved. The resource requirements of eradication might be underestimated for the “last mile”, with increasing marginal costs for high coverage. (The estimate is lower for measles than for polio but might not be realistic given the basic reproduction number of measles.)
- Presentation of results on a dashboard might be informative. The elements to be included could be: time until eradication, which countries will reach elimination, by when, investment required, cost savings, benefits in terms of cases and deaths avoided, and cost-effectiveness ratio.
- The uncertainty in both the epidemiological parameters (represented by the 200 stochastic runs) and the economic parameters (represented by sampling from the distributions of the cost parameters) should be taken into account in the final economic analysis.

Future or continued research programme

- Some of the above recommendations could be met in time for presentation to the SAGE meeting in October 2019; however, most should be part of a longer-term programme of work.
- For the future programme of work, IVIR-AC recommends investigating which global vaccination strategy would achieve worldwide elimination of measles, with further subnational analysis disaggregated per socioeconomic status and geographical setting. Within the future programme, the definition of “elimination of measles” should be revised to reflect disruption of sustained transmission as opposed to reaching a predetermined elimination threshold. Once it is clear which global strategy would achieve elimination according to the new definition, costs should be added and cost-effectiveness and budget impact analysed. In addition, uncertainty and sensitivity analyses should be performed. Further, the models should be validated on the basis of data from the Americas to determine whether they would have predicted elimination of measles in that Region.

Méthode d'établissement des coûts et du rapport coût-efficacité

- La présentation des coûts moyens et des rapports coût-efficacité pour les 93 pays à revenu faible ou intermédiaire n'était pas instructive, car l'hétérogénéité entre les pays n'était pas reflétée, et presque tous les scénarios se révélaient rentables ou économiques. Un graphique ou un tableau présentant les estimations des coûts et de l'impact par pays faciliterait l'exploitation des résultats dans la prise de décisions.
- Les informations présentées aux décideurs devraient inclure les répercussions budgétaires et l'accessibilité économique de l'éradication de la rougeole et de la rubéole. Les coûts et avantages de chaque scénario dans leur ensemble (mais pas nécessairement le rapport coûts-avantages) devraient être présentés pour indiquer combien l'éradication coûtera et quelles économies pourront être réalisées. Les besoins en ressources pour l'éradication pourraient être sous-estimés pour la «dernière ligne droite», les coûts marginaux d'une couverture élevée étant en augmentation. (L'estimation est plus faible pour la rougeole que pour la poliomyélite, mais elle pourrait ne pas être réaliste étant donné le taux de reproduction de base de la rougeole.)
- La présentation des résultats sur un tableau de bord pourrait être instructive. Les éléments à inclure pourraient être les suivants: délai pour parvenir à l'éradication, pays qui parviendront à l'éradication, quand, investissements requis, économies, avantages en termes de cas et de décès évités, et rapport coût-efficacité.
- L'incertitude quant aux paramètres épidémiologiques (représentés par les 200 séries stochastiques) et aux paramètres économiques (représentés par l'échantillonnage à partir des distributions des paramètres de coûts) devrait être prise en compte dans l'analyse économique finale.

Programme de recherche futur ou continu

- Certaines des recommandations ci-dessus pourraient être mises en œuvre à temps pour être présentées à la réunion du SAGE en octobre 2019; toutefois, la plupart devraient faire partie d'un programme de travail à long terme.
- Pour le futur programme de travail, l'IVIR-AC recommande d'étudier la stratégie mondiale de vaccination qui permettrait d'éliminer la rougeole à l'échelle mondiale et de procéder à une analyse infranationale supplémentaire ventilée par statut socioéconomique et par zone géographique. Dans le cadre du futur programme, la définition de l'«élimination de la rougeole» devrait être révisée pour refléter l'interruption d'une transmission durable plutôt que l'atteinte d'un seuil d'élimination prédéfini. Une fois que la stratégie mondiale permettant de parvenir à l'élimination sera clairement identifiée selon la nouvelle définition, il conviendra de déterminer les coûts et d'analyser le rapport coût-efficacité et l'impact budgétaire. En outre, des analyses d'incertitude et de sensibilité devraient être effectuées. Enfin, les modèles devraient être validés sur la base des données provenant des Amériques pour déterminer s'ils auraient permis de prédire l'élimination de la rougeole dans cette Région.

5. Economics of Malaria RTS,S vaccine for policy and decision making

Introduction

A number of economic evaluations have been done to inform the optimization of scaling-up malaria interventions, including the RTS,S vaccine. The objectives of these modelling studies have been to determine when to increase coverage of existing interventions and when to introduce new interventions. Some of the differences in the results of the analyses may have been due to different baseline coverage of interventions (e.g. of long-lasting insecticide-treated nets (LLINs)), differences in assumed unit costs of interventions (particularly for seasonal malaria chemoprevention (SMC) and RTS,S) and assumptions about population coverage of LLINs. IVIR-AC was asked to advise on the performance of economic analyses of RTS,S vaccines in the context of existing preventive malaria interventions and to deliberate on the policy considerations.

Conclusions and recommendations

- IVIR-AC highlighted the following: the burden of malaria in malaria-endemic countries, including morbidity and mortality, is high; currently, preventive interventions (e.g. LLINs, indoor residual spraying, intermittent preventive treatment, SMC) are all partially effective and are difficult to implement in the most disadvantaged communities and poorest households; that individual preventive interventions against malaria should not be assessed as competing interventions or introduced sequentially; and malaria prevention may significantly reduce the incidence of secondary malaria cases.
- Therefore, malaria preventive interventions should be evaluated within packages of multiple, combined interventions. This will require greater consideration of the features of local health systems and interpretation of local malaria control and elimination policies. Furthermore, the synergistic effects and uncertainty in both the impact and costs of preventive interventions (e.g. resistance, LLIN effectiveness, waning vaccine efficacy over time) should be examined. A malaria vaccination programme would interact with countries' currently existing package of preventive malaria interventions, hence, it should be evaluated as complementing such pre-existing national packages.
- Modelling should account for compliance with each intervention. For example, the effectiveness of LLINs depends on compliance with sleeping under the net.
- In policy-making toward UHC, including malaria control and elimination, evidence from economic

5. Considérations économiques liées au vaccin antipaludique RTS,S aux fins du choix des politiques et de la prise de décisions

Introduction

Un certain nombre d'évaluations économiques ont été réalisées pour éclairer l'optimisation de l'intensification des interventions de lutte contre le paludisme, notamment l'utilisation du vaccin RTS,S. L'objectif de ces études de modélisation était de déterminer quand augmenter la couverture des interventions existantes et quand introduire de nouvelles interventions. Certaines différences dans les résultats des analyses peuvent être dues à des différences dans la couverture de base des interventions (par exemple, les moustiquaires à imprégnation durable [MID]), dans les coûts unitaires supposés des interventions (en particulier la chimioprévention du paludisme saisonnier et le vaccin RTS,S) et dans les hypothèses concernant la couverture de la population par les MID. L'IVIR-AC a été invité à donner son avis sur les analyses économiques du vaccin RTS,S dans le contexte des interventions préventives existantes contre le paludisme et sur les considérations politiques.

Conclusions et recommandations

- L'IVIR-AC a souligné les points suivants: i) la charge du paludisme dans les pays d'endémie palustre, comprenant la morbidité et la mortalité, est élevée; ii) actuellement, les interventions préventives (par exemple, les MID, les pulvérisations d'insecticides à effet rémanent à l'intérieur des habitations, les traitements préventifs intermittents, la chimioprévention du paludisme saisonnier) sont toutes partiellement efficaces et difficiles à appliquer dans les communautés les plus défavorisées et les ménages les plus pauvres; iii) les interventions individuelles de prévention contre le paludisme ne doivent pas être considérées comme des interventions concurrentes et ne doivent pas être introduites de manière séquentielle; et iv) la prévention contre le paludisme peut réduire considérablement le nombre de cas de paludisme secondaires.
- Par conséquent, les interventions préventives contre le paludisme devraient être évaluées au sein d'un ensemble d'interventions multiples et combinées. Pour ce faire, il faudra tenir davantage compte des caractéristiques des systèmes de santé locaux et de l'interprétation des politiques locales de contrôle et d'élimination du paludisme. En outre, les effets synergiques et l'incertitude quant à l'impact et aux coûts des interventions préventives (par exemple, la résistance, l'efficacité des MID, la diminution de l'efficacité des vaccins avec le temps) devraient être examinés. Un programme de vaccination antipaludique interagirait avec l'ensemble des interventions préventives existantes dans les pays et devrait donc être considéré comme complémentaire de cet ensemble d'interventions existantes.
- La modélisation devrait tenir compte de l'observation de chaque intervention. Par exemple, l'efficacité des MID dépend de l'observation du fait de dormir sous la moustiquaire.
- Dans l'élaboration des politiques aux fins de la couverture sanitaire universelle, y compris celles relatives à la lutte

analyses should be considered in an open, transparent, deliberative decision-making process and should incorporate considerations of both efficiency and equity, in particular the potential reductions in health disparities and provision of financial risk protection. Hence, economic evaluations specific for malaria should account for heterogeneity in socioeconomic status for both burden and transmission, intervention coverage and delivery costs.

6. WHO/UNICEF estimates of national immunization coverage

Introduction

The method used currently for WHO/UNICEF estimates of national immunization coverage (WUENIC) is based on data reported officially to WHO and UNICEF by Member States, surveys and data reported in published and “grey” literature. In order to further improve the transparency of data inputs as well as the estimation process, and to explore alternative approaches, WHO and UNICEF published a call for expressions of interest (EOI) in early 2019 for a model or another analytical approach to estimate annual national vaccination coverage. EOI were received from 3 academic organizations, namely WorldPop (University of Southampton), Imperial College London and the Swiss Tropical and Public Health Institute (TPH), and all 3 were asked to develop their proposals further. IVIR-AC was requested to comment on the proposed process for reviewing the approaches and to propose high-level principles for evaluating the alternative methods.

Conclusions and recommendations

Proposed process for reviewing approaches for estimating coverage

- IVIR-AC has no major concern about the process proposed for reviewing the approaches and agrees with the proposed plan to work with several technical teams to find alternative approaches (not replacing WUENIC).
- To improve the transparency of the current WUENIC approach and to facilitate comparison with alternative approaches, the current approach should be illustrated in a flow diagram of data inputs and rules for decision-making.

High-level principles for evaluating alternative methods

- Modellers are encouraged to use multiple data sources in the alternative models while recognizing the strengths and weaknesses of each.
- For transparency, the data inputs for the alternative approaches should be clear. In addition, all possible effort should be made to ensure that the model code is freely available and well annotated,

contre le paludisme et son élimination, les données probantes issues des analyses économiques devraient être examinées dans le cadre d’un processus décisionnel ouvert, transparent et délibératif et devraient intégrer des considérations d’efficacité et d’équité, en particulier la réduction potentielle des disparités en matière de santé et la protection contre les risques financiers. Par conséquent, les évaluations économiques spécifiques au paludisme devraient tenir compte de l’hétérogénéité des statuts socio-économiques en ce qui concerne la charge et la transmission du paludisme, la couverture des interventions et les coûts de prestation.

6. Estimations OMS/UNICEF de la couverture vaccinale nationale

Introduction

La méthode actuellement utilisée pour établir les estimations OMS/UNICEF de la couverture vaccinale nationale (WUENIC) est fondée sur les données officiellement communiquées à l’OMS et à l’UNICEF par les États Membres et sur les enquêtes et données issues des publications et de la littérature grise. Afin d’améliorer encore la transparence des données d’entrée et du processus permettant d’établir des estimations, et d’explorer d’autres approches, l’OMS et l’UNICEF ont publié début 2019 un appel à manifestation d’intérêt pour un modèle ou une autre approche analytique permettant d’estimer la couverture vaccinale nationale annuelle. Trois établissements universitaires, WorldPop (Université de Southampton), l’Imperial College London et l’Institut tropical et de santé publique suisse (TPH), ont répondu à l’appel et toutes 3 ont été invitées à développer leurs propositions. L’IVIR-AC a été invité à formuler des observations sur le processus proposé pour l’examen des approches et à proposer des principes de haut niveau pour l’évaluation des autres méthodes.

Conclusions et recommandations

Processus proposé pour l’examen des approches pour l’estimation de la couverture

- L’IVIR-AC n’a pas de préoccupation majeure au sujet du processus proposé pour l’examen des approches et approuve le plan proposé pour travailler avec plusieurs équipes techniques afin de trouver d’autres approches (sans remplacer les WUENIC).
- Afin d’améliorer la transparence de l’approche actuelle utilisée pour établir les WUENIC et de faciliter la comparaison avec d’autres approches, l’approche actuelle devrait être illustrée par un algorithme présentant les données d’entrée et les règles de prise de décisions.

Principes de haut niveau pour l’évaluation des autres méthodes

- Les modélisateurs sont encouragés à utiliser plusieurs sources de données dans les autres modèles tout en identifiant les forces et les faiblesses de chacune de ces sources.
- Par souci de transparence, les données d’entrée pour les autres approches devraient être claires. En outre, tous les efforts possibles devraient être faits pour faire en sorte que le code du modèle soit librement accessible et bien

so that the approach is widely accessible and applicable to as many users as possible. Training in proper implementation and interpretation of the models should be provided.

- Alternative models should include formal quantification of uncertainty. Modellers should not be discouraged by large uncertainty, as quantification of uncertainty can indicate when and what additional data are required to reduce it.
- Appropriate validation should be ensured. Alternative models should be validated against data. Proposed methods for cross-validation and “leave-one-out” validation may not be sufficient. While these are useful forms of internal validation and can indicate particularly influential data points, they cannot be used to test models against “gold-standard” data. IVIR-AC recognizes that the absence of a “gold standard” is a limiting factor.
- Models should be communicated clearly to national stakeholders, and feedback should be taken into account to ensure country “buy-in” and ownership. IVIR-AC suggests establishment of a feedback mechanism between WHO/UNICEF and country focal points according to theory of change. The work of Swiss TPH in understanding local processes and use of data will help in this.
- Models are only as good as the data they are based on. Thus, countries’ capacity for data collection and interpretation should be improved. Not only national but also subnational data could be requested from countries, including subnational surveys. Experience from studies on burden of disease and health service utilization suggests that the lower the level from which data are requested, the better the quality of the data.
- Principles of transparency and engagement with country stakeholders should apply to all estimates of vaccine coverage, for WUENIC and other bodies. ■

annoté, afin que l’approche soit largement accessible et applicable au plus grand nombre possible d’utilisateurs. Une formation à l’utilisation et à l’interprétation appropriées des modèles devrait être dispensée.

- Les autres modèles devraient inclure une quantification formelle de l’incertitude. Les modélisateurs ne doivent pas être découragés par une incertitude élevée, car la quantification de l’incertitude peut donner une indication sur les données supplémentaires qui sont nécessaires pour la réduire et quand ces données doivent être utilisées.
- Une validation appropriée devrait être assurée. Les autres modèles devraient être validés par rapport aux données. Les méthodes proposées pour la validation croisée et la validation «leave-one-out» peuvent ne pas être suffisantes. Bien qu’il s’agisse de formes utiles de validation interne et qu’elles puissent indiquer des points de données ayant une influence particulière, elles ne peuvent pas être utilisées pour tester les modèles par rapport à des données de référence. L’IVIR-AC reconnaît que l’absence de «référence» est un facteur limitatif.
- Les modèles devraient être communiqués aux parties prenantes nationales de manière claire, et le retour d’information devrait être pris en compte pour assurer l’adhésion aux modèles et leur appropriation par les pays. L’IVIR-AC suggère la mise en place d’un mécanisme de retour d’information entre l’OMS/UNICEF et les points focaux nationaux selon la théorie du changement. Le travail de TPH Suisse pour comprendre les processus locaux et l’exploitation des données y contribuera.
- La qualité des modèles dépend des données sur lesquelles ils sont basés. Ainsi, la capacité des pays à collecter et à interpréter les données devrait être améliorée. Des données non seulement nationales mais aussi infranationales pourraient être demandées aux pays, y compris des enquêtes infranationales. L’expérience tirée des études sur la charge de morbidité et l’utilisation des services de santé suggère que plus le niveau auquel les données sont demandées est bas, meilleure est la qualité des données.
- Les principes de transparence et de collaboration avec les parties prenantes nationales devraient s’appliquer à toutes les estimations de couverture vaccinale, pour les WUENIC et les autres organismes. ■

Monthly report on dracunculiasis cases, January-October 2019

In order to monitor the progress accomplished towards dracunculiasis eradication, district-wise surveillance indicators, a line list of cases and a line list of villages with cases are sent to WHO by the national dracunculiasis eradication programmes. Information below is summarized from these reports. ■

Rapport mensuel des cas de dracunculose, janvier-octobre 2019

Afin de suivre les progrès réalisés vers l’éradication de la dracunculose, les programmes nationaux d’éradication de la dracunculose envoient à l’OMS des indicateurs de surveillance des districts sanitaires, une liste exhaustive des cas ainsi qu’une liste des villages ayant signalé des cas. Les renseignements ci-dessous sont résumés à partir de ces rapports. ■

Country – Pays	Date of receipt of the report ^a – Date de réception du rapport ^a	Total no. of rumours ^b of suspected dracunculiasis cases in 2019 – Nombre total de rumeurs ^b de cas suspects de dracunculose en 2019	No. of new dracunculiasis cases reported in 2019 ^c – Nombre de nouveaux cas de dracunculose signalés en 2019 ^c										Total	Total no. of reported cases for the same months of 2018 – Nombre total de cas signalés pour les mêmes mois en 2018	Total no. of villages reporting cases for the same months in – Nombre total de villages signalant des cas pour les mêmes mois en		Month of emergence of last reported indigenous case – Mois d'émergence du dernier cas autochtone signalé ^e
			January – Janvier	February – Février	March – Mars	April – Avril	May – Mai	June – Juin	July – Juillet	August – Août	Sept. – Sept.	Oct. – Oct.			2019	2018	
Endemic countries – Pays d'endémie																	
Chad – Tchad	24 Nov. 2019 – 24 nov. 2019	29764	2	1	1	3	12	9	5	6	4	0	43	14	23	9	Sept. 2019 – Sept. 2019
Ethiopia – Éthiopie	29 Nov. 2019 – 29 nov. 2019	14630	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Dec. 2017 – Déc. 2017
Mali	23 Nov. 2019 – 23 nov. 2019	163	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Nov. 2015 – Nov. 2015
South Sudan – Soudan du Sud	21 Nov. 2019 – 21 nov. 2019	48621	0	0	0	0	0	0	1	1	2	0	4	10	1	9	Sept. 2019 – Sept. 2019
Precertification countries – Pays au stade de la précertification																	
Angola	NR	ND	1	0	0	0	0	ND	ND	ND	ND	ND	1	1	1	1	Jan. 2019 – Jan. 2019
Sudan – Soudan	1 Dec. 2019 – 1 ^{er} déc. 2019	37	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Sept. 2013 – Sept. 2013
Certification countries – Pays au stade de la certification																	
Cameroon – Cameroun	NR	ND	NA	NA	1	NA	NA	NA	NA	NA	NA	NA	1	1	1		March 2019 – Mars 2019
Total		93 215	3	1	2	3	12	9	6	7	6	0	49	25	26	19	

Source: Ministries of Health – *Ministères de la Santé*.

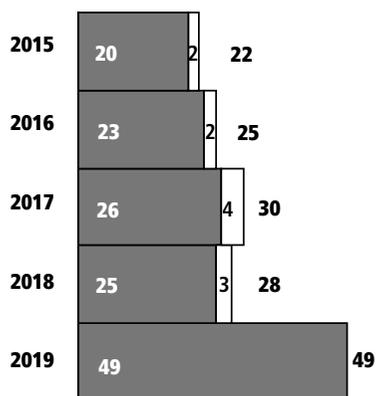
^a Each monthly report is due by the 20th of the following month. – *Chaque rapport mensuel est attendu pour le 20 du mois suivant.*

^b Rumour of dracunculiasis. Information about an alleged case of dracunculiasis (Guinea-worm disease) obtained from any source (informants). – *Rumeur de dracunculose. Information au sujet d'un cas présumé de dracunculose (maladie du ver de Guinée) obtenue à partir de n'importe quelle source (informateurs).*

^c The total number of dracunculiasis cases includes both indigenous and imported cases. – *Le nombre total de cas de dracunculose regroupe les cas autochtones et les cas importés.*

ND: data not available. – *ND: pas de données disponibles.*

NR: no report received on surveillance indicator. – *NR: aucun rapport reçu sur les indicateurs de la surveillance.*



Number of dracunculiasis cases reported worldwide, 2015-2019 – Nombre de cas de dracunculose signalés dans le monde, 2015-2019

The shaded portion indicates the number of dracunculiasis cases reported for the same month in 2019. – *La portion colorée indique le nombre de cas de dracunculose signalés pour le même mois en 2019.*

The value outside the bar indicates the total number of dracunculiasis cases for that year. – *La valeur à l'extérieur de la barre indique le nombre total de cas de dracunculose pour l'année en question.*

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
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
Filariais	http://www.filariais.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_filariais	Filariose 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
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 helminthiasis	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

Session 1:

COVID-19: Risk of SARS-CoV-2 transmission with different immunization services

RISK OF SARS-COV-2 TRANSMISSION WITH DIFFERENT IMMUNIZATION SERVICES

Problem Statement

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COVID-19 Session 1

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

21 September 2020

Safety for health workers and patients

- **WHO Charter: Keep health workers safe to keep patients safe**
 - Published 17 September 2020
 - 5 steps to improve health worker safety and patient safety
 - <https://www.who.int/news-room/detail/17-09-2020-keep-health-workers-safe-to-keep-patients-safe-who>
- While health workers (HWs) are <3% of the population in most countries and <2% in almost all LMICs, around 14% of COVID-19 cases reported to WHO are among HWs, with the proportion as high as 35% in some countries. *(Caveat: Data are limited; not easy to establish source of infection as work place or community.)*

Background – 1: The situation

- In March 2020 as the COVID-19 pandemic unfolded, there was recognition that the pandemic was disrupting immunization services.
- Factors contributing to disruption: lockdowns, COVID-19-related burden on the health system (diversion of health workers and other resources), decreased demand for vaccination (due to transportation limitations, physical distancing requirements, community reluctance, etc.).
- Great concern that disruption of immunization services was increasing the number of unvaccinated and thus susceptible individuals, thereby increasing the risk of vaccine-preventable diseases (VPDs) and related morbidity and mortality.

Background – 2: Guiding Principles

- The Strategic Advisory Group of Experts on immunization (SAGE) and WHO issued the 26 March 2020 *Guiding principles for immunization activities during the COVID-19 pandemic*. Among the 7 principles were **3** which required further thinking/evidence/modeling to provide more practical advice:
 1. *“Immunization is a **core health service** that should be prioritized for the prevention of communicable diseases and safeguarded for continuity during the COVID-19 pandemic, where feasible. Immunization delivery strategies may need to be adapted and should be conducted under safe conditions, **without undue harm** to health workers, caregivers, and the community.”*

Background – 3: Guiding Principles

2. *“Based on current understanding of transmission of the COVID-19 virus and recommendations for physical distancing, mass vaccination campaigns should be temporarily suspended. Countries should monitor and re-evaluate at regular intervals the necessity for delaying mass vaccination campaigns.*
3. *The conduct of outbreak response mass vaccination campaigns will require a careful risk-benefit analysis on a case-by-case basis, assessing risks of a delayed response against the risks associated with an immediate response, both in terms of morbidity and mortality for the VPD and the potential impact of further transmission of the COVID-19 virus.”*

Background – 4: Advice for safe health service delivery

- What advice can be provided regarding the conditions under which vaccination can safely take place?
 - During spring 2020, the understanding of infection prevention control (IPC) requirements for SARS-CoV-2 transmission was limited. Emphasis was on handwashing. There was lack of data/agreement on the role of masks and of aerosol transmission.
 - IPC includes both
 - personal protective equipment (PPE) such as masks and gloves, AND
 - structural and behavioral interventions such as handwashing, frequent cleaning of high-touch surfaces, maintaining physical distance between people, open-air settings, crowd management, etc.
- Clarifying IPC standards for different health service delivery scenarios to protect communities and to protect health workers has required ongoing incorporation of emerging evidence and problem-solving. **The request for this modeling work was to clarify transmission risks and to inform safe approaches for vaccination.**

Background – 5: Risk/Benefit Considerations

Two types of service delivery

1. Routine immunization

- Generally more straightforward ability to control and manage risk for SARS-CoV-2 transmission through IPC interventions
- High benefit for VPD prevention
- Essential health services

[Click to add text](#)
[Click to add text](#)

2. Mass vaccination campaigns or Supplemental Immunization Activities (SIAs)

- Mass gathering creates risk for SARS-CoV-2 transmission
- For *outbreak response SIA*: identified existing risk of VPD and of VPD transmission, so VPD prevention and control benefit clear
- For *preventive SIA*: less clarity on the urgency and risk for VPDs or VPD transmission, so VPD benefit and urgency/necessity less clear

Background – 6: Considerations for preventive SIAs

What is the **worst** case scenario?

- SIA causes significant SARS-CoV-2 transmission with morbidity and mortality in the community AND SIA is poor quality with limited VPD reduction.
- Also need to consider:
 - broader societal and economic repercussions of COVID-19 morbidity and mortality, including stress on health system
 - risk of HW infections which lead to HW COVID-19 deaths which reduce HW workforce and health system strength, possibly leading to future deaths in children and adults as a result

What is the **best** case scenario?

- Cause **no** significant SARS-CoV-2 transmission with **no** COVID-19 morbidity/mortality AND have high quality SIA with dramatic VPD reductions.

	High quality SIA	Poor quality SIA
No risk of SARS-CoV-2 transmission	+/+	+/-
High risk of SARS-CoV-2 transmission	-/+	-/-

Key question posed for modeling analysis

What is the risk of SARS-CoV-2 transmission to communities and to health workers:

- 1) for settings with various levels of COVID-19 burden,
- 2) under different health service delivery conditions (e.g., routine immunization via fixed-site, outreach, and schools; mass vaccination campaigns which are either fixed-site or door-to-door), and
- 3) in consideration of the nature and extent of Infection Prevention Control (IPC) measures implemented?

Questions to IVIR-AC

- Does the model fully address *all* aspects of the key analytic question?
 - What is the risk of SARS-CoV-2 transmission to health workers?
- How robust are the **conclusions of the modelling work?** [Click to add text](#)
 - Are assumptions about roles of children in transmission justified and sufficiently conservative?
 - How can we extrapolate the results from the six analysed settings to other countries? Do country characteristics (different income levels, age pyramids, immunization system strength, health workforce size, rural/urban distribution, HDI) translate into different transmission risks for communities and health workers? If so, how?

The risk of SARS-CoV-2 transmission to communities and to health workers in LMICs under different health service delivery conditions

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What do we already know?

The global SARS-CoV-2 pandemic has delayed many supplementary immunization activities (SIAs) in low- and middle-income countries (LMIC)s due to concerns over the risks of accelerating the transmission of the virus, as well as due to prioritization of the COVID-19 response and diversion of health workers. In addition, some countries have scaled back routine immunization services, including outreach sessions targeted to underserved populations.

When decisions to delay SIAs and reduce services were made, they were appropriate, given the high level of uncertainty around the new disease and how the outbreaks would evolve. However, immunization services are essential, and the substantial risks of morbidity and mortality from vaccine-preventable diseases are well characterized. In risk-benefit assessments of undertaking vaccination activities during the COVID-19 pandemic, understanding SARS-CoV-2 transmission risks and possibilities for mitigating them is critical to inform resumption and implementation of safe vaccination services.

What does this report add?

We estimate the impact of three methods of enhanced immunization service delivery on the transmission of SARS-CoV-2, compared to a baseline of continued in-facility routine immunization programs. We examine effects of varying transmission conditions and across representative country settings. Delivery methods include fixed-post SIAs, house-to-house SIAs, and elevated routine outreach services.

What are the implications for public health practice?

These findings can be used to support decisions around when and how to resume immunization services targeting children, such as measles and polio SIAs and routine outreach programs as well as routine fixed site service delivery.

Executive summary

Purpose: To estimate, for various settings, the impact of vaccination delivery strategies on SARS-CoV-2 transmission in communities and health workers.

Countries: Six countries were examined: Angola, Ecuador, Pakistan, Ukraine, Nepal, and Lao PDR. These countries were selected to include each WHO region and capture various demographic profiles and levels of health system performance, as well as to include countries that are priorities for routine immunization strengthening through EPI and for the Global Polio Eradication Initiative (GPEI).

Background: In light of the COVID-19 epidemic, on March 26th 2020, the WHO issued interim guidance [1] stating that countries should reconsider SIAs, citing the risk of further transmission during such an event. Routine immunization activities have also been disrupted in some countries and sub-national regions due to the COVID-19 pandemic. These changes have substantially reduced availability of immunization services and vaccination coverage. The acute need for continuation of these services must be balanced with the safety of health workers, care givers, and the community.

Primary results:

- Any incremental activity increasing contact rates and transmission of SARS-CoV-2 has an impact on the total number of community infections. However, the effect size is less than 100 community infections per 1000 vaccinations in all scenarios except for SIAs occurring at peak prevalence during outbreaks with overall attack rates in excess of 50%. Due to the high variance in the infection process, many simulated outcomes do not result in excess infections distinguishable from zero.
- The effect of different delivery modalities varies by context.
 - Urban, fixed-post SIAs occurring during periods of high prevalence can be expected to increase infections within the community by around 28 [0, 79] per 1000 vaccinations. These infections may represent an acceleration of the outbreak and not increase the overall attack rate of the epidemic.
 - House-to-house SIAs in mixed urban and rural contexts may import infections into previously naïve communities. Infections are elevated by around 60 [0, 230] per 1000 vaccinations, but outcomes are very sensitive to prevalence of infection in health workers and SIA timing.
- Structural differences between countries influence outcomes.
 - Age pyramid: Younger populations tend to lead to lower transmission intensity and lower prevalence.
 - Proportion of rural population: Larger rural populations tend to correspond with lower transmission intensity, but greater risk that an SIA introduces SARS-CoV-2 circulation to naïve communities.
- Increases in community infections of SARS-CoV-2 due to a vaccination activity tend to be in proportion to the underlying level of SARS-CoV-2 transmission in that community.
- Reducing the SARS-CoV-2 attack rate in health workers performing vaccinations to a level that is equal to or below the attack rate experienced by members of the community eliminates the risk of excess infections.

Glossary

Base case

Simulations without SIAs or routine outreach. Health workers do not have increased relative acquisition/transmission rates. Base case simulations for urban and urban-rural contexts are separate. Moderate distancing is included.

Distancing

Behavior policies that decrease contact rates by route: school, work, and/or community.

Fixed-post (FP)

A fixed-post intervention is a model representation of fixed-post SIA that involves an increase in contacts within the under-5 cohort (children), within the 20-35-year-old cohort (their caregivers), and between the two groups.

House-to-house (H2H)

A house-to-house intervention is a model representation of a house-to-house SIA that involves adjusting the interaction rates between health workers and the general population, to reflect the process by which a vaccinator moves from one house to the next administering vaccinations.

Overall attack rate

Fraction of individuals that are infected by SARS-CoV-2 during the simulation. Simulation duration is 730 days.

Routine outreach

Non-SIA intervention. Both children and adults experience a small increase in intra-community contact rates for a period of three months. About 15% of the <5yr cohort receives single-antigen vaccination.

Relative acquisition/transmission rate (RATR)

Adjusted acquisition and transmission rates of health worker (HW) populations. Levels examined vary from 20x to 1x; levels are for health workers with respect to non-health worker individuals of similar ages. Overall attack rate of HW for a RATR of 1x is representative of their age cohort but may be different from the entire population.

Supplementary Immunization Activity (SIA)

For this study, a simulation with an SIA refers to a simulation with either a fixed-post (FP) intervention or a house-to-house (H2H) intervention.

Urban Context

Simulation with very high mobility rates. All locations are well-connected and transmission between all locations is rapid.

Urban-rural Context

Simulation with intermediate mobility rates. The rural fraction of population is in locations that are networked to the primary urban location, and transmission across the network requires one or more successful importations to connect all individuals.

Introduction

The novel coronavirus SARS-CoV-2 emerged in Wuhan, China, in late Nov or early Dec 2019 [2]. As of July 15th 2020, it is responsible for 8,860,331 confirmed cases and 465,740 deaths worldwide from the disease COVID-19 [3]. After initial emergence in China, travel associated cases started to appear in other parts of the world with strong travel connections to Wuhan [4]. The first importation of SARS-CoV-2 into sub-Saharan Africa was reported in Nigeria on February 27, 2020; since then confirmed cases have risen across the continent [5]. Early importations were primarily found in travelers returning from abroad [6], but with the emergence of community transmission many countries instituted strict lockdowns to prevent expansions of the outbreaks.

On March 26th, the WHO issued interim guidance [1] that immunization activities should be reconsidered in light of the risks of SARS-CoV-2 transmission. Many countries postponed or cancelled planned SIAs; as of April 24th 2020, measles SIAs had been postponed in 24 countries [7], including some with large and vulnerable populations such as Bangladesh, Ethiopia, Nigeria, and the Democratic Republic of the Congo (DRC). Gavi, the Vaccine Alliance, has announced delays in implementation of SIAs against polio, measles, cholera, HPV, yellow fever and meningitis and at least four national routine vaccine introductions [8]. Similar actions have been taken by the Global Polio Eradication Initiative (GPEI), suspending many polio SIAs [9].

The risk of SARS-CoV-2 transmission during SIAs does exist, as there are reports of many health workers becoming ill with the virus, for example in Liberia, Djibouti, and South Africa [10]–[12]. Health workers could potentially transmit to otherwise healthy individuals during a SIA or may become ill themselves after developing COVID-19 during a SIA.

This SIA delay is being driven by concerns over risks of SARS-CoV-2 transmission via SIAs, but there are also health risks, particularly to vulnerable populations, of delay [13]. For example, there is an ongoing measles outbreak in DRC, which killed 6,000 children in 2019 [14]. In Kathmandu, a measles-rubella SIA scheduled for February was suspended [15], and communities are now experiencing outbreaks [16]. Diphtheria and cholera are both making a comeback in several countries [17] and putting particularly vulnerable populations such as refugees at high risk for outbreaks [18], at least in part due to delays in SIAs and diversion of healthcare providers. In addition, health systems weakened by the COVID-19 pandemic are unable to keep up with day-to-day healthcare needs [19], which may leave those who are affected by non-COVID-19 illness more vulnerable to morbidity and mortality.

Countries are now reconsidering earlier choices to postpone SIAs, rescheduling and implementing these SIAs during the ongoing pandemic in 2020 [20]–[22]. The risks of COVID-19 transmission need to be balanced with the benefits of the SIA itself. The WHO has published a framework to support country-decision-making about implementing preventive mass vaccination campaigns [23].

Routine immunization coverage has also been affected by uncertainties about SARS-CoV-2 transmission risks. Reductions in coverage have been documented in communities such as Karachi, Pakistan [24] and globally, the WHO reports that more than half of countries with available data had moderate or severe disruptions to services [25]. The reasons are attributable to a combination of reduced demand (fewer children seeking routine services), reduced numbers of immunization days in clinic, and less frequent outreach services being offered.

The purpose of the study is to estimate, for various settings, the impact of vaccination delivery strategies on SARS-CoV-2 transmission in communities and health worker populations.

Methods

Example country selection

We opted to select six countries that are either upper-middle, lower-middle, or low income as demonstration contexts. The six countries were chosen from each WHO region and include priority countries for the Essential Programme on Immunization (EPI) and for the Global Polio Eradication Initiative (GPEI). We compared countries across the six indicators in table 1 and selected countries to be representative of varying levels of demographics, social structure, overall development, and healthcare system strength. Values for indicators in the selected countries are listed in table 1. See Appendix 4 for indices' definitions, data sources, and 2019 values for other LMIC countries.

Table 1. Representative countries. HDI = human development index. % rural = % of population living in a rural setting. % slum = % of population living in a slum or informal settlement. Appendix 4 contains detailed definitions and data sources.

Country	Region	Income	% Under 15	DTP3 Coverage	Nurses per 1k	HDI	% Rural	% Slum
Angola	AFR	Lower-Middle	46.8	59.0	0.41	0.57	34.5	36.4
Ecuador	AMR	Upper-middle	28.0	85.0	2.51	0.76	36.2	23.0
Lao PDR	WPR	Lower-middle	32.6	68.0	0.95	0.60	65.0	11.0
Nepal	SEAR	Low	30.4	91.0	3.11	0.58	80.3	10.7
Pakistan	EMR	Lower-middle	35.3	75.0	0.67	0.56	63.3	16.7
Ukraine	EUR	Lower-middle	15.8	50.0	6.66	0.75	30.6	-

Transmission modeling

Burden forecasts were generated using EMOD, an individual-based disease modeling platform [26] that has been reviewed by the COVID-19 Multi-Model Comparison Collaboration (CMCC) [27]. Additional details have been included in Appendix 1. Simulations were intended to represent SARS-CoV-2 progression in the chosen contexts and used parameter values appropriate for those representative countries.

Each simulated agent is assigned to an age cohort according to the demographics of the simulated country. Contact rates between agents in the model are stratified across four routes (school, home, work, and community) and sixteen age groups (5-year age bins up to 75 years old, and one age bin for those 75+) using published model estimates [28], and by risk levels (low, medium, and high). Risk levels

provide additional variance within age group without altering mean contact rates. The structure of the model does not distinguish between respiratory droplets, airborne transmission, and surface contamination, but instead applies an overall probability of transmission between contacts, regardless of mode.

The baseline distancing scenario for each country assumes school closures, reduced work contacts, and restricted community gatherings (contact rates for school, work, and community are reduced to 0%, 50%, and 75%, respectively, from the values in [26]). For all distancing policies involving a reduction in work contacts or school contacts, twenty percent of the reduced contacts were redistributed to the home route to reflect extra time spent in the home. No community contacts were redistributed to the home route.

For each country, the model was used to fit a most-likely R_0 value and case reporting rate to match reported case counts [5]. Summary data are included in table 2. Additional details have been included in Appendix 2. Contact rate fractions in table 2 correspond to the scalar product of the vector of population fractions, the matrix of contact rates, and the vector of population fractions.

$$RouteValue = NormalizationConstant * \underline{PopFractions} * \underline{Contacts} * \underline{PopFractions} \quad [1]$$

The route value in equation 1 is a scalar. Scalar results for all four contact matrices are normalized with the same constant such that they sum to exactly one. Alterations to the contact matrix from distancing policy or reduced susceptibility by age cohort are applied after matrix normalization; the indicated value for R_0 in table 2 *does not* account for distancing policy and variable susceptibility with age.

Table 2. Baseline scenario contact rate fraction per route and estimated infectivity; stratified by representative country context.

Country	Contact Rates According to Contact Routes				Baseline R_0
	Home	School	Work	Community	
Angola	0.188	0.264	0.071	0.477	3.6
Ecuador	0.223	0.211	0.137	0.429	3.2
Lao PDR	0.195	0.222	0.067	0.516	3.0
Nepal	0.175	0.242	0.135	0.449	3.2
Pakistan	0.188	0.251	0.043	0.518	3.6
Ukraine	0.256	0.112	0.277	0.356	3.0

Contact fractions by route in table 2 are input parameters from published model estimates [28]; the R_0 values were estimated in this study.

Reduced susceptibility among children is a significant unknown. Several publications [29]–[34] suggest that the under-15 year old cohort acquires and transmits SARS-CoV-2 infections at a lower rate than the general population. This model incorporates a reduction in childhood acquisition of about 55% and childhood transmission of 15%, which has a substantial impact on transmission, reducing the total burden and slowing the speed of the outbreak. Additional details on the effect of reduced childhood susceptibility have been included in Appendix 5.

Connectivity and migration between city centers, peri-urban and rural communities is also poorly documented. In our spatial model, we assume a single large population center, with the sizes of the

other population centers (when present) distributed exponentially. These other population centers represent rural locations and have minimum population of 100 agents (total simulation population is 1 million). The percentage of the population in the large population center is equal to the urban fraction, in alignment with the country's urban/rural distribution in table 1. A network of individual mobility between all population centers was based on the distance and size of population centers. Modeling the outbreak of COVID-19 using this distributed community connectivity results in a slower growth and extended outbreak.

The 'urban' base case is representative of a single major population center without the network of rural locations, while the 'urban-rural' base case is representative of a major population center with surrounding rural locations. No simulations examine a rural-only setting. A rural-only setting would consist of a network of small populations without any single major center, and have outcomes dominated by introduction risk. Both types of base case depicted in figure 1 are used when presenting results for this study.

Note that outcomes depicted in figure 1 (and throughout) are trajectories of mean behavior based on ensembles of 1000 simulations. The stochastic uncertainty of the models is shown later in the results section. Timeseries are depicted with respect to 'days-post-introduction'; novel coronavirus introduction to the community occurs at day-0 on this axis.

Note that the shapes of the base case outbreak in figure 1 vary widely and do not directly correlate with values for the R_0 parameter. Additionally, no adaptive distancing policy is included in these scenarios. For instance, an outbreak as acute as depicted in the Ukraine would be expected to involve significant behavior self-modification, which was not included or examined in this study.

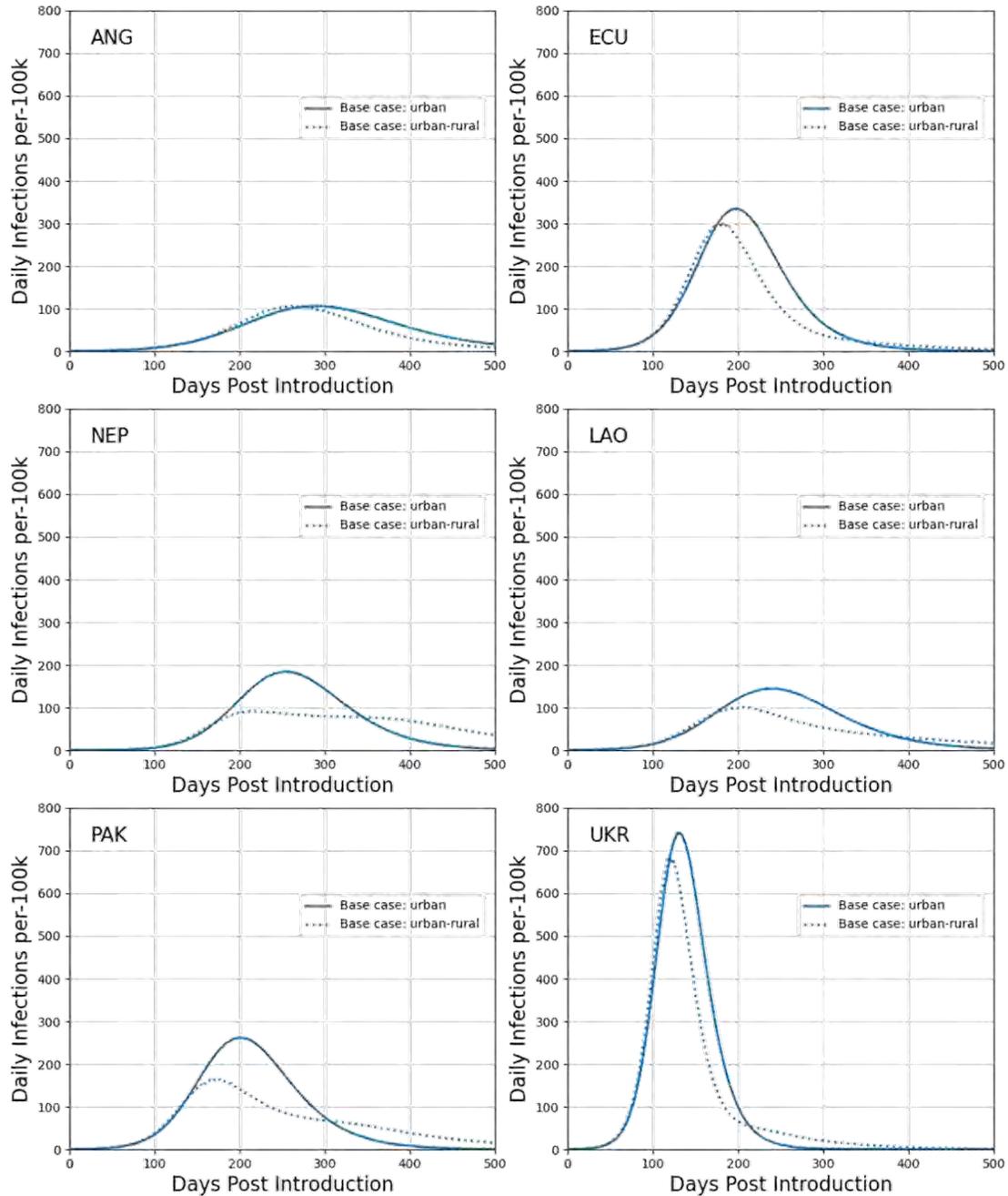


Figure 1. Daily infection trajectories per 100,000 population for the ‘urban’ base case and for the ‘urban-rural’ base case; in the ‘urban-rural’ base case, the urban fraction of the population is in the largest population center and the remainder of the population is distributed across smaller population centers. The x-axis describes the number of days post SARS-CoV-2 introduction to the community.

These scenarios are to be interpreted as illustrative of a wide range of potential outcomes, principally depending on the level of urbanization and shape of the population pyramid. Countries were selected as archetype contexts by demonstrating the variability of these metrics; these outcomes do not seek to reproduce a natural history of the SARS-CoV-2 outbreak for these countries.

Delivery scenarios

The base case scenarios assume the continuation of typical pre-COVID-19 routine immunization services. It is assumed that some fraction of the contacts reported in table 2 are attributable to health facility visits for the purpose of vaccination. All the scenarios described below are incremental to the base case and the impact of each is calculated as the net difference between the delivery scenario described and this base case value.

There are many potential vaccine delivery scenarios. We have chosen to focus on those that are most generalizable, recognizing that the delivery scenarios described below are not exhaustive.

Fixed-post (FP) SIAs were reflected in the model by adjusting the contact rates among different age cohorts for seven days, to reflect the community coming together to a central location and having some level of social interaction as well as travel. This was represented by a 50% increase in contacts within the under-5 cohort (children), a 50% increase in contacts among individuals in the 20-35-year-old cohort (their caregivers), and a 200% increase in contacts between the two groups. This scenario approximates a fixed-post SIA with a single-antigen delivered to children, during which vaccination is provided by a health worker who has brief interactions with each child and caregiver. In these scenarios, the increase in community contacts among and between the target population and their caregivers is the primary cause of additional SARS-CoV-2 infections.

House-to-house (H2H) SIAs were reflected in the model by adjusting the interaction rates between health workers and the general population, to reflect the process by which a vaccinator moves from one house to the next administering vaccinations. No changes were made to general community contacts rates with each other. This implies that the children and their caregivers abide by distancing practices and no additional travel would be required. In these scenarios, the potential infection of households by health workers is the primary cause of additional SARS-CoV-2 infections.

To reflect house-to-house SIAs in urban-rural scenarios, health workers were moved from the urban center to smaller communities. These movement patterns were notable because they did not follow the assumed baseline mobility structure. Base case mobility prioritized local travel according to a gravity-type model (additional details in Appendix 1); vaccination outreach to rural communities was modeled as independent of the distance traveled. For these scenarios, vaccination outreach incorporates many more occurrences of long-distance travel than are present in the baseline mobility structure. In these house-to-house SIAs in rural locations, the potential for health workers to unintentionally introduce SARS-CoV-2 into communities not currently undergoing transmission is the primary cause of additional infections.

In a typical measles SIA, a vaccinator is expected to deliver between 100-150 vaccinations per day in urban settings and 75-100 per day in more rural areas [35]. All scenarios report infections using a per-population basis (e.g. per-100k). Outcomes for fixed-post SIAs incorporate a fractional increase in the number of contacts among the target population and care givers, which accounts for the difference in target population sizes between the contexts. Outcomes for house-to-house SIAs account for the difference in target population sizes by scaling the number of health workers used by the size of the target population (e.g., the size of the <5yr cohort in Angola is 3.6x the size of the <5yr cohort in Ukraine, which corresponds to using 3.6x the number of vaccinators for the duration of the

intervention). SIA durations and frequency were not varied based on context; however, variations in timing independent of context were examined for sensitivity purposes.

For both SIA-based delivery methods, we assumed that infection control interventions (IPC) would be in place and this would result in a longer duration of the SIA, taking 20-25% more time to complete.

Routine outreach was implemented similarly to a fixed-post SIA, with both children and adults experiencing a 20% increase in intra-community contact rates. However, in the case of outreach, the health worker was expected to encounter adults as well as children, since these outreach events are intended to serve a wider population. They are also held periodically and consistently; for these purposes we assumed three days per month for a period of three months, with a cumulative 15% of the target population is receiving health services in this way.

Sensitivity analyses

Timing of the vaccination delivery, including scenarios where the delivery occurred prior to peak, near the peak, or after the peak of the COVID-19 outbreak, was examined as part of the sensitivity analysis.

Impact of infections within health worker populations were varied by simultaneously adjusting the acquisition and transmission rates of health workers; these variations were intended to represent the application of infection prevention and control (IPC) measures. Modifications affected both 1) the acquisition of SARS-CoV2 by the health worker if susceptible and 2) the transmission of SARS-CoV2 by the health worker if infectious. Levels examined include relative acquisition/transmission rates (RATR)s of 20x, 15x, 10x, 5x, and 1x; levels are for health workers with respect to non-health worker individuals of similar ages.

The health worker cohort persists for the entire duration of the simulation, the RATRs in this cohort do not change during the vaccine delivery scenarios. Health worker contact patterns did not follow the age structured matrix used for other groups, see Appendix 2 for details. Relative acquisition and transmission rates are correctly interpreted as an input that controls the overall attack rate of the HW cohort, and not corresponding to a specific implementation of IPC.

Results

Routine outreach and fixed-post scenarios

Time to peak incidence varied by country. For comparability across contexts, vaccination events were timed with respect to time to peak incidence for the urban setting. These timings are reported in Appendix 5.

Routine outreach scenarios did not result in outcomes different from the base case in either the urban only or the urban-rural settings. Mean trajectories were reproduced to within available precision. Base case and routine outreach scenarios for the urban-rural setting are depicted in figure 2.

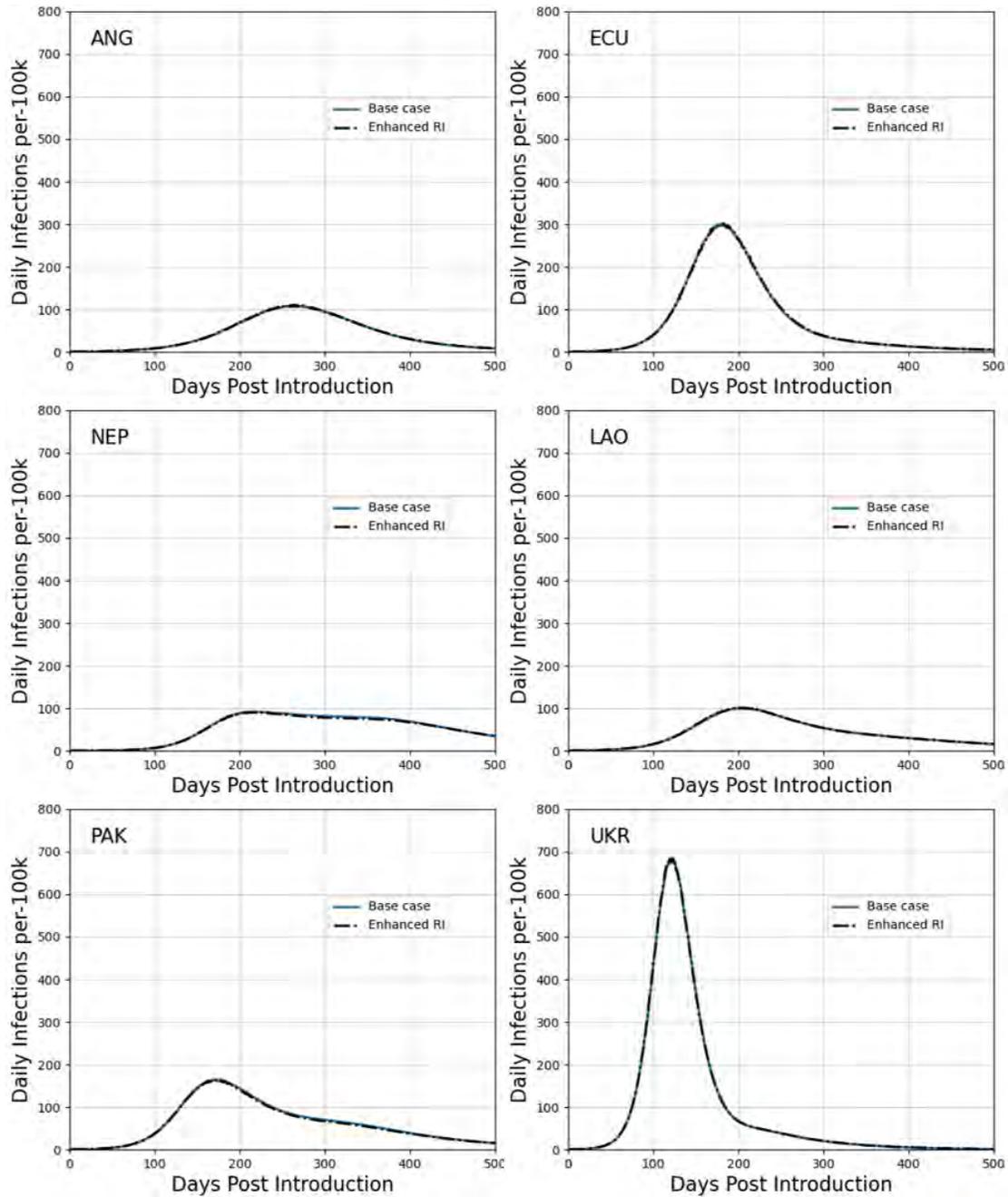


Figure 2. Expected daily infections per 100k individuals for each context. Routine outreach was implemented the 90 days starting 45 days prior to peak incidence.

Urban, fixed-post SIAs were implemented with respect to the time of peak incidence. Scenarios examined implementation of a single event 45 days before, 15 days before, 15 days after, or 45 days after peak incidence. Simulation outcomes in figure 3 implemented each fixed-post SIA independently.

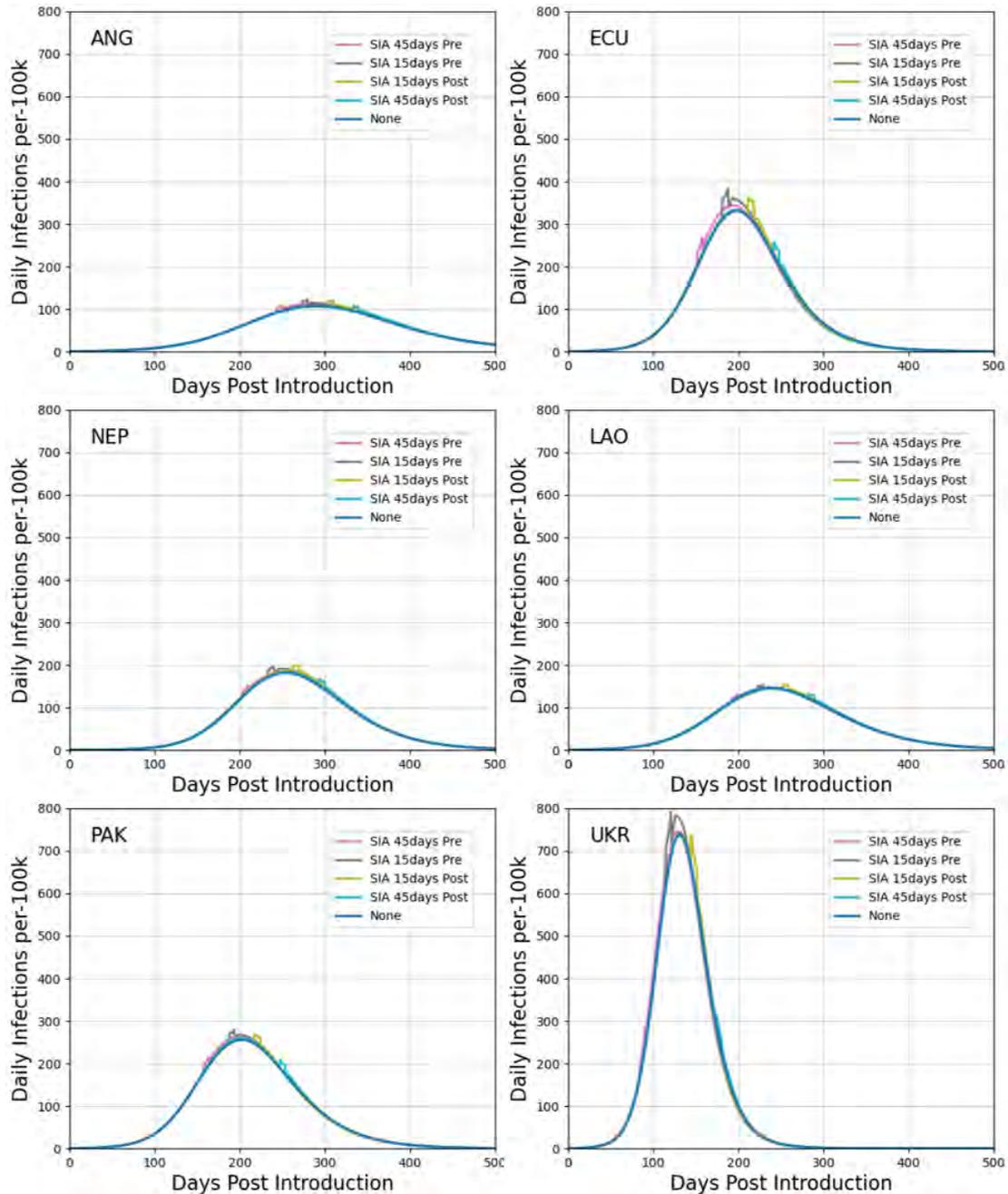


Figure 3. Expected daily infections per 100k individuals for each country examining four possible schedules, with respect to baseline urban scenarios that do not include an intervention. Fixed-post SIA timing with respect to peak incidence was the same for all contexts.

Scenarios implementing all four fixed-post SIA events within a single simulation of an urban context are depicted in figure 4. For these combined event simulations, the increase in infections with respect to the base case is nearly equivalent to a linear combination of increases from the single event simulations. When using one-month intervals between events, non-linear effects appear minimal.

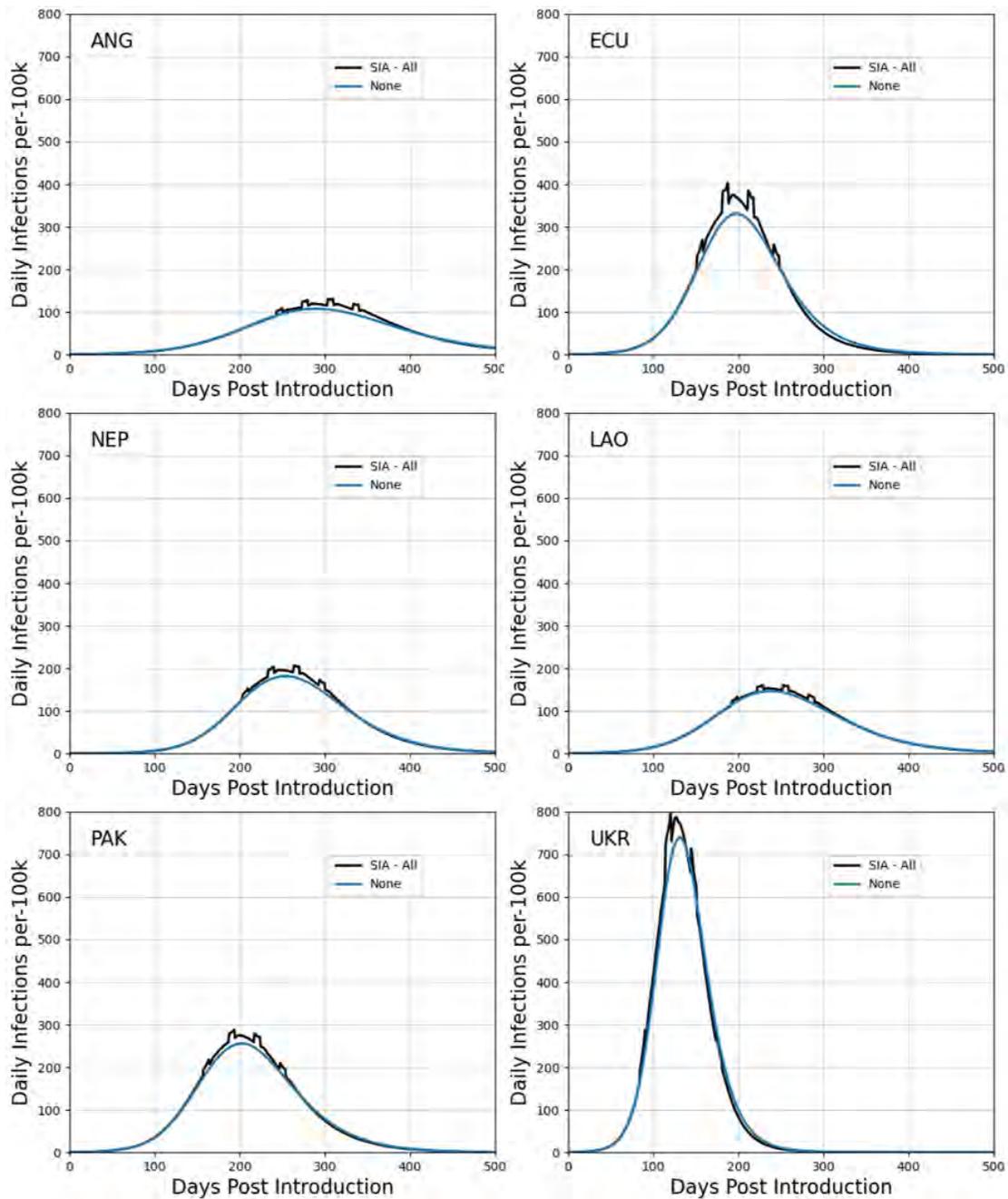


Figure 4. Expected daily infections per 100k individuals for each country examining a single schedule involving four separate fixed-post SIAs spaced 30 days apart, with respect to baseline urban scenarios that do not include an intervention.

Impact of relative acquisition/transmission rates in health workers on transmission

Relative acquisition/transmission rates in health workers affect both the overall epidemic for the general population and the attack rate among health workers themselves. The 10x rate in health workers slightly reduces the time to peak incidence for the epidemic relative to the 1x rate, although this change tends to be small.

Health workers are a small fraction of the total population (0.1%), but their contacts with vulnerable populations tend to give this cohort an outsized impact for its total size. In scenarios where health workers acquire and transmit infections at the 1x rate, the overall attack rate among health workers is reduced by between 40 to 63 percentage points, compared to scenarios where health workers acquire at the 10x rate (see table 3).

Note that these simulations are entirely focused on disease transmission, and do not address the morbidity or mortality effects that may arise from a depletion of health workers availability due to COVID-19, which was documented in West Africa after the Ebola outbreak of 2014 [36].

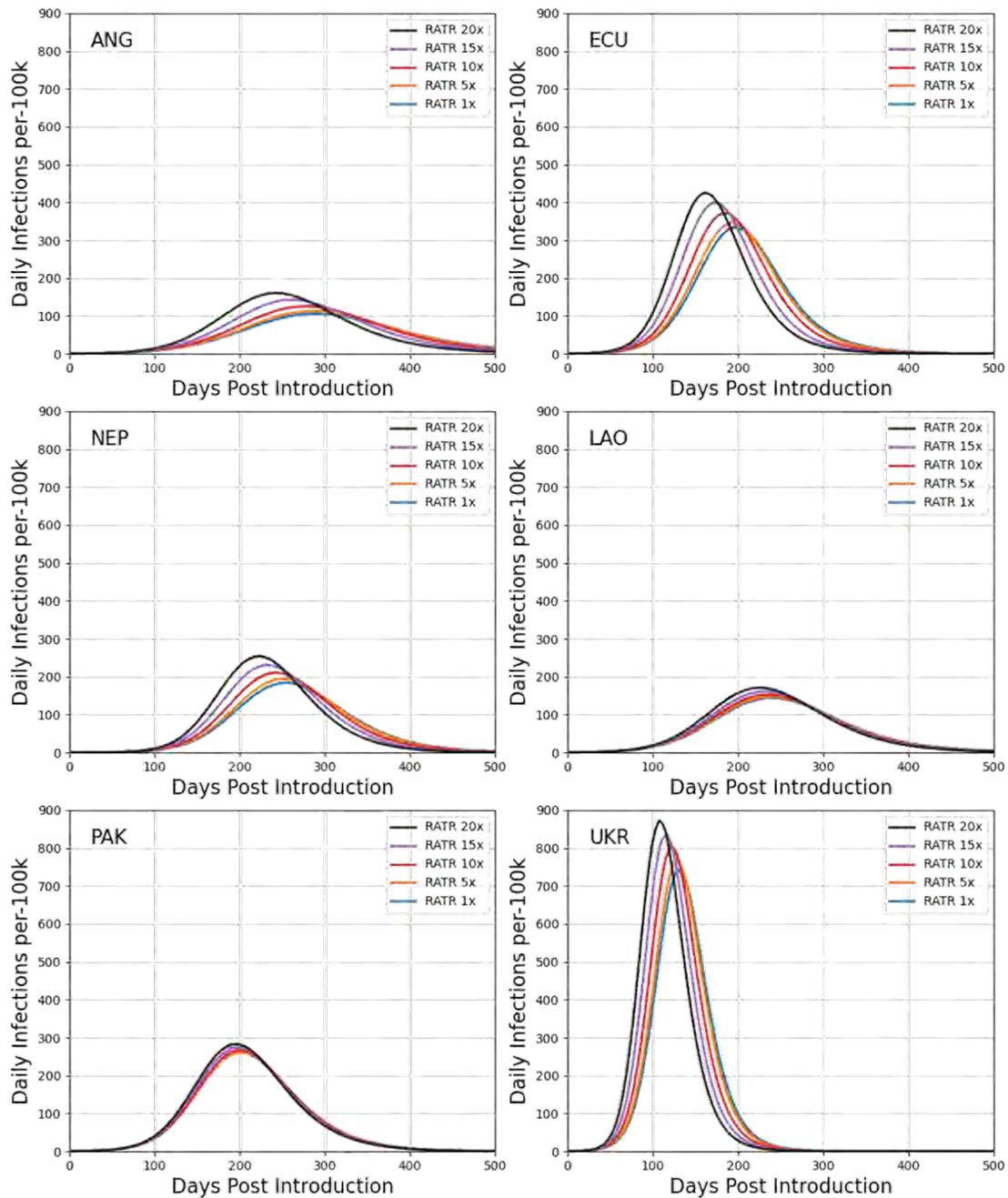


Figure 5. Expected daily infections per 100k individuals for each country when varying the relative acquisition/transmission rates in health workers.

The impact of health worker infections on the progress of the overall epidemic in an urban setting is depicted in figure 5. This impact is very low or negligible for most contexts, but a non-zero factor in others.

The correlate that distinguishes between these outcomes most strongly is the overall attack rate among the HW population. No additional vaccination activities are incorporated in simulations depicted in figure 5.

Table 3. Overall SARS-CoV-2 attack rate among health workers when varying the relative acquisition/transmission rate for the health worker cohort. Simulated outcomes are for the six countries.

Country	Attack Rate in Health Workers – Urban Setting				
	HW RATR 20x	HW RATR 15x	HW RATR 10x	HW RATR 5x	HW RATR 1x
Angola	91%	86%	75%	51%	13%
Ecuador	99%	99%	97%	86%	34%
Lao PDR	81%	75%	63%	42%	11%
Nepal	83%	80%	77%	65%	24%
Pakistan	88%	83%	71%	48%	13%
Ukraine	99%	99%	99%	98%	59%

This overall attack rate was high in all settings when the acquisition/transmission rate for health workers was 10x or greater, as indicated in table 3. For very high overall attack rates (i.e., >75% in table 3) there is also some shift in the mean outbreak trajectory toward earlier times, reflecting an acceleration of community transmission.

Acquisition and transmission rates in the health worker cohort are inputs to the model, and overall attack rates for health workers are nearly independent of the vaccination activities undertaken by those individuals. Contacts rates and patterns occurring outside of vaccination activities represent continuing healthcare activities undertaken by health workers. Results presented in table 3 are the mean attack rates for health workers and in-part reflect the overall force of infection during the epidemic. With sufficiently high levels of infection prevention and control (IPC), it may be possible that health workers experience a lower rate of acquisition and transmission than the general community [37], but those scenarios were not examined in this study.

House-to-house scenarios

House-to-house SIAs in urban environments did not have a measurable impact on infection rates. In these scenarios, health worker contact patterns and rates were reconfigured for the period of the SIA, but this reconfiguration did not result in an elevated number of infections. The dominant consideration for health worker risk is their relative acquisition and transmission rate, which was not varied during the period of the SIA.

Ongoing transmission in the urban environment was the primary consideration in these house-to-house simulations. It is likely that the vaccination activities did lead to SARS-CoV-2 infections, but that they did not occur at a level that was distinguishable from expected base case transmission levels. An important juxtaposition of this outcome is for house-to-house SIAs in mixed urban and rural environments. For the mixed urban-rural environments, urban health workers were used to systematically visit rural locations for vaccination activities. In these simulations, the SIA was again timed to coincide with peak urban incidence.

This delivery method can potentially introduce the virus to locations not experiencing community transmission at the time of the SIA; it is also very sensitive to infections among health workers.

Figure 6 depicts the expected increases in infection rates due to such an SIA for health workers with a 10x relative acquisition/transmission rate.

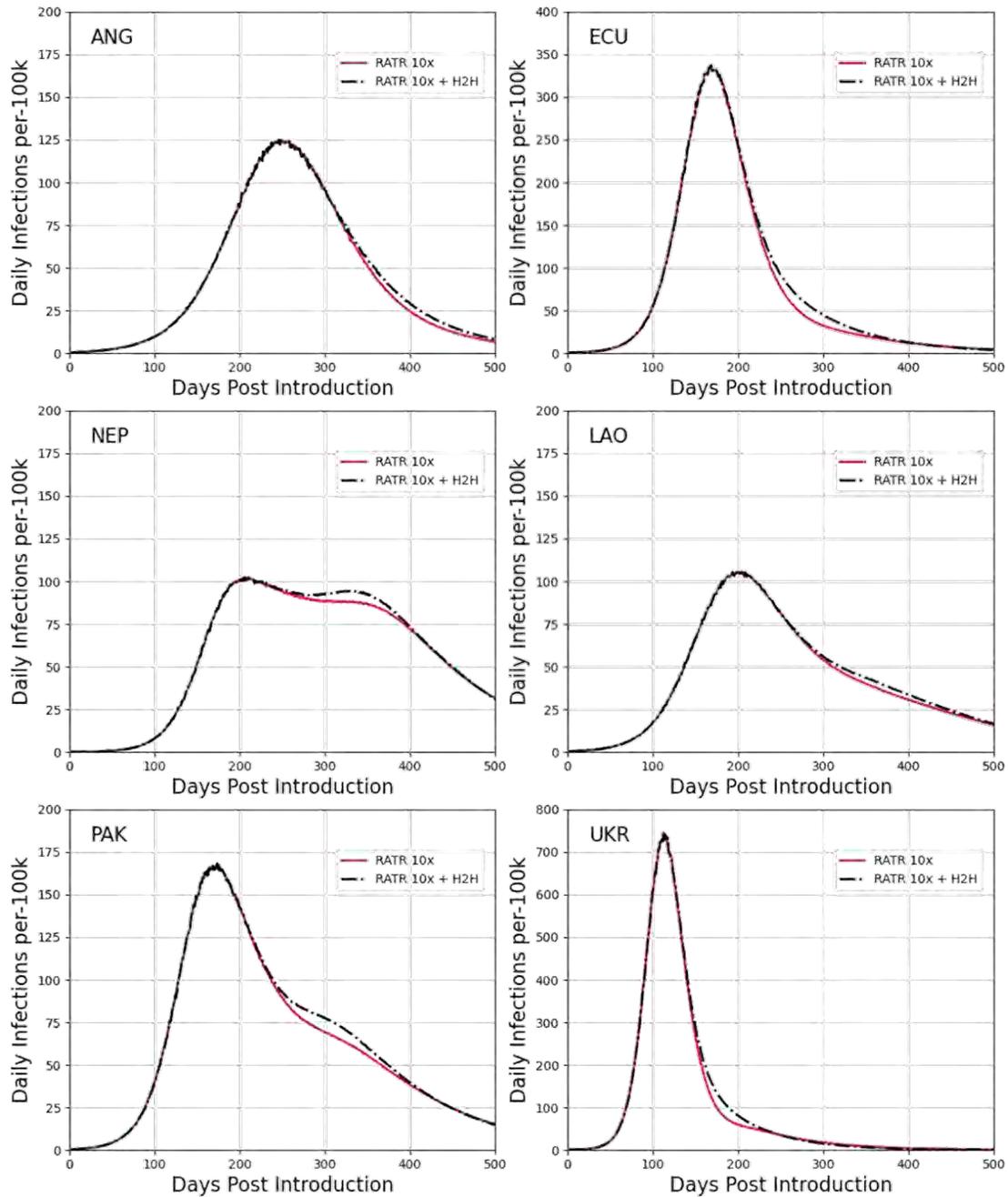


Figure 6. Expected daily infections per 100k individuals for each country for house-to-house SIAs in mixed urban-rural simulations. Health workers have 10x relative acquisition/transmission rate, throughout. Note the variable scale for each context.

Both the level of prevalence and degree of urbanization were contributing factors to the increase in infection rates.

Low levels of urbanization corresponded to a greater number of potentially naïve communities at the time of the SIA; higher prevalence at the time of the SIA increased the likelihood of a HW being infected at the time of the SIA and potentially being the cause of a new introduction. Structural factors, such as the degree of urbanization cannot be changed, but IPC measures could be used to reduce acquisition and transmission rates for health workers.

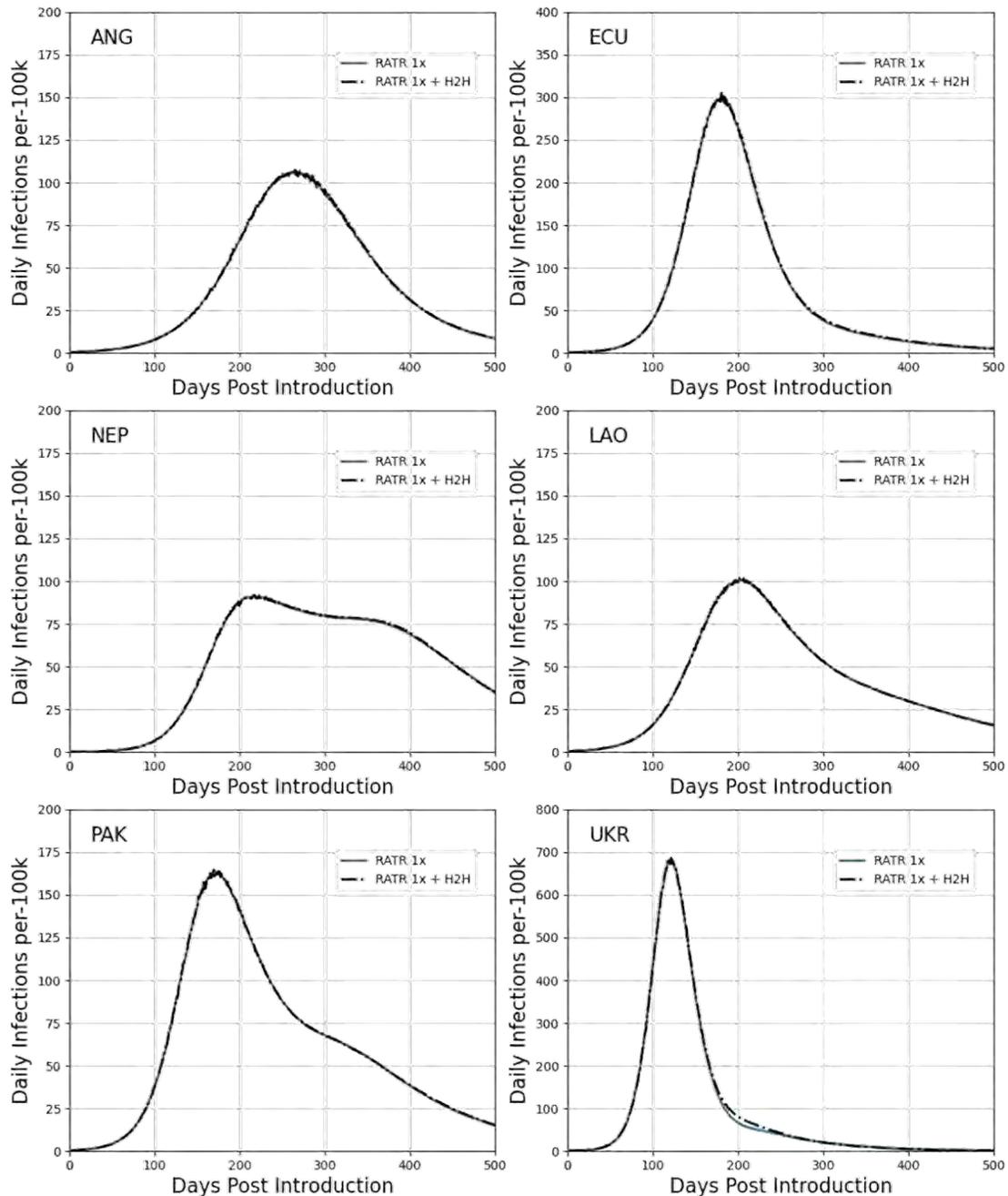


Figure 7. Expected daily infections per 100k individuals for each country for house-to-house SIAs in mixed urban-rural simulations. Health workers have 1x relative acquisition/transmission rate, throughout. Note the variable scale for each country.

The contrast between figures 6 and 7 illustrates that reducing infections in health workers can effectively mitigate the risk of introduction to naïve communities, except in scenarios with very high prevalence. Scenarios with very high prevalence are also extreme outcomes; at 1x relative acquisition and transmission rates for health workers, only an SIA at peak prevalence in a Ukraine-like scenario resulted in seeding new infections to rural locations. Adjusting SIA timing so that it occurs a month or more away from peak incidence was also enough to mitigate the risk of introductions. Outcomes for these simulations suggest elevated risk only when current prevalence is high and HW have a higher probability of being infected than the general community.

Statistics for urban, fixed-post SIA and rural, house-to-house SIA implementation are summarized in table 4. These scenarios are representative of the main results of this study. Fixed-post SIAs were largely insensitive to relative acquisition and transmission risk of health workers. Marginal increases in infections in these scenarios were driven by increased community mixing at fixed-posts and not specific interactions with health workers; they are surrogates for large gatherings. All fixed-post scenarios incorporate zero as a potential expected outcome. These null outcomes suggest that while the infection rate increases for the duration of the SIA, the overall attack rate for the epidemic may not be affected. House-to-house rural SIAs focus on the risk of introduction to naïve communities.

Table 4. Expected excess SARS-CoV-2 infections and infections-per-vaccination, under varying scenarios of relative acquisition and transmission risk for health workers.

Delivery method	HW RATR	Excess infections per 100k total population	Excess infections per 1k vaccinations
Fixed-post SIA urban	20x	310 [0, 550]	27 [0, 75]
	15x	310 [0, 610]	28 [0, 78]
	10x	250 [0, 530]	23 [0, 76]
	5x	230 [0, 560]	22 [0, 77]
	1x	300 [0, 590]	28 [0, 79]
House-to-house SIA rural	20x	400 [0, 970]	64 [0, 140]
	15x	680 [0, 950]	67 [0, 170]
	10x	520 [0, 1300]	60 [0, 230]
	5x	460 [0, 810]	54 [0, 135]
	1x	120 [0, 410]	17 [0, 75]

Summary statistics in table 4 are based on the mean outcomes for the scenarios examined in this study, which will tend to be biased toward larger excess values because SIA implementation was timed to occur around peak incidence. These values should be interpreted as conservative outcomes. Countries are expected to demonstrate significant sub-national heterogeneity in epidemic trajectories due to regionally differing times of first introduction. Nationally implemented SIAs would be expected to occur at multiple different locations along the trajectories described in this study, resulting in fewer excess infections than in table 4.

Uncertainty analyses

SIAs examining rural contexts involve a high level of uncertainty in the outcomes. All importations to COVID-19-naïve communities are stochastic and there are sometimes extreme outcomes due to introductions that results in transmission in additional populations. The uncertainty of whether there will be an outbreak in many peri-urban and rural communities results in a wide cloud of possible outcomes; since there is not always a larger outbreak there are many individual simulations where very little additional transmission occurs. However, when there is an additional community outbreak, the size can be substantial.

Scenarios that involve discrete stochastic importations of disease have a high variability in outcome; some importations lead to outbreaks, and some do not. Figure 8 depicts the range of outcomes (50%, 75%, and 95% clouds) based on the ensembles of 500 or more simulations. Simulations that did not produce an epidemic trajectory in the urban center were excluded.

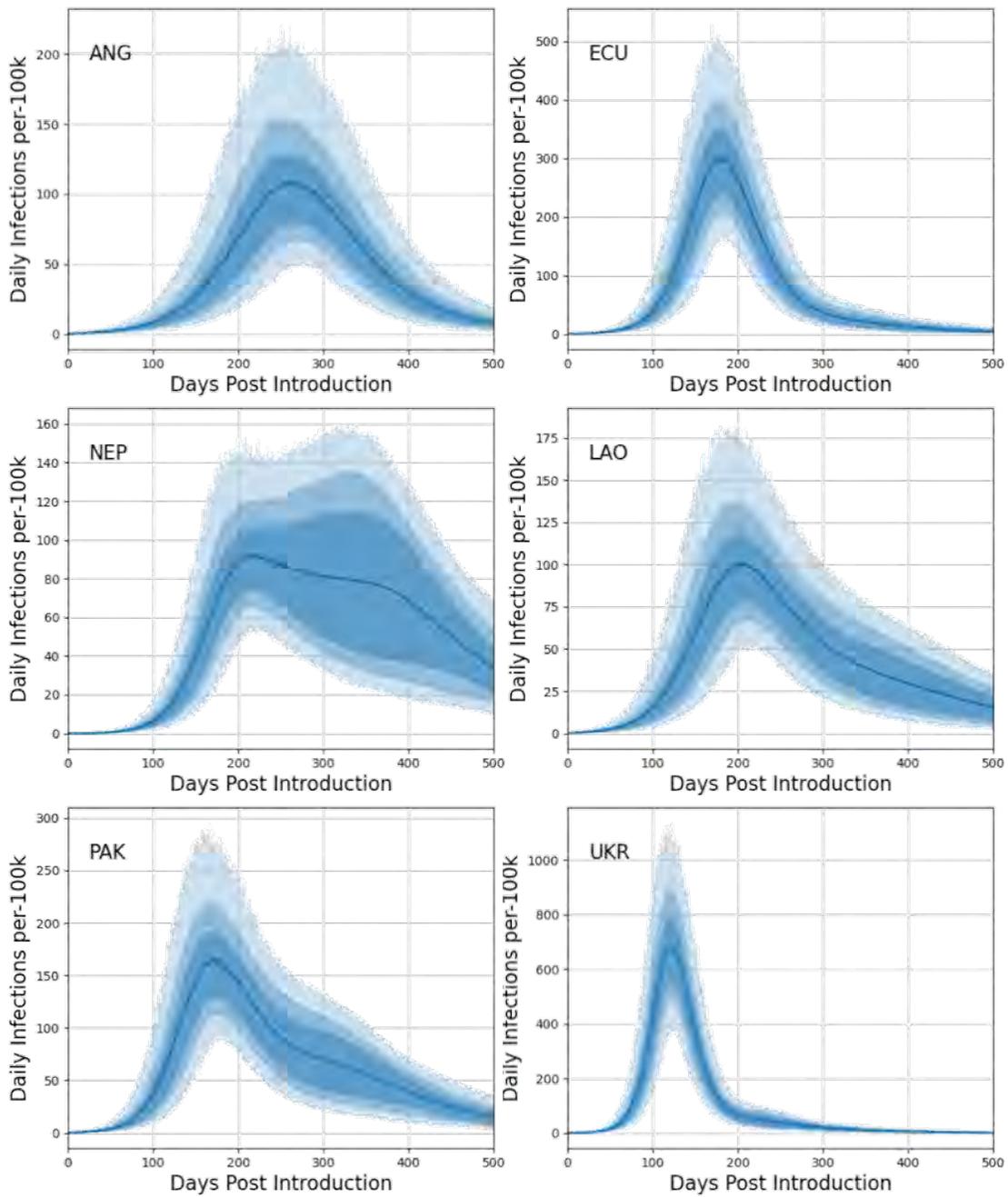


Figure 8. Expected daily infections per 100k individuals for each country in urban-rural environments. No SIAs were implemented. Health workers have 1x relative acquisition/transmission rate, throughout. Note the variable scale for each country.

Discussion

This study helps decisions makers in LMICs in understanding the risk-benefit tradeoff of proceeding with immunization services during the pandemic through stylized modeled simulations. All these scenarios focus on the increase in infections due to vaccination activities, and do not describe the COVID-19 burden specifically. While the benefits of vaccination accrue primarily to the vaccine recipients (here, the <5yr cohort), the COVID-19 burden will fall most heavily on the aged (>50yr cohort) [38].

Routine outreach scenarios would be expected to lead to some number of additional infections because of the model structure that represents them as an increase in total contacts during the outbreak. The rate of contacts present in the base case as typical behavior makes this increase sufficiently low as to be not distinguishable from zero.

Urban, fixed-post SIAs tended to have a low impact on the ongoing epidemic. Average outcomes were about 20 to 30 additional SARS-CoV-2 infections per 1000 vaccinations. This figure is biased upward because most scenarios examined in the study were in proximity to epidemic peak, which is not an outcome that would be expected to occur during implementation of a nationwide SIA. Values are appropriately interpreted as a conservative / high estimate of what would be observed in practice. Additionally, overall attack rates for the entire epidemic were not strongly affected by this SIA implementation. In several scenarios, the change in attack rate was not significantly different from zero even though the rate of infections during the SIA period was elevated. This outcome suggests that infections during the SIA were displacing infections that likely would have occurred later, marginally accelerating the epidemic but not affecting its outcome. This tendency to accelerate the epidemic was most pronounced for interventions occurring before peak incidence. For all fixed-post implementations, excess infections were strongly correlated with prevalence at the time of implementation.

Outcomes describing single-antigen vaccinations are likely extensible to multi-antigen SIAs. Multi-antigen SIAs would be characterized by longer periods of interaction between the health worker and individual receiving vaccination. However, probability of transmission in that interaction is on the order of 1% (assuming one participant is infectious), and this percentage is not believed to vary strongly with respect to moderate changes in exposure duration. A much larger consideration is the probability that a participant in that interaction is infectious, which is a consequence of prevalence and IPC measures at the time of the intervention.

House-to-house SIAs in mixed urban-rural contexts have the potential to import infections to previously naïve communities. This risk is a consequence of using health workers from urban locations that may be infectious at the time of the SIA.

Reducing prevalence among HWs largely eliminates the scenario where communities (such as rural or semi-isolated populations) will see the first introduction of virus during a SIA. Prevalence also strongly affects the importation risk because of the likelihood that a health worker may be exposed prior to rural travel. Marginal increases in infections in these scenarios represented an increase in mean epidemic attack rate and not an acceleration of the outbreak. Increased mobility correlated with greater importation risk; local vaccination staff should be used wherever possible.

How to use this report

Readers should refer to table 1 in the methods section as a starting point for comparing their own context to the results presented in this report. Country-level index values for all countries larger than one million population are reported in Appendix 4.

Primary indicators for this study are the fraction of population younger than 15 years and degree of urbanization. Those two covariates drive most of the variation between contexts.

Limitations

There are many unknowns about how SARS-CoV2 will spread in the LMIC context as well as how healthcare delivery will change operationally in coming months.

The level interconnectedness and mobility across social networks and between communities is uncertain. The social networks in LMIC are not well understood and have likely changed due to distancing policies currently in place, with unknown consequences. Since transmission in our model is based on the number of contacts between sub-populations, this is a key assumption for which we do not have as robust of data as we would like.

Additionally, we do not make any assumption about the risk level of individuals moving between population centers. It is possible that individuals who are more likely to migrate for work or other purposes may also be at higher risk individuals SARS-Cov2, but there is no evidence to demonstrate whether this relationship exists.

The third limitation is that a moderate distancing policy is built into our baseline scenarios. However, it is not clear whether they will be able to sustain this level of distancing over the long term and changes in policy would have direct impacts on the outbreak's progression.

The laboratory capacity in many LMIC is also a constraint because it may limit the number of tests that can be performed and may result in under-reporting of infections, making it more difficult to validate the model results with observed outcomes. We have endeavored to parameterize the modeling assumptions based on realistic assumptions but there is the possibility that we have overlooked transmission dynamics or assumed an infectivity that is too high.

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Appendix 1: Detailed Methods for the Epidemiological Model

Forward burden projections were constructed using IDM's primary software, Epidemiological MODeling (EMOD), a stochastic agent-based model of disease transmission [26]. The Generic branch of this software is not specific to any disease and was used to represent SARS-CoV-2 by selecting appropriate parameter values.

A single EMOD simulation follows a collection of agents through an arbitrary number of discrete time steps. Simulations used a constant length time step constructed to represent one day. Years were approximated as 365 time steps; leap days were neglected. All simulations had a duration of 2 years, which was taken to represent the period from January 2020 to December 2021. Properties that varied on a monthly basis attributed 31 days to January, 28 days to February, etc.

Infection Parameters

Infections were represented by a latent period followed by an infectious period. The progression of disease within each agent was stochastically variable, dictated by the distributions below. At the end of the infectious period, the agent is given total immunity from subsequent infection. Immunity is assumed to not wane over the course of the simulation.

Parameter distributions were selected to reproduce observed dynamics of SARS-CoV-2 transmission [39]–[41]; infectiousness was assumed to be independent of symptomaticity.

<i>Latent Period</i>	Gaussian distribution: mean = 4.0 days; standard deviation = 1.0 days
<i>Infectious Period</i>	Gamma distribution: mean = 8.0 days; standard deviation = 5.7 days
<i>Symptomatic Period</i>	Symptoms begin 2.0 days after latent period ends.
<i>Infectiousness</i>	Exponential distribution: Adjusted so that R_0 is between 2.0 and 4.0, as specified

More recent work suggests a two day period of pre-symptomatic transmission may be incorrect [42], and that a mean period of zero days with elevated variance would be more appropriate. In this model, the symptomatic state is only used for the intervention where 10% of agents with symptoms persistent for two or more days begin self-mitigation behavior (see Intervention Parameters in this appendix). These behaviors have a minor impact on transmission; altering the mean and variance of the onset of symptoms as described above does not alter trajectories in the simulation outcomes.

Parameters correspond to a median generation interval of about 6 days. This interval is not specified as an input parameter but is observable given simulation outputs. Figure A1-1 depicts simulation outcomes for hypothetical situations where transmission blocking interventions are applied to each individual agent the number of days post-infection indicated on the x-axis. In the (hypothetical-only) limit that the intervention is applied at the time of infection, no secondary infections occur. Applying the intervention at 6 days post-infection corresponds to a 50% reduction in secondary transmission. This behavior was independent of the mean level of infectiousness-per-infection (basic reproductive number, R_0).

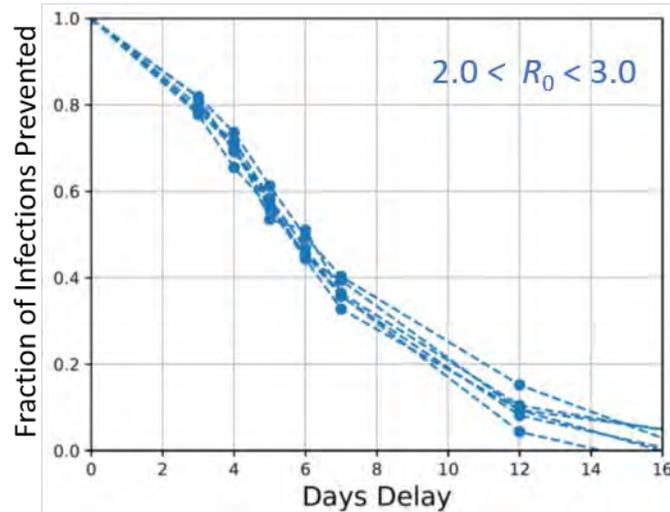


Figure A1-1. The fraction of secondary infections prevented as a function of the delay in applying transmission blocking interventions. Stochastic variation in total number of infections used for the reference case (i.e., no transmission blocking interventions) can lead to negative fractions. The figure above depicts the relative fraction of infection events prevented when individual infectiousness is restricted, as a function of the number of days before that restriction is applied.

Basic Reproductive Number

The overall R_0 of a simulation is equal to the inner product of the age vector and the contact matrix. For a given simulation, the contact matrix was multiplied by the necessary scalar to generate the desired basic reproductive number for that simulation. This value is an input parameter. It was adjusted to best match observed timeseries infection data in the contexts

Demographics Parameters

Age Distributions

A total population of 1M agents was used for each simulation. Each agent was assigned to one of 16 age groups. Simulations were configured to represent an LMIC context by varying the fraction of agents in each age group. Populations and ages were static for the period of the simulation; there were no vital dynamics (i.e., births, non-disease mortality, ageing, net migration, etc.). There was no disease mortality included as part of the simulation; COVID-19 associated morbidity and mortality was calculated based on the age-stratified simulated number of infections

Infection Rates

Infection rates were age-stratified (5-yr age bins) and route-stratified (home, office, school, community) based on contact rates published by K. Prem et al. [28], and risk-stratified (low, mid, high).

Risk stratification was orthogonal to route-stratification. For each age group, 35% of individuals received 60% of the group's mean infection rate (low risk), 50% of individuals received 100% of the group's mean infection rate (medium risk), and 15% of individuals received 193% of the group's mean

infection rate (high risk). This risk distribution was constructed as part of this study to provide additional individual level heterogeneity. It has a mean value of 1.0, which leaves average contact rates for each age group unaffected by the risk distribution.

Reduced Childhood Susceptibility

Children were assumed to have reduced susceptibility [29]–[34]. The magnitude of this reduction is uncertain; it was implemented here as a 55% reduction in the probability of acquisition and a 15% reduction in the probability of transmission based on values in the cited references. The age-stratified implementation of this reduction is provided in table A1-1.

Table A1-1. Reduced childhood susceptibility; percentage reduction in acquisition and transmission by age bin.

Reduced Acquisition					Reduced Transmission				
< 5	5-10	10-15	15-20	20+	< 5	5-10	10-15	15-20	20+
66.5	52.5	42.0	24.5	0.0	19.0	15.0	12.0	7.0	0.0

This reduction was applied after the normalization of the contact matrix. Simulations with reduced childhood susceptibility demonstrate a lower initial effective reproductive number than the specified basic reproductive number (i.e., $R_{eff} < R_0$ prior to outbreak start).

Recent work on pre-existing SARS-CoV-2 immunity in children suggests that this reduced acquisition may be a consequence of a heterologous IgG response [43]. This mechanism may have consequences for the susceptibility of young children (e.g., <6mo) that are naïve to all coronavirus serotypes, but would not affect the conclusions of this work, which focuses on SIAs targeting the 9mo – 5yr cohort within the first year of the Covid-19 pandemic.

Health Workers (HW)

Health workers (HW) were assigned their own demographic group independent of age and risk stratification. This group was assumed to be 0.1% of the total population. The HW group was assumed to consist of individuals with ages between 20 yrs and 60 yrs. The age distribution used for HWs is provided in table A1-2.

Table A1-2. HW age distribution; percentage of group population by age bin.

<20	20-25	25-30	30-35	35-40	40-45	45-50	50-55	55-60	60+
0.0	20.0	20.0	15.0	15.0	10.0	10.0	5.0	5.0	0.0

Contacts for the HW group via the home and community route were calculated based the age distributions in table A1-2. No school contacts were assigned to the HW group.

Total work contact rates were calculated using the HW age distributions and the work contact route. This age structure is provided in table A1-3.

Table A1-3. HW work contact distribution; percentage of contacts by age bin.

< 5	5-10	10-15	15-20	20-25	25-30	30-35	35-40	40-45	45-50	50-55	55-60	60-65	65-70	70-75	75+
1.0	1.0	5.0	5.0	15.0	15.0	10.0	10.0	10.0	10.0	3.0	3.0	3.0	3.0	3.0	3.0

These contact rates were then multiplied by a factor of 20 and re-distributed according to a presumed health worker contact age structure. The factor of 20 was an assumed value, selected such that the unmodified relative risk of infection for health workers was several times greater than the broader community.

Within-group contact rates for the HW were calculated based on the age distribution and unmodified home, work, and community routes. The contact rates for other demographic groups interacting with the HW group were equal to the age stratified HW contact rates multiplied by 5/3.

Spatial Structure

The total population was distributed into multiple nodes (i.e., locations). The number of nodes and distribution of agents among nodes was variable between simulations.

Simulations assigned the urban fraction of the total population to the primary node. The balance of the population was distributed among 100 to 250 additional nodes (the number of secondary nodes varied randomly between simulations and was selected from a uniform distribution). Populations of these secondary nodes were exponentially distributed; each secondary node had minimum population of 100 individuals. Locations of these nodes were distributed randomly on a two-dimensional unit grid. Periodic boundary conditions were enforced at the edges of the unit grid.

Individuals within each node were able to make single day, round-trip transits to any of the 30 closest adjacent nodes. The frequency of transits for each agent was proportional to the population of the destination node, and inversely proportional to the distance to the destination node. The constant of proportionality was an adjustable parameter used to describe connectedness.

For large values of the connectedness parameter, disease transmission outcomes were equivalent to locating all the population within a single node. These scenarios were used to describe urban-like environments. The connectedness parameter value for urban-like simulations was $3.0e-2$.

For intermediate values of the connectedness parameter, disease transmission within the primary node was urban-like, with limited and stochastic importations into the remaining population centers. These scenarios were used to describe urban/rural separations. The connectedness parameter value for urban/rural simulations was $1.0e-3$.

In the limit of very low or zero values of the connectedness parameter, disease transmission would only occur in the primary node and all other locations would be isolated with no infections. No scenarios use this parameterization.

Disease Introduction

Continuous importation of infections was assumed to begin on March 1. This importation only occurred in the primary node and was constant for a duration of one year. The daily rate of importations was equal to 1.2, which was implemented as a Poisson rate of new agents added to the simulation. New agents were not members of any age group and were immediately infectious on introduction.

Contact Rate Calculations

Simulations are based on infection rates; each agent, when infectious, can cause a stochastically variable number of secondary infections. The rates of secondary infections vary by age, risk, and route as described in Demographic Parameters. The number of contacts implied by these rates is calculated independently of the simulation, and is based on probabilities of infection taken from contact tracing studies [30], [44], [45].

Infection probabilities can vary widely. The greatest variation is by route, with home contacts tending to lead to infection with a greater probability than contacts in other settings. Non-home route contacts lead to infection with a probability between 0.1% - 3.0%. For the purposes of this study, the translation of number of contacts into infection rate was most relevant for house-to-house SIAs. These SIAs used a constant, non-home route probability of infection of 1.0% per-contact. A specified number of individuals (as indicated in the main body of the report) were targeted during these SIAs, with associated infection rates implied by 1.0% of the total number of contacts.

Intervention Parameters

1) Distancing

A transition between normal contact patterns and revised contact patterns was implemented by altering the contact patterns for all groups in the simulation. Twenty percent of reduced work and school contacts were redistributed to the home route.

2) Reduced Acquisition/Transmission Rates for Health Workers

Acquisition and transmission in the health worker (HW) group was reduced by either 95%, 75%, 50%, 25% or 0%. These values roughly correspond to 1x, 5x, 10x, 15x, and 20x the acquisition and transmission rates of the broader community.

3) Self-Mitigation

When infected, 10% of individuals with symptoms that persisted for 2 or more days (75% of all infected individuals have symptoms that persist for 2 or more days) start taking measures to reduce their rate of transmission (measures assumed to have 80% effectiveness). These measures were intended to represent self-imposed, non-pharmaceutical interventions.

Scenarios

1) Base case

Base case scenarios incorporated distancing measures applied on March 15 (i.e., 15 days post-introduction) that reduced school contacts to 0%, work contacts to 50%, and community contacts to 75%. Self-mitigation was applied to 10% of symptomatic individuals as described in that intervention.

2) Fixed-post SIAs

These scenarios use the base case configuration with 7-day step-changes in contacts, representative of fixed-post SIAs. Contacts increase by 50% within the under-5yr age group and within the 20 – 35 yr age groups. Contacts increase by 200% between these age groups.

Each 7-day duration change results in a variable increase in the infectivity across the entire population due to the increased contacts, this increase is proportional to the size of the target cohort and caregiver cohort.

3) House-to-house SIAs

These scenarios use the base case configuration and apply a reconfiguration of health worker (HW) contact patterns for a period of 30 days. During contact-pattern reconfiguration, HWs work contacts are redistributed to the <5yr age group (80%) and the 20 - 40 yr age groups (20%). Total contact rates remain unchanged.

4) Routine outreach

Routine outreach vaccination was implemented similarly to a fixed-post SIA, with both children and adults experiencing a 20% increase in intra-community contact rates. However, in the case of outreach, the health worker was expected to encounter adults as well as children, since these outreach events are intended to serve a wider population. They are also held periodically and consistently; for these purposes we assumed three days per month for a period of three months, with a cumulative 15% of the population is receiving healthcare services in this way.

Appendix 2: Detailed Methods for Country Specific Parameters

Demographics Parameters

Age Distributions

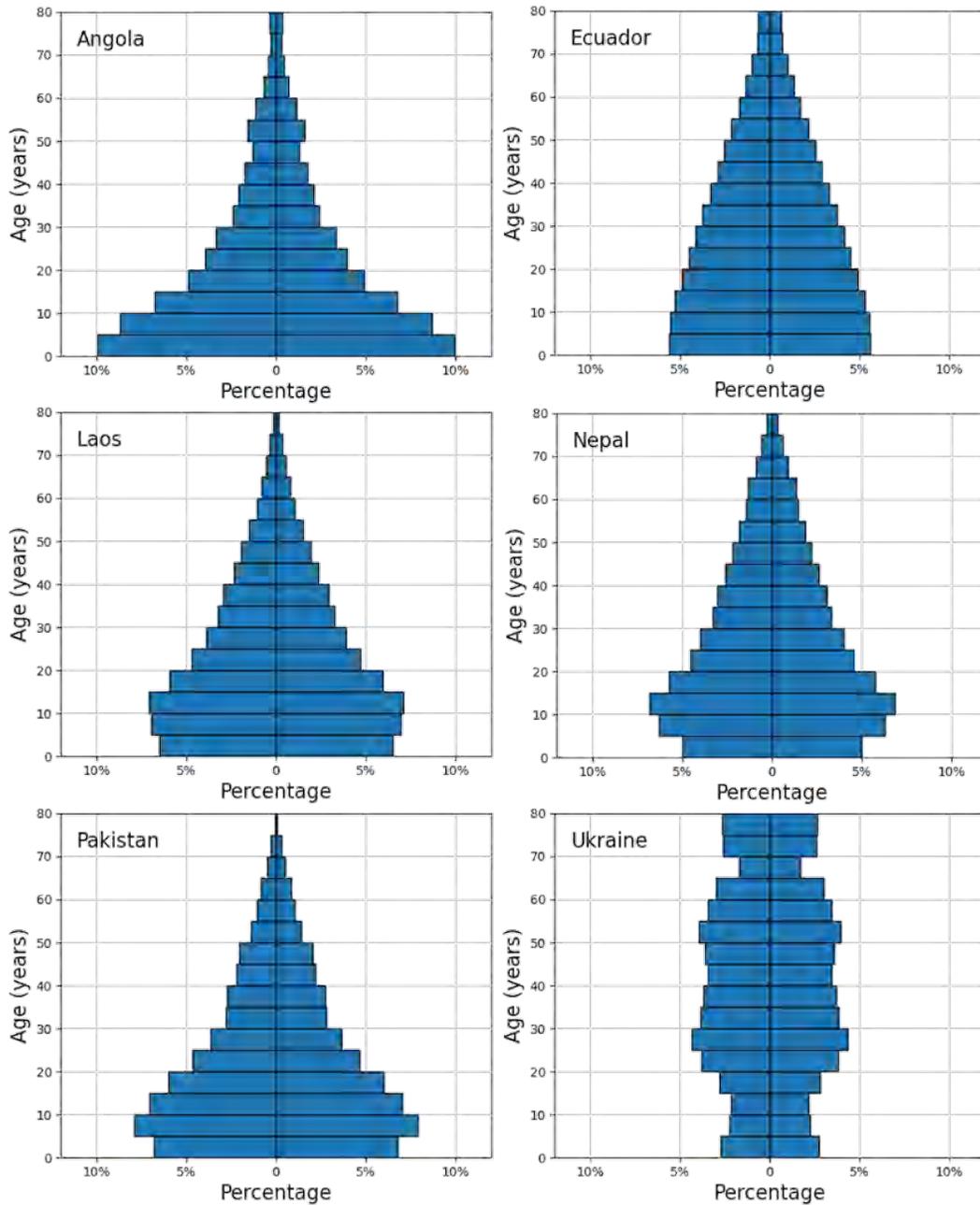


Figure A2-1. Visual representation of age pyramids used for each country.

Population fractions by age bin were taken from K. Prem et al. [28] for Ecuador, Laos, Nepal, Pakistan, and Ukraine. Population fractions by age bin for Angola were taken from the 2016 Demographic and Health survey for that country [46]. Values for all countries are reproduced below in table A2-1.

Table A2-1. Population age distributions by country.

Country	< 5	5-10	10-15	15-20	20-25	25-30	30-35	35-40	40-45	45-50	50-55	55-60	60-65	65-70	70-75	75+
Angola	19.9	17.4	13.5	9.8	7.9	6.7	4.8	4.2	3.5	2.6	3.2	2.3	1.4	0.9	0.6	0.7
Ecuador	11.2	11.1	10.6	9.8	9.0	8.3	7.5	6.6	5.8	5.1	4.3	3.4	2.7	2.0	1.4	1.3
Laos	13.0	13.9	14.2	11.9	9.4	7.8	6.5	5.9	4.7	3.9	3.0	2.1	1.6	1.1	0.7	0.3
Nepal	10.0	12.6	13.7	11.5	9.1	8.0	6.6	6.1	5.2	4.4	3.7	2.9	2.7	1.8	1.2	0.6
Pakistan	13.6	15.8	14.1	12.0	9.3	7.3	5.6	5.5	4.4	4.0	2.8	2.1	1.7	1.0	0.6	0.1
Ukraine	5.5	4.5	4.3	5.6	7.6	8.7	7.7	7.4	6.9	7.2	7.9	6.9	6.0	3.4	5.2	5.3

Contact Rates

Age- and route-stratified contact rates were published by K. Prem et al. [28] for Ecuador, Laos, Nepal, Pakistan, and Ukraine. Published contact rates for Ethiopia [28] were used for Angola. Published contact rate estimates were calculated using household age structure, labor force participation, school enrollment, and other indicators. These indicators are similar for many sub-Saharan countries (e.g., Ethiopia, Congo, Benin). The variation in contact rates between age categories tends to be much larger than the variation in contact rates between countries, suggesting that this substitution is reasonable.

Infection Parameters

Basic Reproductive Number

Estimates of the infectiousness of SARS-CoV-2 vary significantly and are context dependent [47], [48]. In this study, values of between 2.0 and 4.0 were considered for R_0 in each context. When available, timeseries data of confirmed infections were used to calibrate the infectiousness [5]. An insufficient number of confirmed cases were available for this calibration in Angola and Laos; values of 3.6 and 3.0 were used for those countries, respectively. Those values were selected to match the calibration outcomes from other countries.

Confirmed incidence data through Jun 15 was used to calibrate infectivity for Pakistan, Ecuador, and Nepal. Confirmed incidence data through May 1 was used to calibrate infectivity for Ukraine. A Poisson log likelihood objective function with a constant reporting rate was used as the objective in these calibrations. Reporting rate was adjusted to maximize this function. Details on the implementation of this calibration can be found elsewhere [49].

Distancing measures were implemented for each context in line with the University of Oxford Stringency Index [50]. These measures had schools closed (0%) and reduced work (50%) for all countries; implemented as described by Distancing Interventions in Appendix 1 and applied beginning on March 15. Additionally, all countries reduced community-based contact rates (50%) on March 15. These distancing interventions were maintained for Ecuador and Nepal. In Pakistan and Ukraine, a stepped increase in community contact rates was applied on April 15, April 30, and May 15, (to 55%, 65%, and 75% respectively to reflect the policy decisions in those countries.

Figure A2-2 depicts the best-fit trajectories from this calibration. The calibration process demonstrates the selection of appropriate disease parameters for each context; outcomes were not intended to provide a complete history of the infection trajectories in each country.

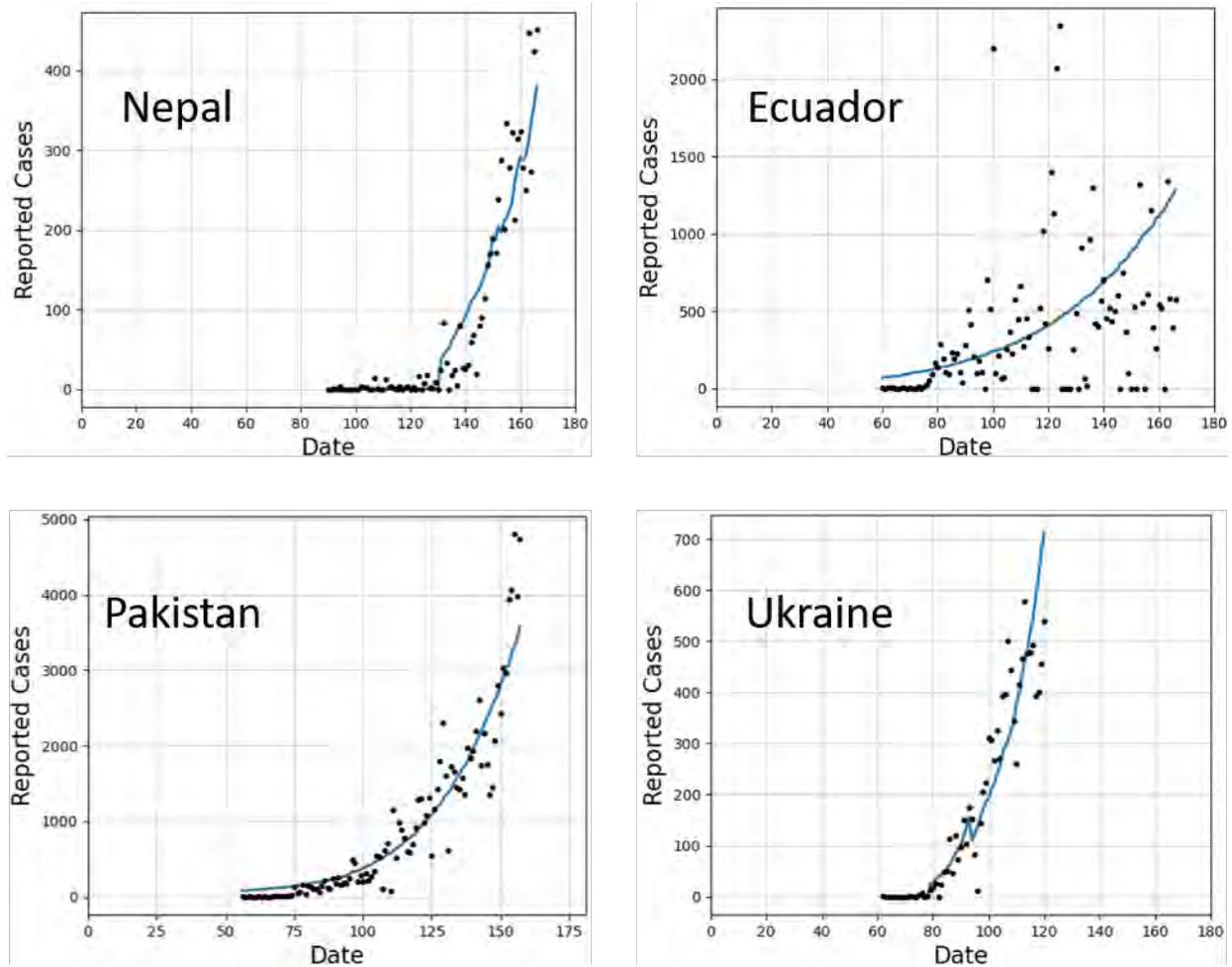


Figure A2-2. Confirmed incidence of SARS-CoV-2 in Nepal, Ecuador, Pakistan, and Ukraine. The date axis corresponds to the day number in 2020, where day 1 is equivalent to January 1st 2020. Mean simulation outcomes are depicted as blue lines.

Infectivity values used for each country are indicated in table 2 in the main text and summarized below in table A2-2.

Table A2-2. Basic reproductive number values by country.

Angola	Ecuador	Laos	Nepal	Pakistan	Ukraine
3.6	3.2	3.0	3.2	3.6	3.0

Appendix 3: Scenario Results and Confidence Intervals

Uncertainty in the simulation modeling results are listed below for each of the primary outcomes, by scenario. Each scenario that was run impacted the total number of infections, maximum prevalence rates, and age groups differently.

Table A3-1 summarizes the total infections count per 100,000 population. Table A3-2 summarizes the infection rate in individuals over age 50 per 100,000 population.

Table A3-1. Results from simulated outbreaks: total infections per 100k population.

Country	Context	RATR	Strategy	Timing	25%	Median	Mean	75%
ANG	Urb	1x			17951	23452	24853	30173
ANG	Urb	5x			18669	24229	25644	31052
ANG	Urb	10x			19810	25503	26964	32481
ANG	Urb	15x			20941	26848	28308	34037
ANG	Urb	20x			21717	27999	29490	35599
ANG	Urb	1x	H2H	0	17865	23363	24746	30051
ANG	Urb	5x	H2H	0	18610	24145	25564	30953
ANG	Urb	10x	H2H	0	19777	25465	26933	32450
ANG	Urb	1x	FP	-45	18200	23735	25141	30498
ANG	Urb	1x	FP	-15	18256	23797	25213	30578
ANG	Urb	1x	FP	15	18255	23795	25207	30568
ANG	Urb	1x	FP	45	18224	23761	25172	30531
ANG	Urb	1x	FP	ALL	19136	24834	26247	31749
ANG	Urb+Rur	1x			9022	15824	21194	27229
ANG	Urb+Rur	5x			9329	16329	21775	27997
ANG	Urb+Rur	10x			9778	17125	22794	29370
ANG	Urb+Rur	1x	H2H	0	9063	15891	21263	27304
ANG	Urb+Rur	5x	H2H	0	9593	16635	22053	28321
ANG	Urb+Rur	10x	H2H	0	10357	17842	23496	30219
ANG	Urb+Rur	10x	H2H	45	9989	17428	23079	29738
ANG	Urb+Rur	1x	RI+		9072	15907	21273	27336
ECU	Urb	1x			32810	40946	42826	50752
ECU	Urb	5x			33195	41530	43457	51574
ECU	Urb	10x			33757	42345	44294	52654
ECU	Urb	15x			34208	42933	44979	53482
ECU	Urb	20x			34500	43525	45613	54349
ECU	Urb	1x	H2H	0	32756	40866	42743	50665
ECU	Urb	5x	H2H	0	33120	41450	43385	51512
ECU	Urb	10x	H2H	0	33703	42289	44237	52591
ECU	Urb	1x	FP	-45	32992	41194	43104	51103
ECU	Urb	1x	FP	-15	33212	41414	43304	51295

ECU	Urb	1x	FP	15	33310	41504	43400	51395
ECU	Urb	1x	FP	45	33226	41394	43290	51254
ECU	Urb	1x	FP	ALL	34342	42715	44656	52838
ECU	Urb+Rur	1x			15941	27572	35850	46552
ECU	Urb+Rur	5x			16068	28032	36538	47435
ECU	Urb+Rur	10x			16475	28654	37239	48374
ECU	Urb+Rur	1x	H2H	0	16193	27885	36165	46869
ECU	Urb+Rur	5x	H2H	0	17833	29837	38095	49005
ECU	Urb+Rur	10x	H2H	0	18088	30442	38836	50054
ECU	Urb+Rur	10x	H2H	45	16708	28912	37464	48603
ECU	Urb+Rur	1x	RI+		15944	27621	35965	46679
NEP	Urb	1x			19218	28289	30128	38928
NEP	Urb	5x			19843	29094	31068	40076
NEP	Urb	10x			20762	30213	32169	41383
NEP	Urb	15x			22013	31696	33503	42879
NEP	Urb	20x			23183	32929	34805	44313
NEP	Urb	1x	H2H	0	19254	28311	30142	38977
NEP	Urb	5x	H2H	0	19790	29044	31016	40024
NEP	Urb	10x	H2H	0	20728	30198	32115	41314
NEP	Urb	1x	FP	-45	19401	28458	30383	39196
NEP	Urb	1x	FP	-15	19386	28542	30391	39213
NEP	Urb	1x	FP	15	19368	28531	30384	39267
NEP	Urb	1x	FP	45	19365	28521	30379	39231
NEP	Urb	1x	FP	ALL	19909	29204	31120	40155
NEP	Urb+Rur	1x			15969	25936	28997	38725
NEP	Urb+Rur	5x			16481	26801	29889	40043
NEP	Urb+Rur	10x			17181	27957	31176	41794
NEP	Urb+Rur	1x	H2H	0	15952	25944	29006	38798
NEP	Urb+Rur	5x	H2H	0	17198	27485	30413	40393
NEP	Urb+Rur	10x	H2H	0	18053	28582	31684	42042
NEP	Urb+Rur	10x	H2H	45	17153	27969	31167	41779
NEP	Urb+Rur	1x	RI+		15889	25959	28985	38736
LAO	Urb	1x			18652	25355	26951	33532
LAO	Urb	5x			19020	25751	27340	33942
LAO	Urb	10x			19426	26305	27960	34696
LAO	Urb	15x			20038	26995	28725	35613
LAO	Urb	20x			20686	27781	29444	36433
LAO	Urb	1x	H2H	0	18664	25358	26946	33504
LAO	Urb	5x	H2H	0	18959	25685	27293	33867
LAO	Urb	10x	H2H	0	19397	26284	27942	34676
LAO	Urb	1x	FP	-45	18824	25557	27146	33732

LAO	Urb	1x	FP	-15	18797	25559	27153	33767
LAO	Urb	1x	FP	15	18829	25596	27198	33820
LAO	Urb	1x	FP	45	18815	25565	27159	33764
LAO	Urb	1x	FP	ALL	19306	26179	27782	34505
LAO	Urb+Rur	1x			11031	18341	22007	28995
LAO	Urb+Rur	5x			11102	18555	22350	29420
LAO	Urb+Rur	10x			11446	19020	22856	30099
LAO	Urb+Rur	1x	H2H	0	11012	18295	21993	28950
LAO	Urb+Rur	5x	H2H	0	11391	18821	22563	29603
LAO	Urb+Rur	10x	H2H	0	12098	19706	23381	30570
LAO	Urb+Rur	10x	H2H	45	11716	19290	23059	30257
LAO	Urb+Rur	1x	RI+		11157	18479	22147	29092
PAK	Urb	1x			27259	35823	37537	45898
PAK	Urb	5x			27278	35934	37732	46176
PAK	Urb	10x			27554	36456	38183	46803
PAK	Urb	15x			27962	36735	38634	47251
PAK	Urb	20x			28324	37259	39149	47923
PAK	Urb	1x	H2H	0	27252	35783	37484	45820
PAK	Urb	5x	H2H	0	27282	35948	37731	46139
PAK	Urb	10x	H2H	0	27524	36399	38152	46759
PAK	Urb	1x	FP	-45	27420	35989	37734	46141
PAK	Urb	1x	FP	-15	27437	36046	37786	46214
PAK	Urb	1x	FP	15	27489	36092	37824	46256
PAK	Urb	1x	FP	45	27476	36042	37774	46142
PAK	Urb	1x	FP	ALL	28039	36793	38534	47109
PAK	Urb+Rur	1x			16577	26967	31652	41534
PAK	Urb+Rur	5x			16660	27233	31787	41775
PAK	Urb+Rur	10x			16987	27669	32282	42468
PAK	Urb+Rur	1x	H2H	0	16574	27005	31668	41604
PAK	Urb+Rur	5x	H2H	0	17286	27710	32226	42054
PAK	Urb+Rur	10x	H2H	0	18166	28592	33110	43036
PAK	Urb+Rur	10x	H2H	45	17311	27896	32495	42643
PAK	Urb+Rur	1x	RI+		16559	27016	31652	41548
UKR	Urb	1x			42697	53469	56116	66502
UKR	Urb	5x			43113	53893	56609	67094
UKR	Urb	10x			43358	54254	57110	67695
UKR	Urb	15x			43330	54627	57570	68535
UKR	Urb	20x			43356	54926	58030	69214
UKR	Urb	1x	H2H	0	42705	53487	56123	66527
UKR	Urb	5x	H2H	0	43094	53878	56595	67076
UKR	Urb	10x	H2H	0	43317	54232	57085	67668

UKR	Urb	1x	FP	-45	42688	53501	56159	66612
UKR	Urb	1x	FP	-15	42954	53789	56425	66891
UKR	Urb	1x	FP	15	43087	53871	56536	66962
UKR	Urb	1x	FP	45	42876	53690	56333	66754
UKR	Urb	1x	FP	ALL	43468	54380	57073	67601
UKR	Urb+Rur	1x			20910	37556	49387	64725
UKR	Urb+Rur	5x			21157	38002	49917	65332
UKR	Urb+Rur	10x			21228	38223	50400	65962
UKR	Urb+Rur	1x	H2H	0	22149	38610	50278	65350
UKR	Urb+Rur	5x	H2H	0	24583	40971	52465	67408
UKR	Urb+Rur	10x	H2H	0	23399	40255	52109	67462
UKR	Urb+Rur	10x	H2H	45	21279	38248	50436	65997
UKR	Urb+Rur	1x	RI+		20978	37572	49439	64743

Table A3-2. Results from simulated outbreaks: total infections in individuals over 50yrs, per 100k population.

Country	Context	RATR	Strategy	Timing	25%	Median	Mean	75%
ANG	Urb	1x			115	218	287	380
ANG	Urb	5x			140	267	340	457
ANG	Urb	10x			170	311	392	538
ANG	Urb	15x			203	348	432	585
ANG	Urb	20x			228	381	465	622
ANG	Urb	1x	H2H	0	113	218	286	378
ANG	Urb	5x	H2H	0	140	267	339	457
ANG	Urb	10x	H2H	0	169	311	390	535
ANG	Urb	1x	FP	-45	119	221	291	388
ANG	Urb	1x	FP	-15	117	221	292	388
ANG	Urb	1x	FP	15	118	223	292	387
ANG	Urb	1x	FP	45	117	222	292	387
ANG	Urb	1x	FP	ALL	130	234	304	403
ANG	Urb+Rur	1x			56	142	245	314
ANG	Urb+Rur	5x			60	169	289	377
ANG	Urb+Rur	10x			70	197	331	443
ANG	Urb+Rur	1x	H2H	0	56	143	246	315
ANG	Urb+Rur	5x	H2H	0	61	173	291	380
ANG	Urb+Rur	10x	H2H	0	74	206	340	457
ANG	Urb+Rur	10x	H2H	45	70	200	335	451
ANG	Urb+Rur	1x	RI+		57	143	246	316
ECU	Urb	1x			769	1060	1148	1428
ECU	Urb	5x			828	1142	1237	1542

ECU	Urb	10x			875	1203	1299	1614
ECU	Urb	15x			914	1248	1345	1670
ECU	Urb	20x			944	1287	1389	1722
ECU	Urb	1x	H2H	0	767	1056	1144	1424
ECU	Urb	5x	H2H	0	822	1134	1230	1537
ECU	Urb	10x	H2H	0	866	1194	1291	1605
ECU	Urb	1x	FP	-45	775	1066	1155	1439
ECU	Urb	1x	FP	-15	780	1073	1161	1443
ECU	Urb	1x	FP	15	784	1075	1163	1447
ECU	Urb	1x	FP	45	781	1073	1161	1443
ECU	Urb	1x	FP	ALL	813	1108	1196	1483
ECU	Urb+Rur	1x			355	692	959	1267
ECU	Urb+Rur	5x			373	740	1039	1371
ECU	Urb+Rur	10x			397	781	1092	1437
ECU	Urb+Rur	1x	H2H	0	360	699	968	1275
ECU	Urb+Rur	5x	H2H	0	414	793	1082	1427
ECU	Urb+Rur	10x	H2H	0	435	834	1138	1499
ECU	Urb+Rur	10x	H2H	45	402	789	1098	1447
ECU	Urb+Rur	1x	RI+		355	694	963	1272
NEP	Urb	1x			298	516	601	810
NEP	Urb	5x			339	581	674	910
NEP	Urb	10x			381	630	728	978
NEP	Urb	15x			423	689	780	1039
NEP	Urb	20x			461	739	828	1094
NEP	Urb	1x	H2H	0	299	514	600	813
NEP	Urb	5x	H2H	0	337	578	671	906
NEP	Urb	10x	H2H	0	376	627	724	969
NEP	Urb	1x	FP	-45	301	519	605	817
NEP	Urb	1x	FP	-15	300	520	605	814
NEP	Urb	1x	FP	15	301	521	606	819
NEP	Urb	1x	FP	45	300	520	606	819
NEP	Urb	1x	FP	ALL	310	535	620	836
NEP	Urb+Rur	1x			224	437	577	805
NEP	Urb+Rur	5x			253	502	647	904
NEP	Urb+Rur	10x			288	567	706	975
NEP	Urb+Rur	1x	H2H	0	226	435	576	802
NEP	Urb+Rur	5x	H2H	0	272	520	658	911
NEP	Urb+Rur	10x	H2H	0	302	583	718	982
NEP	Urb+Rur	10x	H2H	45	288	566	707	975
NEP	Urb+Rur	1x	RI+		224	437	576	804
LAO	Urb	1x			102	197	259	356

LAO	Urb	5x			117	232	296	407
LAO	Urb	10x			137	260	330	449
LAO	Urb	15x			157	284	356	483
LAO	Urb	20x			174	309	377	508
LAO	Urb	1x	H2H	0	101	195	259	355
LAO	Urb	5x	H2H	0	117	230	294	404
LAO	Urb	10x	H2H	0	134	259	328	448
LAO	Urb	1x	FP	-45	104	198	261	358
LAO	Urb	1x	FP	-15	103	198	261	357
LAO	Urb	1x	FP	15	104	199	262	359
LAO	Urb	1x	FP	45	103	198	261	358
LAO	Urb	1x	FP	ALL	108	203	267	363
LAO	Urb+Rur	1x			46	128	211	283
LAO	Urb+Rur	5x			48	146	242	332
LAO	Urb+Rur	10x			54	164	270	372
LAO	Urb+Rur	1x	H2H	0	46	128	211	282
LAO	Urb+Rur	5x	H2H	0	49	148	244	335
LAO	Urb+Rur	10x	H2H	0	57	171	276	381
LAO	Urb+Rur	10x	H2H	45	56	166	272	376
LAO	Urb+Rur	1x	RI+		47	129	213	286
PAK	Urb	1x			190	314	367	483
PAK	Urb	5x			211	349	406	540
PAK	Urb	10x			229	381	440	583
PAK	Urb	15x			245	403	462	609
PAK	Urb	20x			257	420	479	631
PAK	Urb	1x	H2H	0	190	312	366	482
PAK	Urb	5x	H2H	0	209	347	405	539
PAK	Urb	10x	H2H	0	228	379	438	581
PAK	Urb	1x	FP	-45	192	316	369	486
PAK	Urb	1x	FP	-15	192	317	369	486
PAK	Urb	1x	FP	15	193	318	369	486
PAK	Urb	1x	FP	45	192	317	369	485
PAK	Urb	1x	FP	ALL	198	325	376	495
PAK	Urb+Rur	1x			93	210	309	425
PAK	Urb+Rur	5x			95	233	342	472
PAK	Urb+Rur	10x			108	258	372	510
PAK	Urb+Rur	1x	H2H	0	93	211	310	424
PAK	Urb+Rur	5x	H2H	0	100	241	346	473
PAK	Urb+Rur	10x	H2H	0	117	271	381	521
PAK	Urb+Rur	10x	H2H	45	111	260	374	513
PAK	Urb+Rur	1x	RI+		93	211	309	422

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UKR	Urb	1x			5788	7263	7620	9040
UKR	Urb	5x			5923	7421	7793	9249
UKR	Urb	10x			6029	7551	7945	9420
UKR	Urb	15x			6101	7673	8082	9611
UKR	Urb	20x			6168	7796	8223	9795
UKR	Urb	1x	H2H	0	5788	7264	7618	9045
UKR	Urb	5x	H2H	0	5901	7403	7776	9233
UKR	Urb	10x	H2H	0	6000	7529	7919	9393
UKR	Urb	1x	FP	-45	5787	7262	7623	9052
UKR	Urb	1x	FP	-15	5819	7294	7648	9076
UKR	Urb	1x	FP	15	5831	7309	7663	9089
UKR	Urb	1x	FP	45	5805	7287	7641	9067
UKR	Urb	1x	FP	ALL	5880	7358	7717	9151
UKR	Urb+Rur	1x			2841	5107	6694	8756
UKR	Urb+Rur	5x			2914	5230	6877	9003
UKR	Urb+Rur	10x			2961	5326	7018	9176
UKR	Urb+Rur	1x	H2H	0	3020	5274	6832	8886
UKR	Urb+Rur	5x	H2H	0	3371	5651	7222	9300
UKR	Urb+Rur	10x	H2H	0	3247	5608	7249	9396
UKR	Urb+Rur	10x	H2H	45	2967	5334	7023	9183
UKR	Urb+Rur	1x	RI+		2842	5120	6722	8819

Appendix 4: Country-level index values

Index values are presented below for each lower- or middle-income country with a population of greater than one million. These were the countries that were evaluated for use as representative contexts for this report.

Indices were sourced as follows:

- Percent of population under age 15. Source: World Bank. data.worldbank.org metric ID: SP.POP.0014.TO.
- DTP3 vaccine coverage (% of children ages 12-23 months). Source: WUENIC estimates [51].
- Nurses per 1,000 population. Source: World Bank. data.worldbank.org metric ID: SH.MED.NUMW.P3.
- Human development index. Source: UN Development Programme [52].
- Percent of population rural. Source: World Bank. data.worldbank.org metric ID: SP.RUR.TOTL.ZS.
- Percent of population living in a slum setting. Calculated. Defined as % slum of total = (1-% rural) x % of urban living in slum. Source: World Bank. data.worldbank.org metric ID: EN.POP.SLUM.UR.ZS.

Table A4-1. Index values by country. Region classifications as designated by the WHO. Income classifications as designated for 2019 by the World Bank. Low = Low income. LM = Lower middle income. UM = Upper middle income. Blank spaces indicate a lack of data availability.

Country	Region	Income	% U15	DTP3	Nurses per 1k	HDI	% Rural	% Slum
Afghanistan	EMR	Low	43.1	66.0	0.18	0.50	74.5	16.0
Albania	EUR	UM	17.7	99.0	3.65	0.79	39.7	
Algeria	AFR	UM	30.1	91.0	1.55	0.76	27.4	
Angola	AFR	LM	46.8	59.0	0.41	0.57	34.5	36.4
Argentina	AMR	UM	24.8	86.0	2.60	0.83	8.1	15.3
Armenia	EUR	UM	20.6	92.0	6.11	0.76	36.9	9.1
Azerbaijan	EUR	UM	23.4	95.0	6.43	0.75	44.3	
Bangladesh	SEAR	LM	27.7	98.0	0.41	0.61	63.4	20.2
Belarus	EUR	UM	16.9	97.0	11.00	0.82	21.4	
Benin	AFR	Low	42.4	76.0	0.39	0.52	52.7	29.1
Bolivia	AMR	LM	31.1	83.0	1.56	0.70	30.6	30.2
Bosnia & Herzegovina	EUR	UM	14.8	73.0	5.73	0.77	51.8	
Botswana	AFR	UM	34.1	95.0	5.40	0.73	30.6	
Brazil	AMR	UM	21.3	83.0	10.12	0.76	13.4	19.3
Bulgaria	EUR	UM	14.6	92.0	4.82	0.82	25.0	
Burkina Faso	AFR	Low	44.9	91.0	0.88	0.43	70.6	19.3
Burundi	AFR	Low	45.5	90.0	0.85	0.42	87.0	7.5
Cambodia	WPR	LM	31.2	92.0	0.69	0.58	76.6	12.9
Cameroon	AFR	LM	42.6	79.0	0.92	0.56	43.6	21.3
CAR	AFR	Low	44.3	47.0	0.21	0.38	58.6	38.6

Country	Region	Income	% U15	DTP3	Nurses per 1k	HDI	% Rural	% Slum
Chad	AFR	Low	47.1	41.0	0.23	0.40	76.9	20.3
China	WPR	UM	17.9	99.0	2.66	0.76	40.8	14.9
Colombia	AMR	UM	23.1	92.0	1.33	0.76	19.2	10.6
DRC	AFR	Low	46.2	81.0	1.11	0.46	55.5	33.3
Congo, Rep.	AFR	LM	41.8	75.0	0.63	0.61	33.1	31.4
Costa Rica	AMR	UM	21.3	94.0	3.41	0.79	20.7	4.4
Cote d'Ivoire	AFR	LM	41.9	82.0	0.60	0.52	49.2	28.4
Cuba	AMR	UM	16.2	99.0	7.56	0.78	23.0	
Dominican Republic	AMR	UM	28.0	94.0	1.38	0.75	18.9	9.8
Ecuador	AMR	UM	28.0	85.0	2.51	0.76	36.2	23.0
Egypt	EMR	LM	33.8	95.0	1.93	0.70	57.3	4.5
El Salvador	AMR	LM	27.1	81.0	1.83	0.67	28.0	20.8
Equatorial Guinea	AFR	UM	37.1	25.0	0.50	0.59	27.9	47.8
Eswatini	AFR	LM	38.1	90.0	4.14	0.61	76.2	7.8
Ethiopia	AFR	Low	40.8	72.0	0.71	0.47	79.2	15.3
Gabon	AFR	UM	37.0	70.0	2.95	0.70	10.6	33.1
Gambia, The	AFR	Low	44.3	93.0	1.54	0.47	38.7	21.3
Georgia	EUR	UM	19.8	93.0	4.73	0.79	41.4	
Ghana	AFR	LM	37.6	97.0	4.20	0.60	43.9	21.2
Guatemala	AMR	UM	34.4	86.0	0.07	0.65	48.9	17.6
Guinea	AFR	Low	43.9	45.0	0.12	0.47	63.9	15.6
Guinea- Bissau	AFR	Low	42.3	88.0	0.69	0.46	56.6	35.7
Haiti	AMR	Low	33.2	64.0	0.68	0.50	44.7	41.1
Honduras	AMR	LM	31.7	90.0	0.74	0.62	42.9	15.7
India	SEAR	LM	27.1	89.0	1.73	0.65	66.0	8.2
Indonesia	SEAR	LM	26.6	79.0	2.41	0.71	44.7	12.1
Iran	EMR	UM	24.5	99.0	2.63	0.80	25.1	22.7
Iraq	EMR	UM	38.4	84.0	2.04	0.69	29.5	33.3
Jamaica	AMR	UM	23.8	97.0	0.81	0.73	44.3	33.7
Jordan	EMR	UM	34.2	96.0	2.82	0.72	9.0	11.7
Kazakhstan	EUR	UM	28.5	98.0	7.29	0.82	42.6	
Kenya	AFR	LM	39.8	92.0	1.17	0.58	73.0	15.1
Kyrgyz Republic	EUR	LM	32.4	94.0	5.94	0.67	63.6	
Lao PDR	WPR	LM	32.6	68.0	0.95	0.60	65.0	11.0
Lebanon	EMR	UM	26.1	83.0	1.67	0.73	11.4	47.0
Lesotho	AFR	LM	32.7	93.0	3.26	0.52	71.8	14.3
Liberia	AFR	Low	41.1	84.0	0.53	0.47	48.8	33.6
Libya	EMR	UM	28.3	97.0	6.53	0.71	19.9	
Madagascar	AFR	Low	40.7	75.0	0.15	0.52	62.8	28.7
Malawi	AFR	Low	43.9	92.0	0.44	0.49	83.1	11.3

Country	Region	Income	% U15	DTP3	Nurses per 1k	HDI	% Rural	% Slum
Malaysia	WPR	UM	24.0	99.0	3.47	0.80	24.0	
Mali	AFR	Low	47.5	71.0	0.36	0.43	57.6	23.8
Mauritania	AFR	LM	40.1	81.0	0.93	0.53	46.3	42.9
Mauritius	AFR	UM	17.8	97.0	3.52	0.80	59.2	
Mexico	AMR	UM	26.6	88.0	2.40	0.77	19.8	8.9
Moldova	EUR	LM	15.9	93.0	4.92	0.71	57.4	
Mongolia	WPR	LM	30.4	99.0	3.89	0.74	31.6	29.2
Morocco	EMR	LM	27.2	99.0	1.39	0.68	37.5	8.2
Mozambique	AFR	Low	44.7	80.0	0.68	0.45	64.0	28.9
Myanmar	SEAR	LM	26.4	91.0	1.00	0.58	69.4	12.5
Namibia	AFR	UM	36.9	89.0	1.95	0.65	50.0	16.6
Nepal	SEAR	Low	30.4	91.0	3.11	0.58	80.3	10.7
Nicaragua	AMR	LM	30.2	98.0	1.53	0.65	41.5	26.6
Niger	AFR	Low	50.0	79.0	0.27	0.38	83.6	11.5
Nigeria	AFR	LM	43.9	57.0	1.18	0.53	49.7	25.3
North Macedonia	EUR	UM	16.5	91.0	3.79	0.76	42.0	
Pakistan	EMR	LM	35.3	75.0	0.67	0.56	63.3	16.7
Papua New Guinea	WPR	LM	35.8	61.0	0.45	0.54	86.8	
Paraguay	AMR	UM	29.4	88.0	1.66	0.72	38.4	10.8
Peru	AMR	UM	25.8	84.0	2.44	0.76	22.1	26.6
Philippines	WPR	LM	31.0	65.0	4.94	0.71	53.1	18.0
Romania	EUR	UM	15.5	86.0	7.39	0.82	46.0	
Russian Federation	EUR	UM	17.9	97.0	8.54	0.82	25.6	
Rwanda	AFR	Low	40.0	97.0	1.20	0.54	82.8	9.2
Senegal	AFR	LM	43.1	81.0	0.31	0.51	52.8	18.6
Serbia	EUR	UM	15.7	96.0	6.09	0.80	43.9	
Sierra Leone	AFR	Low	41.1	90.0	0.22	0.44	57.9	31.8
South Africa	AFR	UM	29.1	74.0	1.31	0.71	33.6	15.3
South Sudan	AFR	Low	41.8	49.0	0.70	0.41	80.4	18.8
Sri Lanka	SEAR	UM	24.2	99.0	2.18	0.78	81.5	
Sudan	EMR	LM	40.5	93.0	0.70	0.51	65.4	31.7
Syrian Arab Republic	EMR	Low	31.4	47.0	1.54	0.55	45.8	10.5
Tajikistan	EUR	Low	36.8	96.0	4.75	0.66	72.9	
Tanzania	AFR	Low	44.1	98.0	0.58	0.53	66.2	17.1
Thailand	SEAR	UM	17.1	97.0	2.76	0.77	50.1	12.5
Timor-Leste	SEAR	LM	37.8	83.0	1.67	0.63	69.4	
Togo	AFR	Low	41.3	88.0	0.41	0.51	58.3	21.4
Tunisia	EMR	LM	24.2	97.0	2.51	0.74	31.1	5.5
Turkey	EUR	UM	24.6	98.0	2.71	0.81	24.9	8.9
Turkmenistan	EUR	UM	30.8	99.0	4.43	0.71	48.4	

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Country	Region	Income	% U15	DTP3	Nurses per 1k	HDI	% Rural	% Slum
Uganda	AFR	Low	46.9	93.0	1.24	0.53	76.2	12.7
Ukraine	EUR	LM	15.8	50.0	6.66	0.75	30.6	
Uzbekistan	EUR	LM	28.7	98.0	11.28	0.71	49.5	
Venezuela	AMR	UM	27.7	60.0	0.94	0.73	11.8	28.2
Vietnam	WPR	LM	23.2	75.0	1.45	0.69	64.1	9.8
Yemen, Rep.	EMR	Low	39.6	65.0	0.79	0.46	63.4	22.3
Zambia	AFR	LM	44.9	90.0	1.34	0.59	56.5	23.5
Zimbabwe	AFR	LM	42.4	89.0	1.93	0.56	67.8	8.1

Appendix 5: Additional Modeling

Sensitivity to Latent Period

A mean latent period (duration between infection and onset of contagiousness) of 4.0 days was used throughout this work; see Appendix 1 for parameter details. The standard fixed-post SIA duration of 7.0 days, when paired with a mean latent period of 4.0 days, implies that an average of only one additional generation of infections would occur during a typical fixed-post SIA. A shorter latent period could potentially lead to additional compounding of infections during the period of a fixed-post SIA, and significant uncertainty remains with respect to the true mean of the latent period of SARS-CoV-2.

An additional analysis was conducted that examines the impact of using a mean latent period of 2.5 days, examining Pakistan only. The procedure for determining best-fit infectivity described in Appendix 2 was repeated. Outcomes using a latent period of 2.5 days are contrasted with outcomes using a latent period of 4.0 days in figure A5-1.

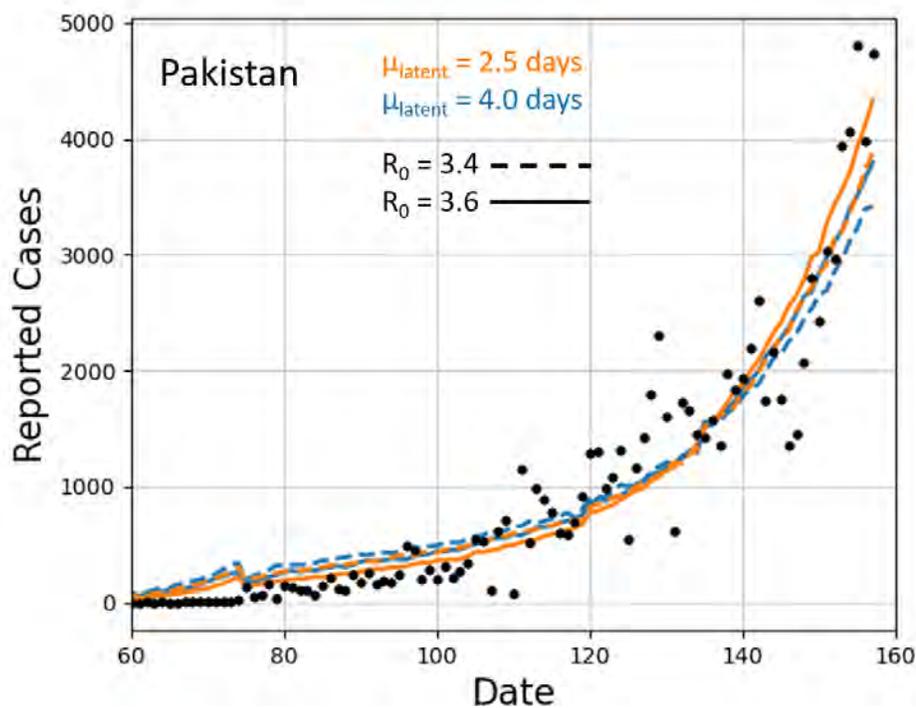


Figure A5-1. Simulated trajectories of best fit to Pakistan incidence data; see Appendix 2 for procedural details. Timeseries outcomes for a mean latent period of 2.5 days with an R_0 value of 3.4 are nearly identical to outcomes for a mean latent period of 4.0 days with an R_0 value of 3.6.

Using a mean latent period of 2.5 days implies a best-fit infectivity of $R_0 = 3.4$. Calibrated optima using timeseries data are nearly identical; these data do not inform a preferred value for the mean latent period.

Fixed-post SIA interventions for Pakistan were simulated using the 2.5 day mean latent period and infectivity of $R_0 = 3.4$. Intervention duration and timing with respect to peak incidence were unchanged.

Outcomes for fixed-post SIA interventions in an urban setting are depicted in figure A5-2.

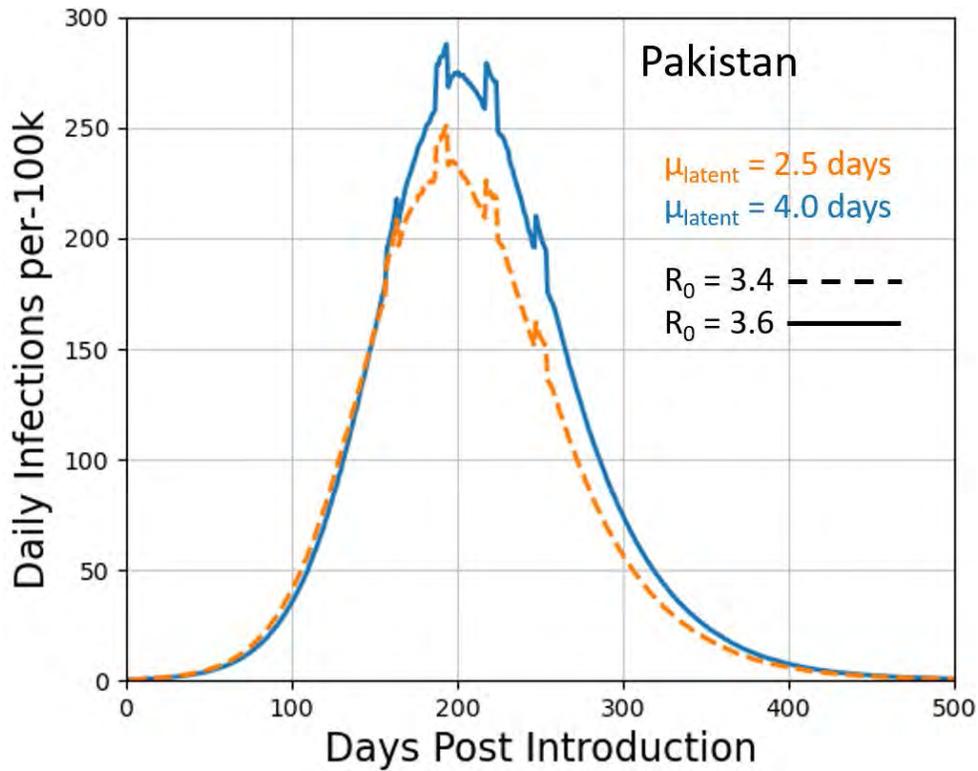


Figure A5-2. Expected daily infections per 100k individuals for Pakistan examining a single schedule involving four separate fixed-post SIAs spaced 30 days apart, urban scenarios only.

Using the shorter latent period corresponds to a lower overall infectivity required to match observed timeseries data. This lower overall infectivity is the dominant effect on simulation outcomes. Fixed-post SIA interventions have qualitatively the same impact on SARS-CoV-2 transmission for both parameterizations. When using a shorter latent period, the absolute effect of fixed-post SIAs on transmission is smaller because of the lower infectivity.

Reduced Childhood Susceptibility

Scenarios depicted in figure A5-3 as 'No Child Reduction' are for illustrative purposes only. No results are used for scenarios *without* reduced childhood susceptibility.

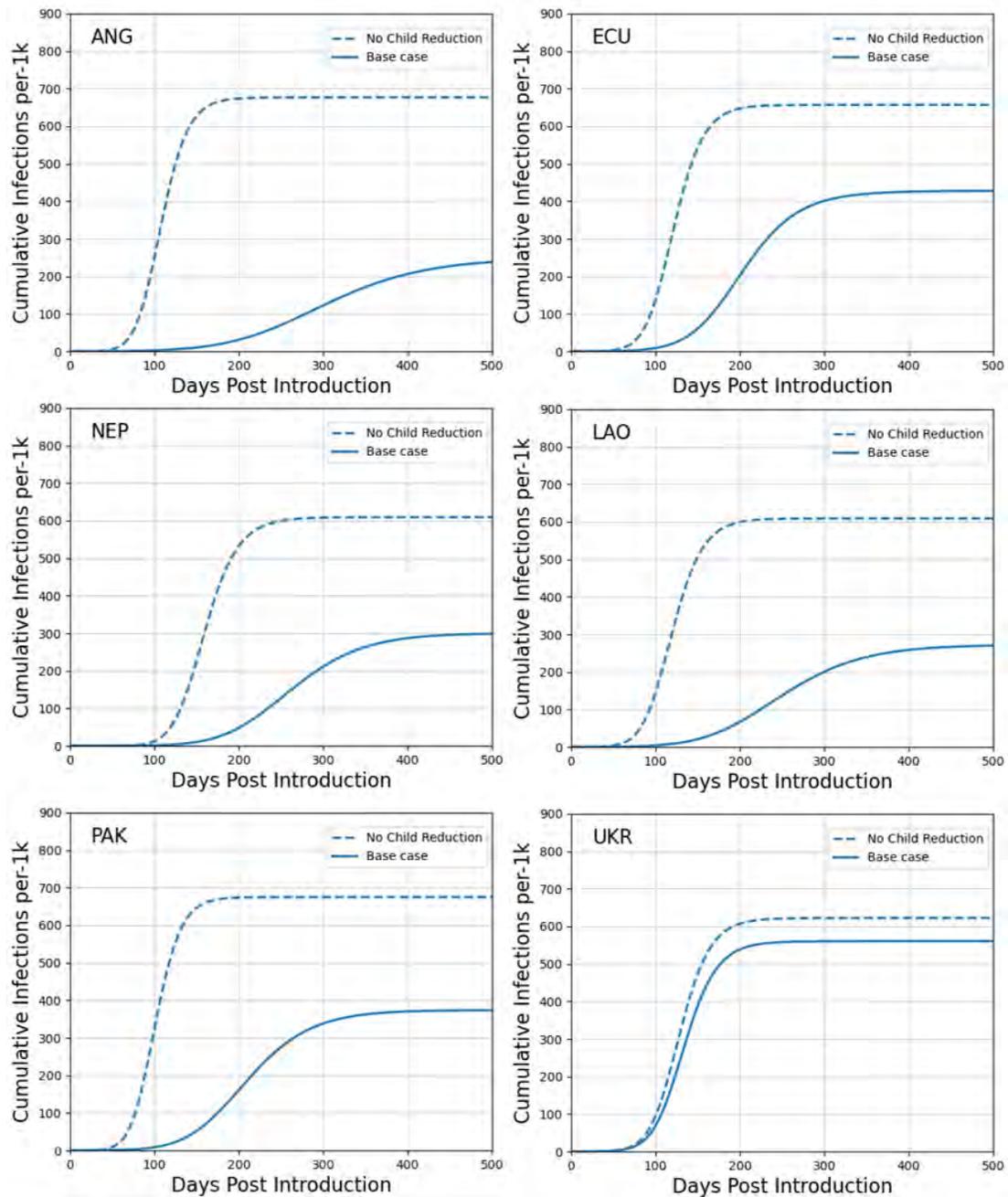


Figure A5-3. Cumulative infection trajectories for SARS-CoV-2 in an urban environment when varying the level of susceptibility in the under-15-year-old cohort. The base case incorporates a reduction in childhood acquisition of about 55% and childhood transmission of 15%.

Time to Peak Incidence: Urban

For ease of comparison between contexts, interventions were scheduled based on the time of peak incidence in urban-only simulations.

Table A5-1. Time interval between introduction and peak incidence for an urban setting. Simulated outcomes for the six country contexts.

Country	Peak Incidence Urban Setting (days)
Angola	290
Ecuador	197
Lao PDR	239
Nepal	250
Pakistan	204
Ukraine	131

Values in table A5-1 are representative of the example scenarios and not intended to reflect the natural history for a country. All simulations outcomes assume uniform government policy across contexts. Distancing, mask wearing, quarantine measures, and other non-pharmaceutical interventions can have a substantial impact on the timing of peak incidence.

Excess Infections Above Baseline: Urban Rural Routine Outreach Vaccination

Scenarios depicted in figure A5-4 are the outcomes depicted in figure 2 from the main text when subtracting daily incidence from the base case.

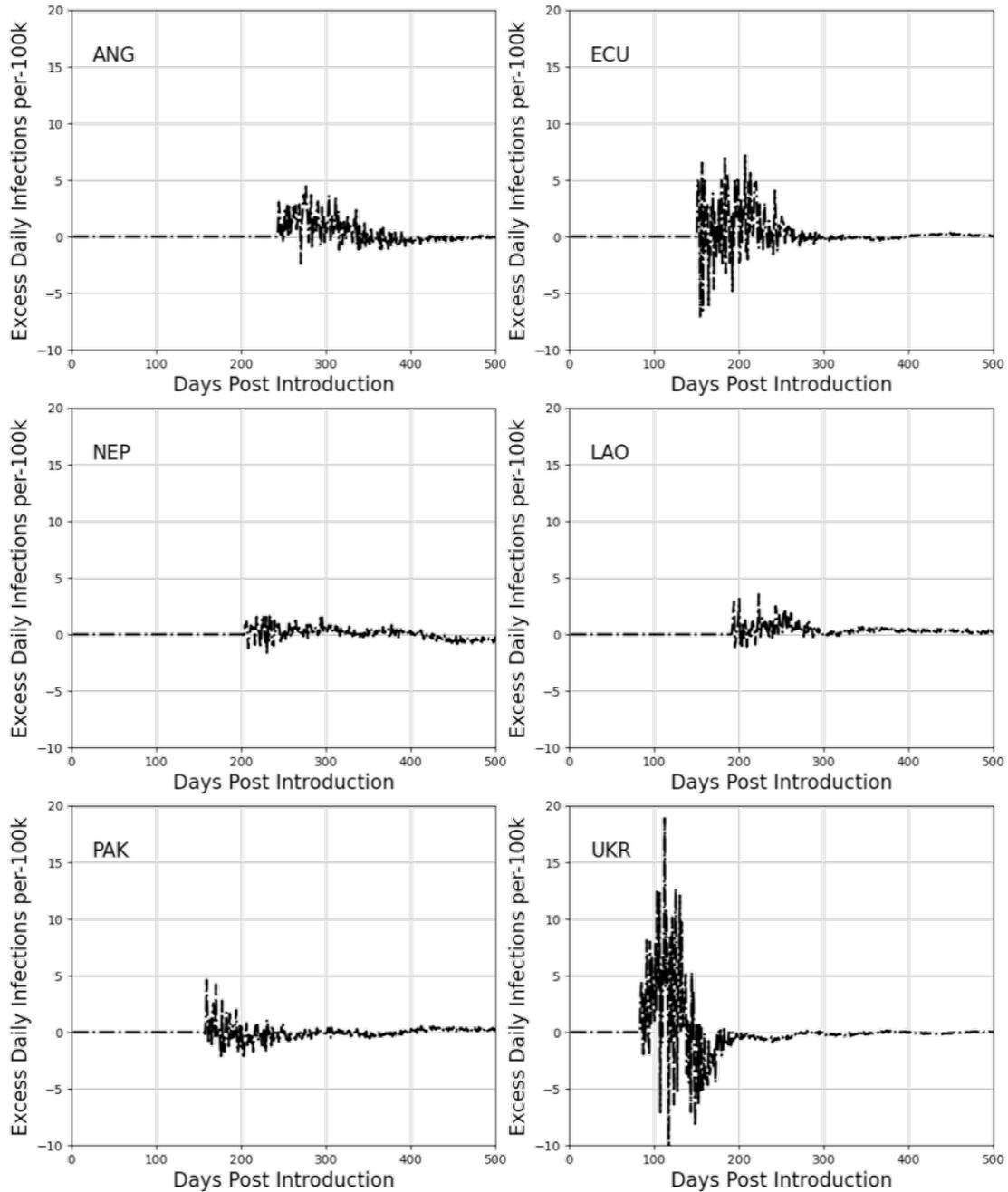


Figure A5-4. Expected excess daily infections per 100k individuals for each country. Routine outreach was implemented symmetrically around peak incidence.

Excess Infections Above Baseline: Urban Fixed-Post

Scenarios depicted in figure A5-5 are the outcomes depicted in figure 3 from the main text when subtracting daily incidence from the base case.

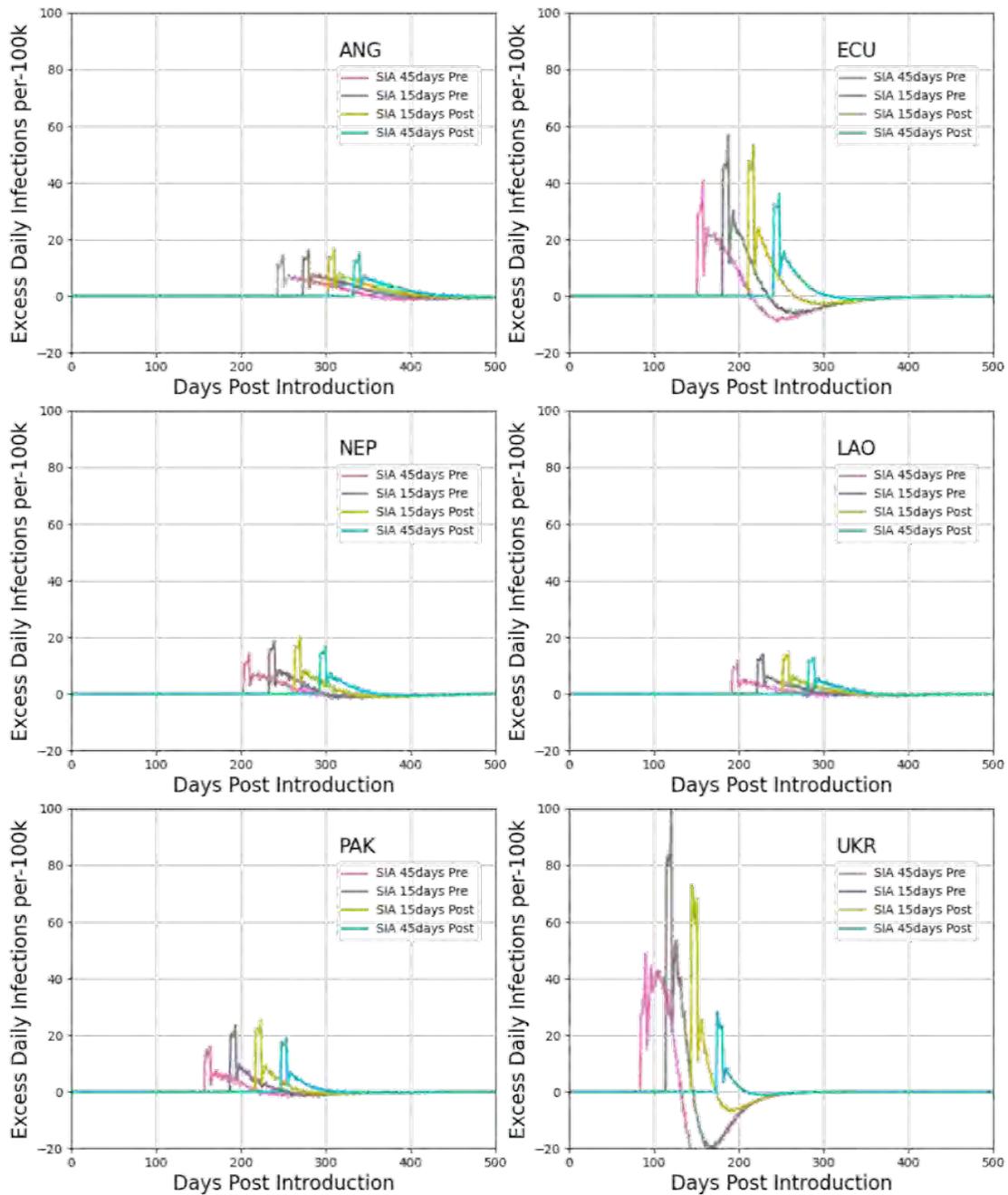


Figure A5-5. Expected excess daily infections per 100k individuals for each country examining four possible schedules, with respect to baseline urban scenarios that do not include an intervention. Fixed-post SIA timing with respect to peak incidence was the same for all contexts.

Excess Infections Above Baseline: Urban-Rural House-to-House

Scenarios depicted in figure A5-6 are the outcomes depicted in figure 6 from the main text when subtracting daily incidence from the base case.

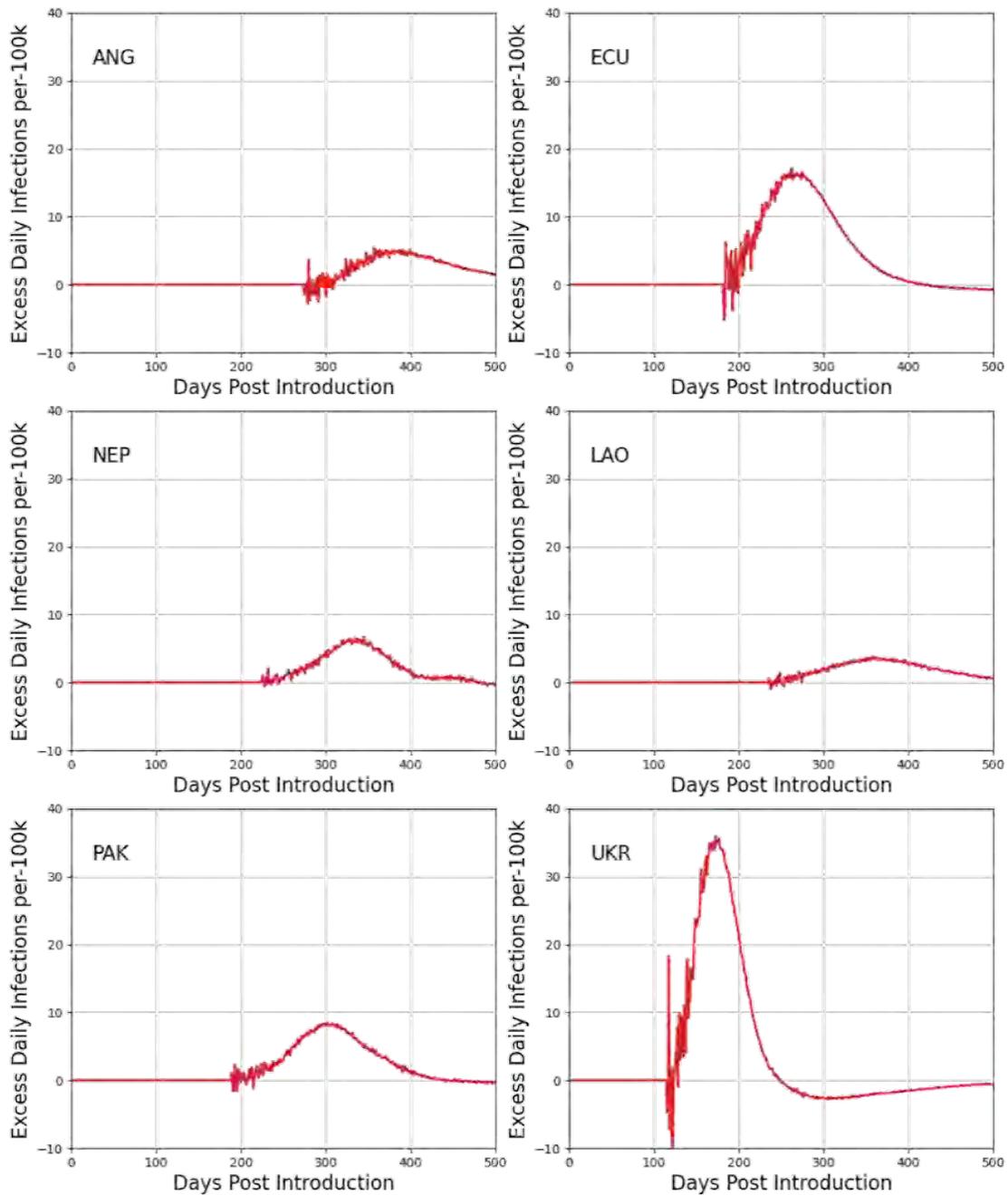


Figure A5-6. Expected excess daily infections per 100k individuals for each country for house to house SIAs in mixed urban-rural environments. Health workers have 10x relative acquisition/transmission rate, throughout.

Session 2:

COVID-19: Frameworks and methods to guide COVID 19 vaccine development



**World Health
Organization**

SAGE Working Group on COVID-19 Vaccines

Three components inform the formulation of vaccination strategies

2: Strategic Advisory Group of Experts (SAGE)

Provides guidance and policy advice in the context of specific candidates, e.g. on vaccination strategies

1: Allocation Framework

Sets frame for overarching public health goals and priorities (candidate independent)

3: Regulatory, Safety & Monitoring

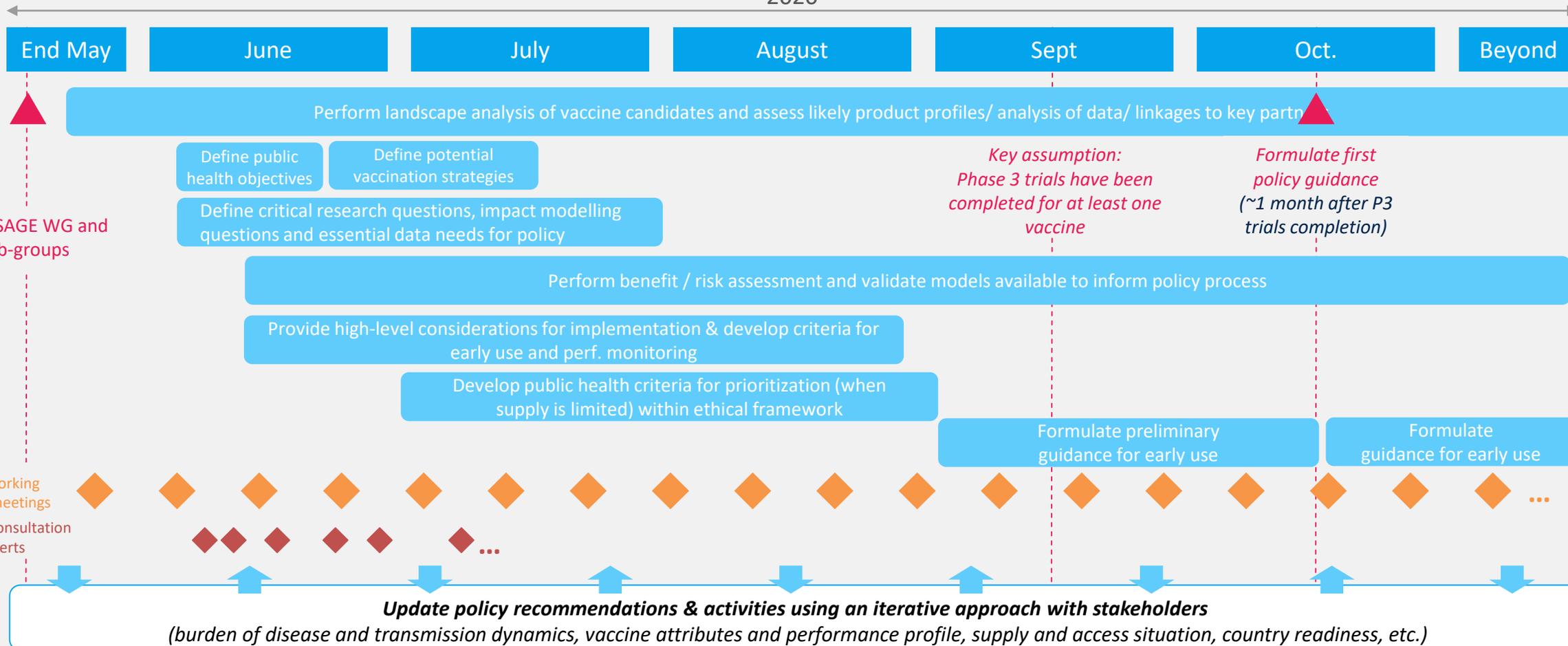
Provides guidance on regulatory issues, safety and monitoring both for candidate specific and system specific approaches

Countries

Responsible for final decision on policy, allocation and vaccination strategy

SAGE WG-Tentative timeline for policy process

2020



Work Group Considerations: Objectives of the COVID-19 Vaccine Program

- Ensure safety and effectiveness of COVID-19 vaccines
- Reduce transmission, morbidity, and mortality in the population
- Help minimize disruption to society and economy, including maintaining healthcare capacity
- Ensure equity in vaccine allocation and distribution

Sub-groups:

#	Sub-group	TORs	Short-term priority	Liaisons
1	Public health objective(s) & prioritization	<ul style="list-style-type: none"> • Formulate public health objectives for vaccination under consideration of initially limited vaccine supply • Gather available epidemiological data to define the risk of disease and morbidity/mortality in different population groups; identify main sources of transmission in order to guide prioritization of vaccination, together with modelling WG • In conjunction with modelling WG propose priority populations for vaccination • Provide a broader social, anthropological and ethical framework in support of vaccine prioritization 	Review public health objective initial framework	<ul style="list-style-type: none"> • K. A.H. Vandemaële • Ethics group within WHO • ...
2	Evidence gathering on vaccines in clinical trials	<ul style="list-style-type: none"> • Draft critical research questions to inform literature review (to be vetted by the entire group) • Provide continuous review of the available evidence on the progress of candidate vaccines against COVID-19, and provide regular updates to SAGE WG • Provide continuous review of Phase 1-3 trial results as they become available (immunogenicity, efficacy and safety), including the optimal vaccination schedules to be used for each vaccine, • Gather evidence on the safety of vaccines when safety data from wider population use become available, in close collaboration with Global Advisory Committee on Vaccine Safety (GACVS) 	Define questions to further assess most promising candidates	<ul style="list-style-type: none"> • CEPI • GACVS • etc
3	Vaccine impact modelling	<ul style="list-style-type: none"> • Provide guidance for the development of critical questions for modelling groups • Commission and review prediction and impact models to determine the optimal age groups and target populations for vaccine introduction and guide vaccine introduction for optimal impact, and contribute to updates of target product profiles of vaccines for outbreak and for endemic use • Provide interpretation of modelling results to inform policy development 	Define impact modelling needs	<ul style="list-style-type: none"> • IVIRAC • external groups • ...
	Future sub-groups or plenary (based on inputs of all 3 sub-groups)	<ul style="list-style-type: none"> • Prepare policy advice to SAGE on the accelerated use of vaccines (pre-licensure and post-licensure) to mitigate the public health impact of COVID-19, to possibly curtail the ongoing pandemic, as well as to prevent or reduce the risk of spread of disease in the future. • Issue recommendations on monitoring of vaccine performance (safety, effectiveness, impact), together with GACVS and Brighton 	n/a	<ul style="list-style-type: none"> • All 3 sub-groups above • GACVS • Brighton • ...

Table 1. Values Framework

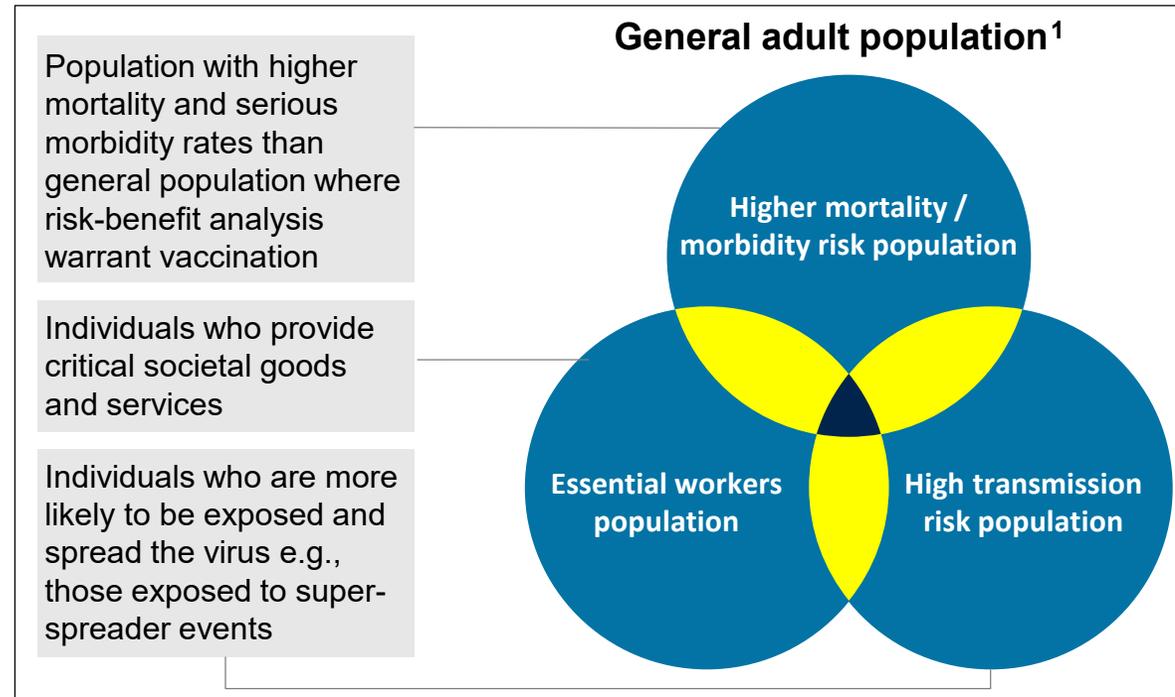
Goal Statement	COVID-19 vaccines must be a global public good. The overarching goal is for COVID-19 vaccines to contribute significantly to the equitable protection and promotion of human well-being among all people of the world.
Principles	Objectives
Human Well-Being	Reduce deaths and disease burden from the COVID-19 pandemic;
	Reduce societal and economic disruption by containing transmission, reducing severe disease and death, or a combination of these strategies;
	Protect the continuing functioning of essential services, including health services.
Equal Respect	Treat the interests of all individuals and groups with equal consideration as allocation and priority-setting decisions are being taken and implemented;
	Offer a meaningful opportunity to be vaccinated to all individuals and groups who qualify under prioritization criteria.
Global Equity	Ensure that vaccine allocation takes into account the special epidemic risks and needs of all countries; particularly low-and middle-income countries;
	Ensure that all countries commit to meeting the needs of people living in countries that cannot secure vaccine for their populations on their own, particularly low- and middle-income countries.
National Equity	Ensure that vaccine prioritization within countries takes into account the vulnerabilities, risks and needs of groups who, because of underlying societal, geographic or biomedical factors, are at risk of experiencing greater burdens from the COVID-19 pandemic;
	Develop the immunization delivery systems and infrastructure required to ensure COVID-19 vaccines access to priority populations and take proactive action to ensure equal access to everyone who qualifies under a priority group, particularly socially disadvantaged populations.
Reciprocity	Protect those who bear significant additional risks and burdens of COVID-19 to safeguard the welfare of others, including health and other essential workers.
Legitimacy	Engage all countries in a transparent consultation process for determining what scientific, public health, and values criteria should be used to make decisions about vaccine allocation between countries;
	Employ best available scientific evidence, expertise, and significant engagement with relevant stakeholders for vaccine prioritization between various groups within each country, using transparent, accountable, unbiased processes, to engender deserved trust in prioritization decisions.

There are three priority populations which include multiple potential target groups

WHY

Priority populations are defined by the rationale for their vaccinations i.e., why would you want to vaccinate this population?

Priority populations



Vaccines should also be prioritized / reserved for disease outbreaks

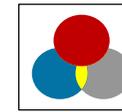
1. Non-adult populations require further consideration

WHO

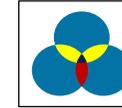
Target groups are who you would want to vaccinate and are defined by a common characteristic (e.g., age, health status, occupation) which allows you to identify them

Examples of potential target groups

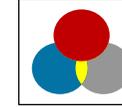
(ordering does not imply sequencing or prioritization)



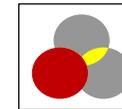
Elderly (>65 years)



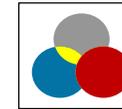
Workers in health and social care settings



<65 with co-morbidities



Other essential workers



Adults in densely populated areas



Rest of adult population



Vx strategy methodology for calculating size of underlying health condition risk target group draws on recent Lancet modelling



Published June 15th 2020

Link to article is [here](#)

Underlying health condition risk

Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study



Andrew Clark, Mark Jit, Charlotte Warren-Gash, Bruce Guthrie, Harry H X Wang, Stewart W Mercer, Colin Sanderson, Martin McKee, Christopher Troeger, Kanyin L Ong, Francesco Checchi, Pablo Perel, Sarah Joseph, Hamish P Gibbs, Amitava Banerjee, Rosalind M Eggo, with the Centre for the Mathematical Modelling of Infectious Diseases COVID-19 working group*

Research considers 11 underlying conditions which confer higher COVID-19 risk based on CDC, Public Health England and WHO guidance¹

- (1) Cardiovascular disease, including cardiovascular disease caused by hypertension
- (2) Chronic kidney disease, including chronic kidney disease caused by hypertension
- (3) Chronic respiratory disease
- (4) Chronic liver disease
- (5) Diabetes
- (6) Cancers with direct immunosuppression
- (7) Cancers without direct immunosuppression, but with possible immunosuppression caused by treatment
- (8) HIV/AIDS
- (9) Tuberculosis (excluding latent infections)
- (10) Chronic neurological disorders
- (11) Sickle cell disorders

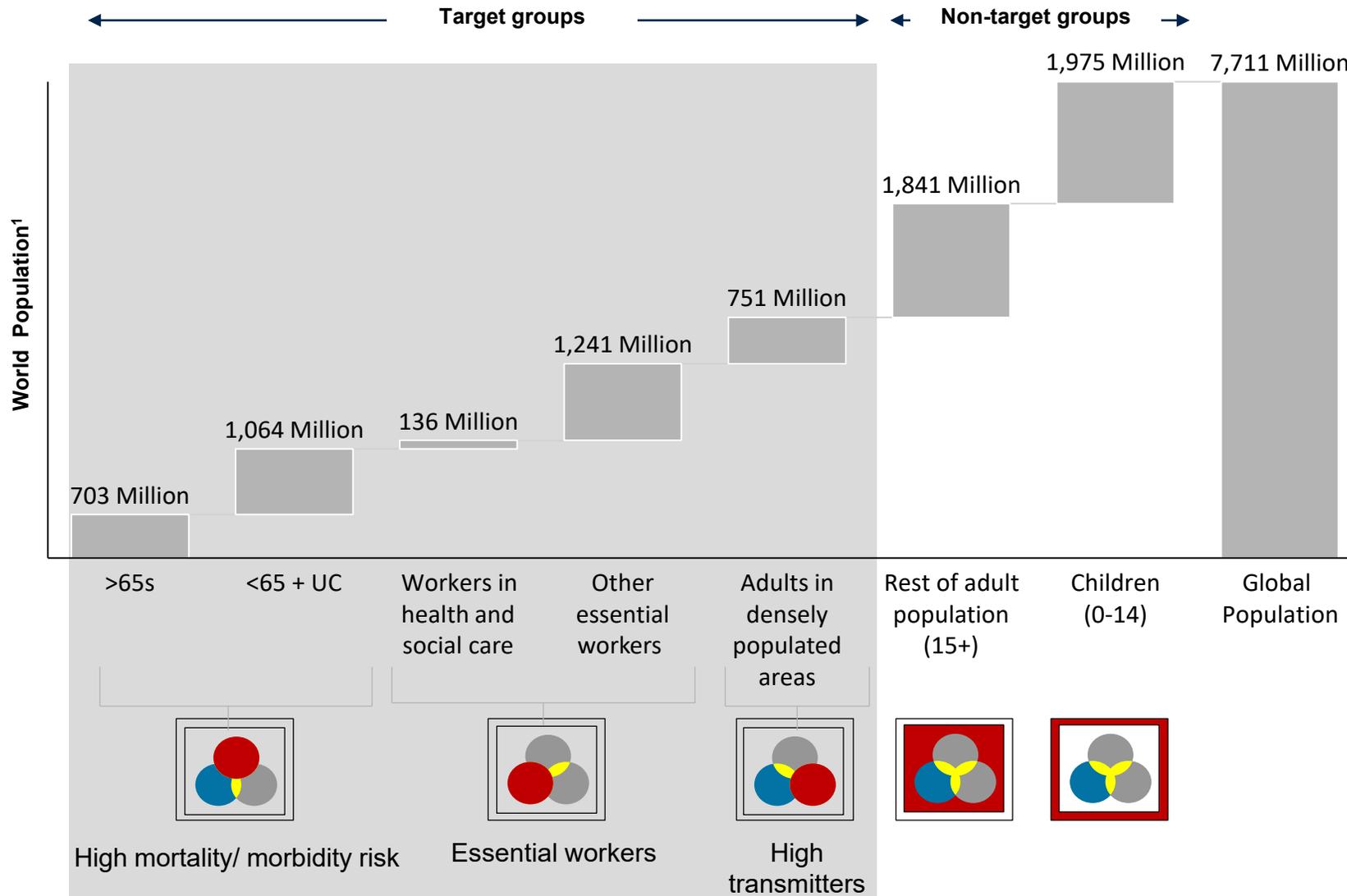
Quantification is by age (5-year age groups), sex, and country for 188 countries using prevalence data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017 and UN population estimates for 2020

1. Centers for Disease Control and Prevention. People who are at higher risk for severe illness. Coronavirus Disease 2019 (COVID-19). 2020. <https://www.cdc.gov/coronavirus/2019-ncov/need-extraprecautions/people-at-higher-risk.html>; Public Health England. Guidance on social distancing for everyone in the UK. March 30, 2020. <https://www.gov.uk/government/publications/covid-19-guidance-on-social-distancing-and-forvulnerable-people/guidance-on-social-distancing-for-everyone-inthe-uk-and-protecting-older-people-and-vulnerable-adults>; WHO. COVID-19 and NCDs. Information note on COVID-19 and noncommunicable diseases. March 23, 2020. <https://www.who.int/who-documents-detail/covid-19-and-ncds>

Number of individuals in millions at increased risk of severe COVID-19 illness by age, number of conditions, region, and age threshold

	Africa (n=1338.8 million)	Asia (n=4632.9 million)	Europe (n=747.1 million)	Latin America and the Caribbean (n=652.2 million)	Northern America (n=368.7 million)	Oceania (n=41.9 million)	Global (n=7781.7 million)
Population by number of conditions							
No conditions							
<15 years	519.2 (39%)	1042.4 (22%)	117.2 (16%)	151.6 (23%)	65.0 (18%)	9.5 (23%)	1905.0 (24%)
15-49 years	533.6 (40%)	1985.9 (43%)	274.3 (37%)	291.6 (45%)	146.6 (40%)	16.7 (40%)	3248.8 (42%)
50-54 years	24.8 (2%)	184.3 (4%)	33.4 (4%)	22.9 (4%)	14.5 (4%)	1.5 (4%)	281.5 (4%)
55-59 years	17.6 (1%)	136.9 (3%)	29.4 (4%)	18.0 (3%)	12.9 (3%)	1.3 (3%)	216.1 (3%)
60-64 years	11.6 (<1%)	95.8 (2%)	22.6 (3%)	12.5 (2%)	10.0 (3%)	1.0 (2%)	153.6 (2%)
65-69 years	7.0 (<1%)	69.5 (1%)	16.0 (2%)	8.3 (1%)	6.7 (2%)	0.7 (2%)	108.2 (1%)
≥70 years	6.6 (<1%)	73.8 (2%)	23.2 (3%)	9.9 (2%)	8.5 (2%)	1.0 (2%)	122.9 (2%)
All ages	1170.5 (84%)	3588.5 (77%)	516.1 (69%)	514.8 (79%)	264.4 (72%)	31.8 (76%)	6036.0 (78%)
One condition only							
<15 years	19.9 (1%)	43.5 (<1%)	2.7 (<1%)	4.0 (<1%)	1.6 (<1%)	0.3 (<1%)	71.9 (<1%)
15-49 years	100.8 (8%)	367.6 (8%)	49.1 (7%)	45.1 (7%)	23.9 (7%)	2.9 (7%)	585.2 (8%)
50-54 years	13.4 (1%)	82.3 (2%)	14.1 (2%)	10.3 (2%)	6.6 (2%)	0.6 (2%)	127.3 (2%)
55-59 years	12.2 (<1%)	77.4 (2%)	17.3 (2%)	10.4 (2%)	8.4 (2%)	0.7 (2%)	126.4 (2%)
60-64 years	10.5 (<1%)	68.6 (1%)	18.3 (2%)	9.5 (2%)	9.2 (2%)	0.7 (2%)	116.8 (2%)
65-69 years	8.3 (<1%)	61.2 (1%)	17.5 (2%)	8.1 (1%)	8.6 (2%)	0.6 (2%)	104.3 (1%)
≥70 years	11.3 (<1%)	92.1 (2%)	39.4 (5%)	14.5 (2%)	17.4 (5%)	1.4 (3%)	176.1 (2%)
All ages	176.4 (13%)	792.6 (17%)	158.4 (21%)	102.0 (16%)	74.6 (20%)	7.3 (18%)	1308.2 (17%)
Multiple (two or more) conditions							
<15 years	1.3 (<1%)	2.8 (<1%)	0.2 (<1%)	0.3 (<1%)	0.1 (<1%)	0.0 (<1%)	4.6 (<1%)
15-49 years	14.1 (1%)	55.1 (1%)	7.9 (1%)	6.9 (1%)	3.2 (<1%)	0.4 (1%)	87.7 (1%)
50-54 years	3.8 (<1%)	27.3 (<1%)	4.0 (<1%)	2.9 (<1%)	1.9 (<1%)	0.2 (<1%)	36.0 (<1%)
55-59 years	4.3 (<1%)	23.1 (<1%)	6.0 (<1%)	3.7 (<1%)	3.0 (<1%)	0.2 (<1%)	44.3 (<1%)
60-64 years	4.6 (<1%)	29.8 (<1%)	8.0 (1%)	4.1 (<1%)	4.0 (1%)	0.3 (<1%)	50.8 (<1%)
65-69 years	4.5 (<1%)	33.1 (<1%)	9.5 (1%)	4.4 (<1%)	4.6 (1%)	0.3 (<1%)	56.4 (<1%)
≥70 years	9.3 (<1%)	80.6 (2%)	37.1 (5%)	13.2 (2%)	16.0 (4%)	1.3 (3%)	157.6 (2%)
All ages	41.9 (3%)	251.8 (5%)	72.7 (10%)	35.5 (5%)	32.8 (9%)	2.8 (7%)	437.4 (6%)
Population at increased risk of severe COVID-19							
People with at least one condition (all ages), assuming no age-based threshold	218.3 (16%)	1044.4 (23%)	231.0 (31%)	137.4 (21%)	104.4 (28%)	10.1 (24%)	1745.6 (22%)
Older people with no conditions*							
≥50 years	67.7 (5%)	560.3 (12%)	124.6 (17%)	71.5 (11%)	52.7 (14%)	5.5 (13%)	882.3 (11%)
≥55 years	42.9 (3%)	375.9 (8%)	91.2 (12%)	48.7 (7%)	38.2 (10%)	4.0 (9%)	600.8 (8%)
≥60 years	25.2 (2%)	239.1 (5%)	61.8 (8%)	30.7 (5%)	24.6 (7%)	2.6 (6%)	384.8 (5%)
≥65 years	13.6 (1%)	143.2 (3%)	39.3 (5%)	18.2 (3%)	15.3 (4%)	1.6 (4%)	231.2 (3%)
≥70 years	6.6 (<1%)	73.8 (2%)	23.2 (3%)	9.9 (2%)	8.5 (2%)	1.0 (2%)	122.9 (2%)
People with at least one condition plus older people with no conditions*							
≥50 years	286.0 (21%)	1604.7 (35%)	355.7 (48%)	209.0 (32%)	157.1 (43%)	15.6 (37%)	2627.9 (34%)
≥55 years	261.2 (20%)	1420.4 (31%)	322.3 (43%)	186.1 (29%)	142.6 (39%)	14.0 (34%)	2346.5 (30%)
≥60 years	243.5 (18%)	1283.5 (28%)	292.8 (39%)	168.1 (26%)	129.7 (35%)	12.7 (30%)	2130.4 (27%)
≥65 years	231.9 (17%)	1187.7 (26%)	270.3 (36%)	155.6 (24%)	119.7 (32%)	11.7 (28%)	1976.8 (25%)
≥70 years	224.9 (17%)	1118.2 (24%)	254.2 (34%)	147.3 (23%)	112.9 (31%)	11.0 (26%)	1868.6 (24%)
<small>Data are number of individuals in millions (percentage of total population of the region). *Older people with no conditions could be considered at increased risk by virtue of age alone.</small>							
Table 1: Number of individuals in millions at increased risk of severe COVID-19 illness by age, number of conditions, region, and age threshold							

Target groups by population size. WHO is currently proposing to work with 5 target groups.



1. Population sizes taken from a range of sources including the UN databank, ILO and other data reports. They do not account for overlaps between the three priority populations

Scenarios for making recommendations

● Epidemiological scenario ● Authorization for use ● Vaccine supply ●

		Emergency Use	Conditional/Full licensure	Limited	Unlimited
1	Widespread transmission (increasing incidence; $R > 1$)				
2	Countries which managed to contain the outbreak with nonpharmaceutical interventions (decreasing incidence, $R < 1$)				
3	Countries with no reported cases but at high risk if imported				
4	Prevention of importation (akin to yellow fever vaccination?)				
6	Prevention of future outbreaks (stock piles and reactive campaigns, preventive campaigns, routine immunization?)	/			

The Big Unknowns

(1) Vaccine type:

transmission blocking

OR

protection against severe disease only

OR

transmission and disease blocking?

(2) **Efficacy in high risk groups:** older age groups or those with significant comorbidities

(3) **Efficacy and Safety: Risk-benefit assessment**



Questions to IVIRAC



Are additional epidemiologic and economic model criteria needed?



What is IVIR-AC's advice on strategies to address gaps?



How could IVIRAC support future review processes and quality of modelling?

□ SAGE Working Group on COVID-19 Vaccines: Impact Modelling subgroup update to IVIR-AC

Participants

Nicholas Grassly, Imperial College London, UK (co-chair, modelling subgroup)

Sarah Pallas, CDC, US (co-chair, modelling subgroup)

Hanna Nohynek, Finnish Institute for Health and Welfare (chair of WG)

Gagandeep Kang, CMC, India (chair SEARO RITAG)

Peter Figueroa, University of the West Indies, Jamaica (chair PAHO RITAG)

Mary Ramsay, PHE, UK

other WG members (esp. Ruth Faden, Sonali Kochhar, Saad Omer)

WHO : Annelies Wilder-Smith, Raymond Hutubessy

Aim and ToR (reminder)

Overall aim: ensure high-quality modelling informs policy recommendations by SAGE on COVID-19 vaccination

- Provide guidance for the development of critical questions for modelling groups
- Commission and review models
- Contribute to updates of target product profiles of vaccines
- Provide interpretation of modelling results to inform policy development

Prioritized Infectious Disease and Economic Modelling Questions (released 31 July after IVIR-AC input 28 July, deadline 4 Sep)

WHO Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 Vaccines: Prioritized Infectious Disease and Economic Modelling Questions

Request for Information

- As part of its scoping of the landscape of modelling groups and initiatives related to COVID-19 vaccines, we invite modellers and economists to provide information about their work on COVID-19 vaccination that addresses prioritized modelling questions to contribute to informing deliberations around policy recommendations from the WHO SAGE on Immunization.
- Groups are encouraged to share early stage and interim results for any of the questions as part of the ongoing process of evidence review, gap identification, and refinement of priority questions and scenarios.
- We particularly encourage models that have been fit to available epidemiological and/or economic data or validated through comparison with these data. Model review and future invitations to participate in presentations to the Working Group will be based on assessment of model performance and minimum standards as described in this document.
- Brief summaries of any completed work or work planned or underway for any question may be sent via email to the WHO SAGE Secretariat at: vaccineresearch@who.int.
- Initial responses are requested as soon as possible and no later than **4th September 2020** for consideration in initial reviews and deliberations. This will be an ongoing process of consultation with the modelling community and we will also be seeking input at later dates.

COVID-19 vaccine impact models

WHO Strategic Advisory Group of Experts (SAGE) on Immunization
Working Group on COVID-19 Vaccines:
Response Form for Request for Information on
Prioritized Infectious Disease and Economic Modelling Questions

Thank you for your interest in sharing information with the WHO SAGE Working Group on COVID-19 Vaccines. Please refer to the prioritized questions available at:
https://www.who.int/immunization/policy/sage/SAGE_WG_COVID19_Vaccines_Modelling_Questions_31July2020.pdf?ua=1

* Required

1. What is your name? *

Enter your answer

2. What is your organization? *

Enter your answer

3. What is your Email address? *

Prioritized Infectious Disease and Economic Modelling Questions: Health and epidemiological impacts

1. 'priority groups'

1. What would be the impact of vaccinating each of the following target groups on SARS-CoV-2 infections, COVID-19 deaths, and COVID-19 years of life lost, for vaccines given during 2020-21 when vaccination is added to counterfactual scenarios of: (i) no interventions, or (ii) continued implementation of non-pharmaceutical interventions (NPIs)?
 - a. older adults (50+, 65+ or 75+ years), younger adults (18-49 years), school-age children (5-17 years)
 - b. those at high risk because of underlying health conditions
 - c. key workers
 - d. groups at high risk of infection

2. 'optimal strategy'

2. What are the optimal vaccination strategies in terms of target groups under different possible supply scenarios for COVID-19 vaccine during 2020-21 to achieve the maximum reduction in SARS-CoV-2 infections, COVID-19 deaths or years of life lost?

3. 'equity'

3. How would health impacts be distributed across country income groups (high, middle, low) and within countries across household wealth quintiles for the different vaccination targeting approaches described in Questions 1-2?

Prioritized Infectious Disease and Economic Modelling Questions: Economic and social impacts

4. 'essential services'

5. 'return to normal'

6. 'economic impact'

7. 'cost-effectiveness'

8. 'full value of vaccine'

4. What would be the impact on protecting essential services (e.g., health and social care, education) of the different vaccination targeting approaches described in Questions 1-2?
5. At what level of vaccine efficacy and vaccination coverage for which target groups could those NPIs that are most economically and societally disruptive (e.g., lockdowns, travel restrictions) be discontinued?
6. What would be the impacts in terms of economic welfare (e.g., as measured by GDP growth) and economic security (e.g., as measured by number of people living in poverty) of different vaccination targeting approaches (e.g., those in Questions 1-2) across country income groups (high, middle, low)?
7. From the societal perspective, what would be the cost-effectiveness per averted SARS-CoV-2 infection, COVID-19 death, and COVID-19 year of life lost for the vaccination targeting approaches described in Questions 1-2?
8. In monetary terms, what is the full public health and societal value of vaccination with a COVID-19 vaccine?

Provision of core shared scenarios and assumptions

Counterfactual scenario	Vaccine characteristics scenario	Coverage scenario	Supply scenario	Analytic horizon
I. No intervention	A. Efficacy vs. disease and infection*, all ages	1. High (80%)	a. COVAX	i. Short term (end-2021)
II. Continued NPIs	B. Efficacy vs. disease, all ages	2. Mid (50%)	b. COVAX + direct	ii. Medium term (end-2022)
	C. Efficacy vs. disease, younger ages only	3. Low (20%)	c. COVAX + direct (shared)	iii. Long term (end-2030)

Responses received from **20 unique modelling groups** across academic, industry, government, and multilateral organizations willing to share information on their work with SAGE Working Group on COVID-19 Vaccines

Prioritized question(s) that modeling group work addresses	Modeled geography by country income group*				
	HIC	HIC (MIC/LIC)	MIC	HIC/MIC/LIC	Total
Q1a) Health impacts: vaccinating older adults	6	5	2	5	18
Q1b) Health impacts: vaccinating younger adults	6	5	2	5	18
Q1c) Health impacts: vaccinating school-age children	6	5	2	5	18
Q1d) Health impacts: vaccinating those at risk due to comorbidities	4	2		3	9
Q1e) Health impacts: vaccinating key workers	2	1		1	4
Q1f) Health impacts: vaccinating those at high risk of infection	3	3	1	1	8
Q2) Optimal vaccination strategies to minimize adverse health impacts	4	5	2	4	15
Q3) Equity of health impacts across countries & wealth quintiles				2	2
Q4) Vaccination impact on essential service provision	1		1	1	3
Q5) Optimal vaccination strategies to minimize disruptive NPIs	5	5	1	3	14
Q6) Vaccination impact on economic welfare (GDP, poverty)	3			4	7
Q7) Cost-effectiveness of vaccination	4	1	1	4	10
Q8) Full societal and public health value of vaccination	3	1	1	2	7

*HIC (MIC/LIC) refers to models that currently are for only a high-income country setting but could be applied to other MIC/LIC settings.

Modelling groups that have responded to RfI,
by geographic location of institution

Availability of results (subset of groups)

WHO SAGE modelling subgroup activities



Review of responses to RfI and continued engagement/
commissioning of work



Ad hoc presentations of modelling groups with most advanced work
(weekly)



Systematic review of the literature (published and preprints)

Timelines

WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination

14 September 2020



NASEM (US) Preliminary Framework for Equitable Allocation of COVID-19 Vaccine

Phase 1

Phase 1a "Jumpstart Phase":
• High-risk workers in health

Phase 2

• Critical risk workers—workers who are both in industries

Phase 3

• Young adults
• Children

Phase 4

• Everyone residing in the United States

guidance led to be ritization perts on

ld guide llocating

nature

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Who gets a COVID vaccine first? Access plans are taking shape

Advisory groups around the world release guidance to prioritize healthcare workers and those in front-line jobs.



- 5 October 2020 - SAGE meeting, initial recommendations of priority groups, modelling presentation

SAGE modelling subgroup:

- October – completion of 1st round of systematic review and evidence synthesis
- Oct/Nov? – phase 3 trial results, SAGE product/platform-specific recommendations -> assess need for any updates to modelling assumptions & scenarios
- October – potential development of RfP for specific work
- *looking for help from IVIR-AC members (syst review, model assessment)**¹⁴¹

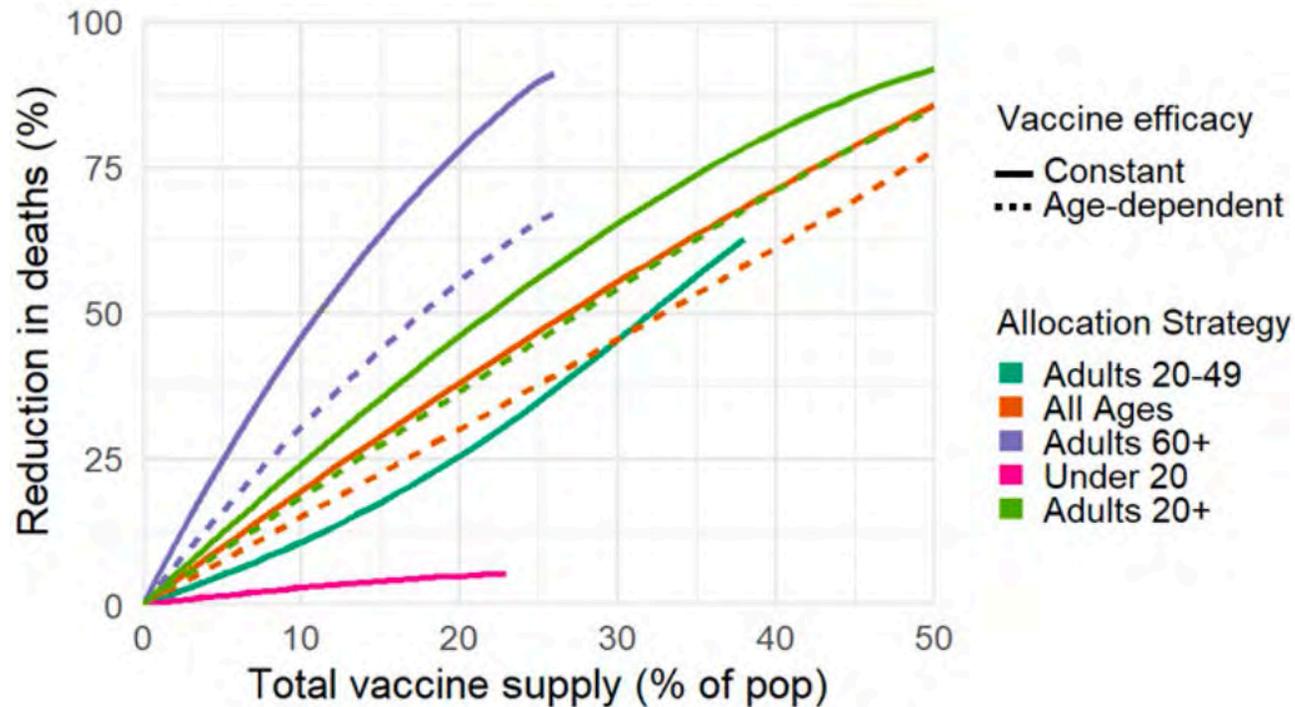
Literature review approach and progress to date

	Search approach	Search sources	# initial results	# retained after abstract screening	# retained after full text screening
Epidemiologic modeling	Initial test searches	PubMed, medRxiv, arXiv, bioRxiv, SSRN, ChemRxiv, Research Square	N=207	N=21	N=10
	Systematic searches		N=338	<i>In process</i>	
Economic modeling	Systematic searches	<i>[Sources above]</i>	N=1091	<i>In process</i>	
		Web of Science, NBER, CEPR, IZA, World Bank, IMF, OECD, ILO, CGD	N=370	N=32	<i>In process</i>

Model assessment criteria

- List of elements to be extracted (similar to CMCC): analysis scope, model features, vaccine characteristics, conclusions
- Quality score based on modified GRADE for modeling (GRADE working group; Brozek et al. 2020 *J Clin Epidemiol* in press)
- Alignment with prioritized questions and inform evidence to recommendations tables from WHO SAGE

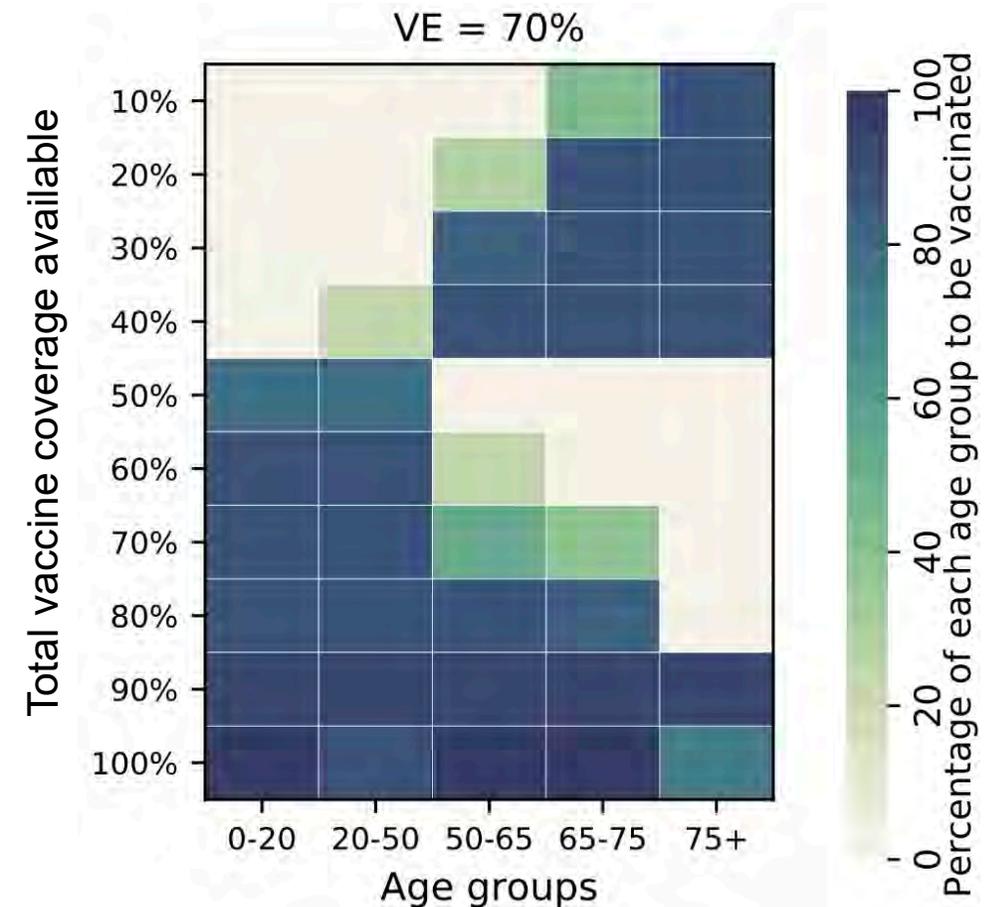
Highlight: initial findings and likely challenges (1)



Example 1: model of impact of targeting different age groups for vaccination in Belgium

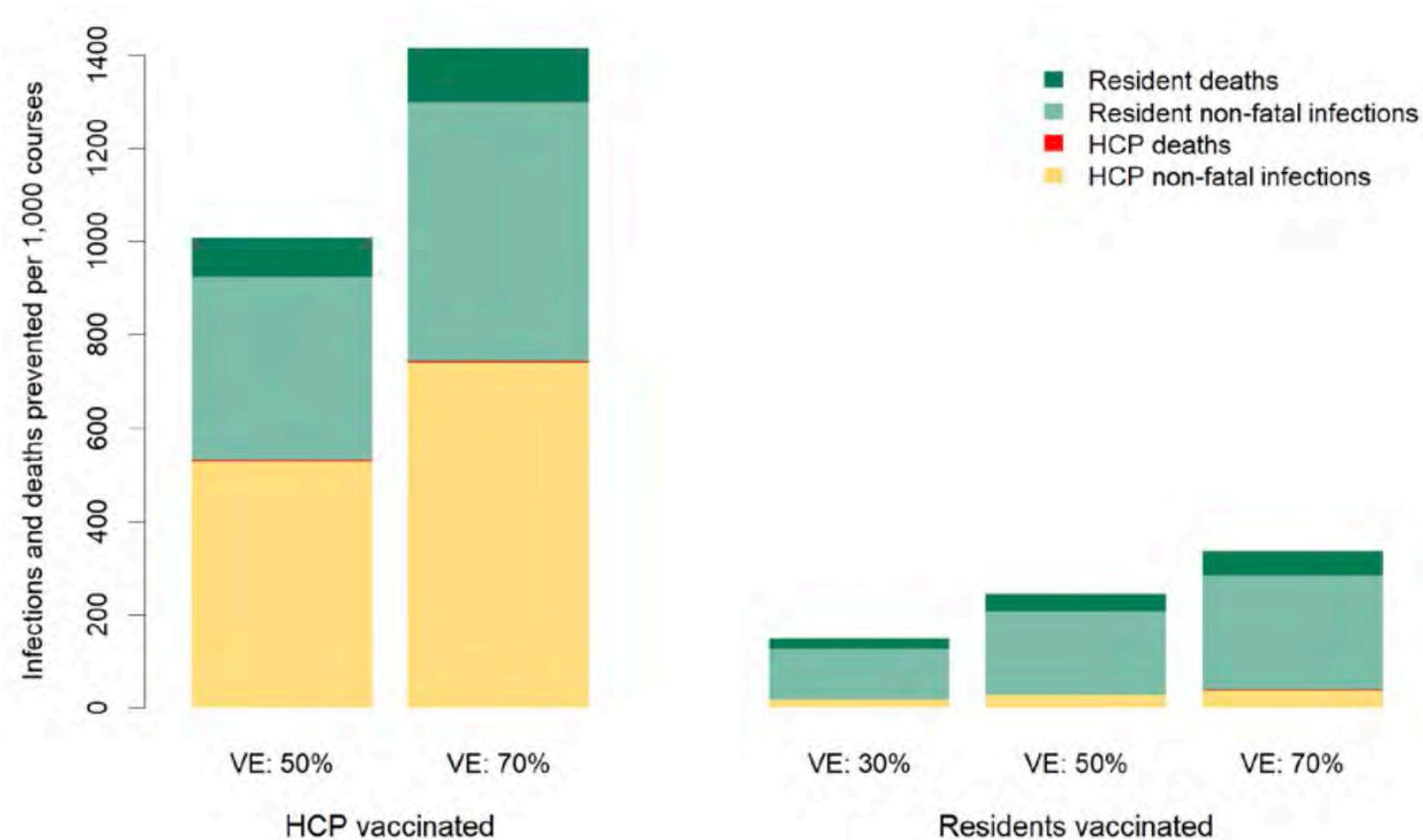
(Bubar et al. 2020 www.medrxiv.org/content/10.1101/2020.09.08.20190629v1)

Highlight: initial findings and likely challenges (2)



Example 4: model of optimal vaccine allocation by age as a function of supply (coverage) of US
(Matrajt et al. 2020 www.medrxiv.org/content/10.1101/2020.08.14.20175257v1)

Highlight: initial findings and likely challenges (3)



Summary

- Limited modelling results currently available across prioritized questions
- Available evidence skewed towards analyses of individual countries, high-income countries, vaccination prioritization by age group, epi outcomes
- More modelling work in the pipeline, including for multi-country, LMIC, and economic analyses
 - However, unlikely to be available to inform SAGE October meeting
- Gap in existing/pipeline work around modelling impacts of:
 - Prioritizing vaccination of essential workers (besides HCWs)
 - Vaccination prioritization scenarios on delivery of essential services besides health care (e.g., education, public safety) as an outcome
- Some key uncertainties around SARS-CoV-2 epidemiology and vaccine performance that may remain at the time a recommendation is made

Questions for IVIR-AC feedback (from agenda)

Are additional epidemiologic and economic model criteria needed?

What is IVIR-AC's advice on strategies to address knowledge gaps?

How could IVIR-AC support future review processes and quality of modelling?

**WHO Strategic Advisory Group of Experts (SAGE) on Immunization
Working Group on COVID-19 Vaccines:
Prioritized Infectious Disease and Economic Modelling Questions**

Request for Information

- As part of its scoping of the landscape of modelling groups and initiatives related to COVID-19 vaccines, we invite modellers and economists to provide information about their work on COVID-19 vaccination that addresses prioritized modelling questions to contribute to informing deliberations around policy recommendations from the WHO SAGE on Immunization.
- Groups are encouraged to share early stage and interim results for any of the questions as part of the ongoing process of evidence review, gap identification, and refinement of priority questions and scenarios.
- We particularly encourage models that have been fit to available epidemiological and/or economic data or validated through comparison with these data. Model review and future invitations to participate in presentations to the Working Group will be based on assessment of model performance and minimum standards as described in this document.
- Brief summaries of any completed work or work planned or underway for any question may be sent via email to the WHO SAGE Secretariat at: vaccineresearch@who.int.
- Initial responses are requested as soon as possible and no later than **4th September 2020** for consideration in initial reviews and deliberations. This will be an ongoing process of consultation with the modelling community and we will also be seeking input at later dates.

I. Background

- The Terms of Reference for the SAGE Working Group on COVID-19 Vaccines include:
 - Provide guidance for the development of prediction models to determine the optimal age groups and target populations for vaccine introduction and guide vaccine introduction for optimal impact, and contribute to updates of target product profiles of vaccines for outbreak and for endemic use;
- Recognizing the evolving landscape of evidence on SARS-CoV-2, COVID-19, and vaccine candidates, the Working Group has developed an initial set of prioritized modelling questions with the intent to help focus efforts in the modelling community towards results that would be useful in informing SAGE deliberations about any eventual specific vaccine candidates.
- The Working Group does not anticipate that all questions would necessarily be addressed by the same model or modelling group, as different modelling approaches may be needed for different questions. Modelling addressing any of the questions can contribute to the Working Group's deliberations.
- The prioritization of modelling questions reflects the Working Group's current understanding of:
 - the epidemiology of SARS-CoV-2 and COVID-19, the vaccine landscape, and possible vaccine supply and uptake scenarios;
 - the groups that have been proposed for possible prioritization for vaccination according to different public health objectives (e.g., reducing morbidity and mortality; reducing transmission; protecting essential services; minimizing economic and societal disruption);
 - the available models and data elements at this time (i.e., which questions may be most tractable to address first).
- The prioritization of questions or of analysis features does not imply any value judgment about how different public health objectives should be weighted, or any recommendation about which groups should be prioritized for vaccination under any given scenario.
- The scenarios provided are hypothetical and intended to facilitate (i) comparison across models, and (ii) exploration of the sensitivity of model results to different assumptions about key parameters. The scenarios are not intended as an endorsement of any particular vaccine or vaccination strategy, but rather to inform the Working Group and SAGE about the potential ranges of outcomes depending on scenario assumptions.
- None of the elements of this document – including questions, scenarios, key data, and analysis features – are official WHO or SAGE recommendations, nor do they have any legal or policy status.
- Given the rapidly evolving evidence base and dynamic policy and supply environment, the prioritized questions, scenarios, key data elements, and analysis features may be updated as new evidence and needs emerge.

II. Modelling Questions

Note: See “III. Initial Scenarios and Essential Data” for assumptions about vaccine characteristics, coverage, supply, analytic horizon, and target population definitions. See “IV. Analysis Features” for additional measures and analysis extensions of interest. Modelling groups are requested to consider sections III and IV in addressing the questions.

Health and epidemiological impacts

1. What would be the impact of vaccinating each of the following target groups on SARS-CoV-2 infections, COVID-19 deaths, and COVID-19 years of life lost, for vaccines given during 2020-21 when vaccination is added to counterfactual scenarios of: (i) no interventions, or (ii) continued implementation of non-pharmaceutical interventions (NPIs)?
 - a. older adults (50+, 65+ or 75+ years)
 - b. younger adults (18-49 years)
 - c. school-age children (5-17 years)
 - d. those at high risk of severe disease because of their underlying health conditions (e.g., cardiovascular disease, kidney disease; *see section III*)
 - e. key workers (e.g., workers in health and social care, teachers; *see section III*)
 - f. groups at high risk of infection (e.g., dense urban slums/informal settlements; *see section III*)
2. What are the optimal vaccination strategies in terms of target groups under different possible supply scenarios for COVID-19 vaccine during 2020-21 to achieve the maximum reduction in SARS-CoV-2 infections, COVID-19 deaths or years of life lost?
3. How would health impacts be distributed across country income groups (high, middle, low) and within countries across household wealth quintiles for the different vaccination targeting approaches described in Questions 1-2? (*Note: distribution of impacts across other social groups is also of interest; see section IV.*)

Economic and social impacts

4. What would be the impact on protecting essential services (e.g., health and social care, education) of the different vaccination targeting approaches described in Questions 1-2?
5. At what level of vaccine efficacy and vaccination coverage for which target groups could those NPIs that are most economically and societally disruptive (e.g., lockdowns, travel restrictions) be discontinued?
6. What would be the impacts in terms of economic welfare (e.g., as measured by GDP growth) and economic security (e.g., as measured by number of people living in poverty) of different vaccination targeting approaches (e.g., those in Questions 1-2) across country income groups (high, middle, low)?
7. From the societal perspective, what would be the cost-effectiveness per averted SARS-CoV-2 infection, COVID-19 death, and COVID-19 year of life lost for the vaccination targeting approaches described in Questions 1-2?
8. In monetary terms, what is the full public health and societal value of vaccination with a COVID-19 vaccine?

III. Initial Scenarios and Essential Data

Note: Initial scenarios are hypothetical and exploratory. Additional scenarios may be identified and requested as evidence and needs evolve.

Summary of scenario dimensions

Counterfactual scenario	Vaccine characteristics scenario	Coverage scenario	Supply scenario	Analytic horizon
I. No intervention	A. Efficacy vs. disease and infection*, all ages	1. High (80%)	a. COVAX	i. Short term (end-2021)
II. Continued NPIs	B. Efficacy vs. disease, all ages	2. Mid (50%)	b. COVAX + direct	ii. Medium term (end-2022)
	C. Efficacy vs. disease, younger ages only	3. Low (20%)	c. COVAX + direct (shared)	iii. Long term (end-2030)

*Vaccine protects against becoming infected and therefore being infectious to others (see "Vaccine characteristics" below).

Counterfactuals

- Vaccination scenarios should be implemented for each counterfactual (i.e., counterfactual vs. counterfactual + vaccination):
 - No intervention*: Assume no NPIs are in place and pandemic runs its course. This captures the value of vaccines that allow a return to 'normal' with no NPIs in place.
 - Continued NPIs*: Assume that there is continued implementation of NPIs that keep the effective reproduction number at its level prior to the introduction of the vaccine, potentially allowing for seasonal and herd immunity effects.
- As different approaches to modelling the effects of NPIs have been adopted, and as NPI implementation and effectiveness varies across countries, modelling groups should describe their methods and data sources for modelling NPI effects or justify their choice of a particular reproduction number(s) if NPIs are not explicitly modelled. Analyses that model the effects of different combinations of NPIs for different vaccination scenarios and epidemiological and country settings are desirable; see *IV. Analysis Features*.

Vaccine characteristics

- Scenario parameter values provided below with desired sensitivity analysis ranges in parentheses. For example, a 2-dose schedule would be the base case with sensitivity analysis of how results would change if a 1-dose schedule was administered.

Scenario	Schedule	Efficacy against COVID-19 (%)	Efficacy against SARS-CoV2 infection* (%)	Relative efficacy in 65+ age-group	Mean duration of immunity (years)
A. Efficacy vs. disease and infection, all ages	2 doses (1 dose)	70 (10-90)	70 (0-90)	1.0 (0.5-1.0)	1 (0.5-lifelong)
B. Efficacy vs. disease only all ages	2 doses (1 dose)	70 (10-90)	0	1.0 (0.5-1.0)	1 (0.5-lifelong)
C. Efficacy vs. disease only, younger ages only	2 doses (1 dose)	70 (10-90)	0	0.3 (0-0.5)	1 (0.5-lifelong)

*Protection against infection and therefore infectiousness to others. Vaccines may protect against COVID-19 disease but not against becoming infected and potentially being infectious to others. Explicit modelling of differential infectiousness of breakthrough infections among vaccinated individuals is desirable; see *IV. Analysis Features*.

Vaccination uptake and coverage

1. *High uptake*: 80% coverage of the target group. Follow “greatest benefit” prioritization within target group up to the supply constraint; if supply is insufficient to cover 80% of target population, prioritization in order of “greatest benefit” (e.g., highest impact age range, highest risk comorbidity, highest exposure to infection) within the target population up to the supply constraint.
 2. *Mid-range uptake*: 50% coverage of the target group. Follow “greatest benefit” prioritization within target group up to the supply constraint.
 3. *Low uptake*: 20% coverage of the target group. Follow “greatest benefit” prioritization within target group up to the supply constraint.
- For Question 1, it is anticipated that vaccination coverage scenarios would be implemented individually for each target group (e.g., 80%/50%/20% coverage in children vs. 0% coverage in other age groups). For Question 2, it is anticipated that analyses would consider different coverage levels across combinations of target groups.
 - Vaccination uptake and coverage assumptions are intended to serve as proxy measures of the intersection of other critical underlying variables related to: (i) programmatic feasibility of vaccination delivery (e.g., available delivery platforms, cold chain requirements, human resource requirements, feasibility of identifying/accessing the target population), and (ii) vaccine acceptance and demand (e.g., knowledge, attitudes, perceptions, values, norms, intentions, behaviours of potential vaccine recipients, caregivers, and providers). Analyses specifically exploring the effect of these supply and demand variables on coverage are desirable; see *IV. Analysis Features*.

Supply

- All supply scenarios are hypothetical and exploratory. Analyses exploring the sensitivity of results to different supply scenarios (e.g., earlier vs. later) are encouraged. Supply scenarios may also consider buffer stock (e.g., 5%) and wastage rates (e.g., 15%).

Supply scenario	Total by end-2021	Incremental availability by end of quarter* (millions of doses)					Distribution across countries (LIC: low-income, LMIC: lower-middle-income, UMIC: upper-middle-income, HIC: high-income)
		2020	2021				
		Q4	Q1	Q2	Q3	Q4	
a. COVAX Facility	2 B doses	100	100	400	600	800	<ul style="list-style-type: none"> • Assume 90 LICs + LMICs, and 76 UMICs + HICs participating • 3% of total population initial allocation target among participating countries • Additional supply tranches allocated as available based on countries' share of phase I cumulative allocation target of 20% of total population among participating countries
b. COVAX + direct country procurement	4.25 B doses	400	400	800	1200	1450	<ul style="list-style-type: none"> • COVAX scenario assumptions + • Self-procuring HICs: 1.15B doses • Self-procuring MICs: 1.10B doses
c. COVAX + direct country procurement (shared)	4.25 B doses	400	400	800	1200	1450	<ul style="list-style-type: none"> • COVAX + direct scenario + • Self-procuring HICs allocate excess doses to MICs and LICs (e.g., through COVAX Facility) after achieving their coverage scenario target for target groups (for target groups with unmet coverage targets in MICs/LICs)

*Assume that dose availability in each quarter is equally distributed over the 3 months of that quarter.

Analytic horizon

- Defined as the timeframe over which benefits from vaccination during 2020-21 are counted (e.g., years of life saved).
 - i) short-term (from Q4 2020 to end-2021);
 - ii) medium-term (from Q4 2020 to end-2022);
 - iii) long-term (from Q4 2020 to end-2030).

Vaccine and vaccination delivery costs

- Economic evaluations should explore a range of potential vaccine prices across country income groups (high, middle, low) and report assumptions used.
- Economic evaluations should describe their assumptions about the delivery modality used (e.g., facility-based, outreach, campaign) and data sources used for delivery cost estimates, with consideration for how the context of COVID-19 affects delivery costs.

Prevalence of comorbidities by age

- Ideally, use estimates published in Clark, A., et al. (2020). "Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study." The Lancet Global Health.

Key worker groups

- Examples of possible groups below without any order of priority. Note that these show some overlap with groups at high risk of infection but modelled separately as rationale for prioritization for vaccination is different.
- Analyses should specify definitions and data sources used.
- In the absence of detailed data, when considering vaccine supply constraints, analyses may make the simplifying assumption that workers in health and social care are 3% of the total population and other essential workers are up to an additional 5% of the total population.
 - Workers in health care
 - Workers in care homes and other social care
 - Teachers, childcare providers
 - Emergency response and public safety personnel
 - Sanitation, including sewage and garbage removal
 - Utility workers (e.g., water, electricity, gas, communications)
 - Public works and infrastructure maintenance/repair workers
 - Transportation workers
 - Food and agriculture workers
 - Retail workers for provision of food and essential goods (e.g., pharmacies, medical supplies, fuel)
 - Critical banking/financial services workers for processing and maintaining access to currency and payments
 - Mortuary services
 - Critical manufacturing of essential goods (e.g., medical equipment, supplies)

Groups at high risk of infection

- Examples of possible groups below without any order of priority. Note that these show some overlap with key worker groups but modelled separately as rationale for prioritization for vaccination is different.
- Analyses should specify definitions and data sources used.
- In the absence of detailed data, when considering vaccine supply constraints, analyses may make the simplifying assumption that workers in health and social care are 3% of

the total population and other essential workers are up to an additional 5% of the total population.

- Workers in health care
- Workers in care homes and other social care
- Emergency response and public safety personnel
- Those living in dense urban slums or informal settlements
- Refugees, internally displaced persons

Provision of essential services

- Examples of possible outcomes below without any order of priority. Analyses should specify definitions and data sources used.
 - Healthcare system capacity (as measured by hospital beds, ventilators, high-flow oxygen, Intensive Care Unit (ICU) beds in settings where applicable) is not exceeded due to COVID-19 caseload.
 - Proportion of students able to access primary and secondary education (may be operationalized through different measures, e.g., as inverse of proportion of learners affected by country-wide school closures as measured by UNESCO).

IV. Analysis Features

Essential:

Feature	Questions for which most relevant
● Differences in COVID-19 severity by age	Q1-2
● Different vaccine profiles	All
● Separate analyses for high-, middle- and low-income countries or country groups	All
● Uncertainty and sensitivity analysis to model parameters	All
● Counterfactual analysis	All

Desirable:

(in no particular order)

Feature
● Indirect (herd) effects of vaccination (including consideration of acquired immunity and its variation across countries) and age-dependent transmission risk
● Differences in COVID-19 severity by comorbidities, ideally stratified by age
● Additional health, social, and economic outcome measures, e.g., <ul style="list-style-type: none"> ○ COVID-19 cases, hospitalisations, cases with long-term sequelae, years lived with disability, DALYs, SEYLL; ○ SARS-CoV-2 infection averted per dose; COVID-19 death averted per dose; COVID-19 YLL averted per dose; ○ Excess deaths and years of life lost due to the COVID-19 pandemic generally; ○ In GNI, poverty gap, GNI per capita, income inequality, employment
● Potential reduction in infectiousness of breakthrough infections among vaccinated individuals
● Potential differences in vaccine efficacy against mild or severe/fatal COVID-19 disease

<ul style="list-style-type: none"> • Risk/benefit analysis for vaccines with hypothetical risks of adverse outcomes (e.g., vaccine-associated enhanced disease) at different frequencies
<ul style="list-style-type: none"> • Health system capacity (ventilators, ICU beds) and available therapies and non-vaccine pharmaceutical interventions (e.g., therapeutics, monoclonal antibodies) that may affect the infection fatality rate (IFR)
<ul style="list-style-type: none"> • Distribution of impacts across social groups (e.g., gender, rural/urban, race/ethnicity)
<ul style="list-style-type: none"> • Impact of vaccinating seropositives, and potential impact of pre-vaccination serological testing and exclusion of seropositives from vaccination
<ul style="list-style-type: none"> • Impact of inclusion/exclusion of pregnant women from groups eligible for vaccination
<ul style="list-style-type: none"> • Effect on coverage, cost, and cost-effectiveness of different programmatic delivery assumptions (e.g., delivery platforms such as facility-based, outreach, campaign; cold chain availability; human resource requirements) and how this may vary among countries
<ul style="list-style-type: none"> • Effect on coverage of different vaccine acceptance and demand assumptions and how this may vary among countries
<ul style="list-style-type: none"> • Scenarios exploring impacts of combinations of different COVID-19 vaccines with different characteristics
<ul style="list-style-type: none"> • Effects of different combinations of NPIs for different vaccination scenarios and epidemiological and country settings
<ul style="list-style-type: none"> • Cost-effectiveness analyses conducted from other perspectives (e.g., health system, government)
<ul style="list-style-type: none"> • Sensitivity analysis of results to potential viral mutation and antigenic change
<ul style="list-style-type: none"> • Detailed analysis of exemplar country(ies) that have good epidemiologic data
<ul style="list-style-type: none"> • Implementation of models or model results in interactive software that can be used in countries by decision makers to explore scenarios

*Responses received from **20 unique modelling groups** across academic, industry, government, and multilateral organizations willing to share information on their work with SAGE Working Group on COVID-19 Vaccines*

Prioritized question(s) that modeling group work addresses	Modeled geography by country income group*				
	HIC	HIC (MIC/LIC)	MIC	HIC/MIC/LIC	Total
Q1a) Health impacts: vaccinating older adults	6	5	2	5	18
Q1b) Health impacts: vaccinating younger adults	6	5	2	5	18
Q1c) Health impacts: vaccinating school-age children	6	5	2	5	18
Q1d) Health impacts: vaccinating those at risk due to comorbidities	4	2		3	9
Q1e) Health impacts: vaccinating key workers	2	1		1	4
Q1f) Health impacts: vaccinating those at high risk of infection	3	3	1	1	8
Q2) Optimal vaccination strategies to minimize adverse health impacts	4	5	2	4	15
Q3) Equity of health impacts across countries & wealth quintiles				2	2
Q4) Vaccination impact on essential service provision	1		1	1	3
Q5) Optimal vaccination strategies to minimize disruptive NPIs	5	5	1	3	14
Q6) Vaccination impact on economic welfare (GDP, poverty)	3			4	7
Q7) Cost-effectiveness of vaccination	4	1	1	4	10
Q8) Full societal and public health value of vaccination	3	1	1	2	7

*HIC (MIC/LIC) refers to models that currently are for only a high-income country setting but could be applied to other MIC/LIC settings.

Session 3:
WUENIC 2.0

WUENIC 2.0: Shaping the vision and scope

Problem Statement

Since the establishment of the current approach to produce WHO/UNICEF Estimates of National Immunization Coverage (WUENIC), immunization schedules, data availability, coverage levels and estimation techniques/tools have changed significantly. The immunization programme has gone from targeting infants to targeting the life-course, with more vaccines being used. Use-cases of WUENIC have also expanded beyond the traditional monitoring of performance of national immunization programmes (NIPs) over time and production of global/regional summary statistics. New use cases include a demand for national estimates suitable for performance-based financing decisions¹ and identifying year-to-year very fine (small) changes in coverage over time as well as small area estimates at subnational levels. This has led to challenges in producing “credible” estimates of national immunization coverage on an annual basis that satisfy the needs for *all use cases* or at least several of them.

This document provides some background on the current WUENIC methodology (referred in this document as WUENIC 1.0) and the context around the revision of WUENIC 1.0. More importantly, this document shall guide WHO and UNICEF on defining the scope and vision for the next phase of WUENIC (i.e. WUENIC 2.0).

This document is not meant to provide detailed guidelines, but rather an opportunity to clarify the role that WUENIC 2.0 should play in the next decade within the existing immunization data ecosystem.

WUENIC 1.0 (From 1999 to now)

WHO and UNICEF have been jointly producing national immunization coverage estimates for over 20 years. A brief description of the methodology and current immunization data ecosystem is provided in this section. The limitations and challenges discussed go beyond the WUENIC methodology to address the whole process (e.g. parallel estimates, need and sources of funding, expectations from partners including for subnational data, use of the estimates). This information provides the backdrop for the next phase of developing WUENIC 2.0.

Methodology

Prior to 1998, both UNICEF and WHO² separately published immunization coverage data as reported by Member States, without a formal review of these data. In 1998, an unexpected decline in the population-weighted global coverage for the most recent period was observed. This prompted a detailed review which revealed that coverage data from household surveys, rather than from national routine administrative reports were reported for India, Indonesia, and Bangladesh which accounted for this large drop in coverage. In 1998, after considering the three following options, SAGE recommended the 3rd option which started WUENIC development.

¹ Examples: <https://www.mcc.gov/>;

² WHO disseminates health statistics under its constitutional mandate to provide ‘epidemiological and statistical services’ and ‘information...and assistance in the field of health’.

1. Continue monitoring vaccination coverage by the current method [i.e., reporting coverage data as it came from countries]
2. Discontinue [global] monitoring vaccination coverage
3. Continue monitoring with increased resource investment to improve the completeness, accuracy and precision of vaccination coverage estimates [from their origin at country level].

WUENIC 1.0 methodology is an annual process driven by WHO and UNICEF. WUENIC 1.0 fundamental approach is comprised of a triangulation of reported country immunization coverage data, independent assessment of results (which is for the most part review of survey data reports) and additional information (e.g. stock-outs, data quality assessments, socio-economic, conflict or other “shocks”). As new data become available, the entire time-series is revised, consistent with other UN agencies. The approach is rule-based which means that estimates are derived from deterministic rules and no stochastic or probabilistic approach is involved. Furthermore, expert-based opinion is used to overrule automatic decisions if deemed not reflective of the national situation for a given vaccine-dose and year e.g. unreasonable change of the denominator which significantly affects coverage. In practice, WHO and UNICEF conduct an annual critical review of all data on a country by country basis to produce these estimates and associated Grade of Confidence (GoC)³ for each country-vaccine-year estimate. The process also includes consultation with 195 countries (Boerma 2015⁴: the country consultation process provides a platform for member states to understand how estimates are derived, and for UNICEF and WHO to identify additional data sources that can be used to improve the accuracy of estimates). During the consultation period (mid-May to June), the draft estimates are sent to countries for an additional input that UNICEF and WHO may have missed. At the end of the process, WHO and UNICEF provide descriptions of the data, decisions and disseminate final coverage estimate results.

Limitations / Challenges

As previously mentioned, WUENIC 1.0 is rule-based (not probability-based) which leads to no quantitative measure of uncertainty for the estimates. Depending on the use case, the lack of quantitative measure of uncertainty may limit the ability to monitor progress or change over time or across geographies.

While the current process includes a consultation with countries, and the WUENIC working group uses that opportunity to support countries to improve their official estimates, the quality of the input data (admin data and often times survey data also) remains a challenge⁵. The current approach provides minimal support to countries to improve their official estimates which are a critical input to the WUENIC methodology; though support is provided by WHO, UNICEF and partners as a separate activity.

The fact that the WUENIC working group is limited to UNICEF and WHO is a recognized limitation, especially given the expert-based nature of the rules. The WUENIC working group shares publicly all the expert-based decisions made for the estimates; however, it is reasonable to think that transparency can be improved by

³ Grade of Confidence (GoC) is a qualitative measure, with three categories, on the WHO/UNICEF estimates.

⁴ Boerma T, Mathers CD. The BMC Med. 2015 Mar 10;13:50. doi: 10.1186/s12916-015-0286-7.

⁵ Harrison et al. Factors Limiting Data Quality in the Expanded Programme on Immunization in Low and Middle-Income Countries: A Scoping Review. Vaccine 2020; Cutts et al. Monitoring vaccination coverage: Defining the role of surveys. Vaccine. 29;34(35):4103-4109. doi: 10.1016/j.vaccine.2016.06.053; SAGE Data WG Report 2019.

opening the WUENIC group to other experts (e.g., UN-IGME is comprised of a broader group of experts beyond WHO and UNICEF).

There are adjustments and thresholds that have been set for WUENIC 1.0 that are also subjective, e.g. systematic recall-bias adjustment. While, these adjustments and thresholds are often small (possible) issues in the grand scheme of things and decisions that are subject to debate, they are nonetheless seen as potential limitations of the current methodology. For vaccines beyond infancy, data are limited though WUENIC is still produced for MCV2⁶. Additionally, there is a perception that WUENIC 1.0 could use other data/information such as more detailed stock data and disease surveillance data to improve the estimates. Whether such data would provide marginal improvements, requires further assessment and may depend on the use case at hand.

Sustainability of the current method, which is time and labor-intensive, is an increasing challenge.

- A small working group of WHO/UNICEF staff are expected to maintain, refine and implement the current method. The ability of this group to manage the workload depends in part on the number of antigens that need to be reviewed, and the amount of data sources received per country.
- The number of antigens for which estimates are produced has increased. It went from estimating five vaccine-doses (i.e. BCG, DTP3 Polio3, MCV1 and HepB3) to 14 in 2017.
- The amount of data received and reviewed is large and increasing.
- Annual timelines between receiving and vetting data and the production of coverage estimates are very narrow vis-à-vis current staffing levels at headquarters and regional office levels.

The communication of the current WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) methods have remained a challenge, despite several attempts at documenting them (QUIVER, papers, regional and country activities, etc.).

- Current formalized WUENIC process ends with the production of estimates, but more could be done to better visualize the data and translate these data into action at the global, regional and national level.
- [GATHER](#) – where current WUENIC meets most criteria, except for comparison with “other models” and providing quantitative uncertainty

Context and use cases

WUENIC revision (ongoing). Since 1999, WUENIC has been reviewed in 2009 and 2011 by QUIVER; and 2020 is a review year. However, contrary to previous revisions, during 2020 the current methodology will be assessed against alternative statistical methods. The revision has involved the following steps:

- Call for proposals for alternative approaches (under IVIR-AC guidance⁷) launched in 2019 and three modelling approaches, plus a stakeholder analysis to be available in Q1-2020.

⁶ HPV estimates have started to be produced using a different methodology given the vaccination schedules and recording practices. [IVIR-AC](#) endorsed this approach in 2019.

⁷ [Immunization and vaccines related implementation research advisory committee \(IVIR-AC\)](#)

- Three institutions (WorldPop, Swiss Tropical Public Health Institute (TPH) , Imperial College London with LSHTM) are developing alternative statistical models for producing national immunization coverage estimates⁸.
- Swiss Tropical Public Health Institute (TPH) conducted a stakeholder analysis to better understand uses cases and needs from stakeholders, and to inform their model.
 - The results of this analysis are being considered to refine WUENIC 2.0 use-cases
- WHO and UNICEF are planning a formal consultation⁹ to better define parameters for evaluating the alternative models and deciding if and how, or under what conditions, WHO and UNICEF can complement or replace their current WUENIC approach.
 - Following the consultation, a costed roadmap towards an improved estimation process and/or approach, based on the criteria proposed in the consultation and recommended by IVIR-AC will be produced and implemented.
- The aim is to implement the new or revised methodology or approach, i.e. WUENIC 2.0, in 2021.

IHME immunization coverage estimates. IHME produces annual estimates for some but not all vaccine-doses included in WUENIC 1.0 and the release schedule is different from WUENIC. For example, in May 2020, IHME will release estimates for 1980-2019, but 2019 estimates will be forecasted data, while in July 2020, WHO and UNICEF will release estimates from 1980-2019 including reported data available for 2019. More formal *information exchange* has started with IHME.

Subnational immunization data. Since 2016, WHO and UNICEF collect district level administrative immunization coverage data through the joint reporting form (JRF) at the global level. At this point, the data are not used in the WUENIC process. In-country WUENIC-like exercises have been conducted to improve the countries' official coverage estimates¹⁰. With the equity agenda, subnational level monitoring goals and other subnational strategies, there is a high interest in further using subnational immunization coverage data.

Use cases

Regional / Global Monitoring framework. WUENIC is used in several regional and global monitoring frameworks as listed below. In some cases, WUENIC has been used to help make financial decisions; despite SAGE's advice to "use caution" in interpreting the coverage estimates for performance-based financing¹¹.

- Sustainable Development Goals (SDG)
 - Note on SDG Monitoring guiding principles: Country-owned, strengthening ability of countries to produce health statistics
 - Call for subnational disaggregation

⁸ As of 25 Feb 2020, full proposals and outputs have been received from Swiss TPH and Imperial College London.

⁹ Under the guidance of IVIR-AC and with participation of other groups that produce estimates, including UNAIDS HIV estimates, the UN Inter-Agency Group for Child Mortality Estimation (IGME), etc plus immunization partners and the modelling groups working on vaccination coverage estimates.

¹⁰ India (2015), Indonesia (2017), Pakistan (2018), Ethiopia (2018), Cote d'Ivoire (2019), though only India and Pakistan were able to use this exercise to revise subnational estimates and the official coverage reported to WHO and UNICEF.

¹¹ Meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization. Weekly Epidemiological Record, No. 1, 6 January 2012. <https://www.who.int/wer/2012/wer8701.pdf?ua=1>

- Framework for global initiatives
 - End of Global Vaccine Action Plan (GVAP)
 - Beginning of IA2030 and Gavi 5.0
- [Millennium Challenge Corporation \(MCC\)](#) uses DTP3 and MCV1 to access countries' eligibility

Impact on VPD occurrence

- Used to relationship between service delivery and disease occurrence
- Input to diseases burden estimates, and measles risk assessment

Used in other models

- For example the model used by Gavi's Secretariat for vaccine demand forecasting, especially for new vaccines

Advocacy

- Used for advocacy purposes by WHO, UNICEF and other stakeholders

National level and other uses

- It is unclear how much WUENIC is used in different countries. From the Swiss TPH stakeholder survey, WUENIC use cases are mainly supra-national.
- Forecasting performance

Important Considerations

- UN call for Universal Access to Information
- WHO position on country data: "country data belongs to countries" (WHO in EB Feb 2020)
- Ability to implement modern statistical procedures has improved significantly in recent years (open-source statistical packages, new statistical methods [example Gaussian processes], computing power, etc.). Modeling approaches widely used for other health estimates, big data
- There might be a need to produce state/province level estimate for large countries
 - But under which criteria (top 10 larger birth cohorts? only low-middle income?)

WUENIC 2.0

As noted above, WUENIC 1.0 preceded the creation of GAVI (now Gavi, the Vaccine Alliance) in 2000. At the time, national immunization coverage was lower for most countries and certainly at regional and global levels. There were fewer household surveys and limited availability of microdata. There were fewer vaccines on the national immunization agendas recommended by WHO and only a handful vaccine-doses coverage rates were initially produced then expanded over the years. Timelines of producing estimates were less stringent.

Today the immunization landscape is very different and considering the current context, there is an opportunity to revisit the WUENIC 1.0 estimation approach and guiding principles (see Annex A for more details on the guiding principles). In the process of shaping WUENIC 2.0, it may be useful to try to address or take a stand on a couple of fundamental questions. These includes:

1. **Shall WHO and UNICEF keep the full ownership of WUENIC?** The answer to this question is more complex than yes or no; many options are possible with pros/cons for each. The current model may raise transparency questions while a fully externally driven process can lead to coordination, resources, and country ownership issues. Something in between may make sense.
2. **Should WUENIC 2.0 focus on estimating annual performance or predict trend / average coverage?** Essentially, this question is about the level of smoothing. Is it more important to reflect annual performance or trend over years? Some of these annual performances are due to specific shocks (e.g. conflict, strikes, stockouts, etc.) impacting the health system. Stochastic approach can also incorporate most of these shocks (especially if forecasting is not of concern); however, it will require incorporating systematically the shock information in the model - which means an effort should be put at augmenting the availability and use of covariates.
3. **What additional input data are needed and how should they be incorporated into the model?** One additional source of input data for the estimation is vaccine supply data, but other data could also be incorporated e.g. socio-economic or conflict information. For this to happen, a significant investment needs to be made in streamlining the acquisition, processing, understanding and use of these external data sources. Some of the models do use proxies related to socio-economic, development and conflict information and there are consequences to doing so, particularly in the absence of such data and borrowing across country boundaries.
4. **What is required to achieve strong country support to improve official estimates?** Regardless of the methodology used for WUENIC 2.0, better official data from countries, both from administrative systems and surveys, will improve the estimates. However, to continue and increase support/technical assistance to countries to produce these data and develop further skills will require a significant investment. Under WUENIC 2.0, it should be a priority to design and dedicate resources to country support strategies that considers countries' situations (e.g. large countries, countries with significant data quality issues, etc.); this is consistent with SAGE recommendations.
5. **What to do with the subnational immunization coverage data?** Other groups use pixel level modeling to obtain subnational coverage e.g. 100m by 100 m level modelling. Given the instability of the health district definitions and the use of pixels for modeling, how should the collection of district level administrative coverage data be continued? The uses of these data by WHO and UNICEF and partners should be clarified.
6. **What should WHO and UNICEF do to improve the communication and use of WUENIC?** In order to effectively communicate coverage estimates, it is critical to identify and understand the needs of the different audiences/users. But also, it is important to be clear on purpose and limitations of WUENIC and, in general, issues around accuracy of coverage estimates, as no gold standard exists¹².

As mentioned at the beginning, the goal for this paper is to start the discussion on what is the vision for WUENIC 2.0. In the context of IA2030 and Gavi 5.0, WHO and UNICEF with the partners, should set the scope for WUENIC 2.0, define the collaboration framework with all the partners, and identify resources for delivering relevant immunization coverage estimates for the next decade.

¹² Re-stated by IVIRC-AC in 2019, and the SAGE Data WG in its 2019 report, which was endorsed by SAGE in Oct 2019.

Annex A. WUENIC 1.0 guiding principles.

- Coverage estimates are meant to reflect immunization system performance (which is different from estimation of burden of disease) – not immunity. There is no supplementary immunization activity (SIA) performance included.
- Produce coverage estimates for all WHO and Member States, and aggregates to various regional groupings and global levels
 - No exclusion of small populations, or income-level, or countries in conflict, for example
- Produce an estimate for each country, vaccine-dose, year, if vaccine in national immunization schedule and coverage data for that vaccine-dose reported to WHO/UNICEF at least once
 - No nowcasting/forecasting
 - If no data reported for a vaccine-dose year, interpolation or extrapolation used
- No borrowing data from another country (country-specific) ¹³
- No use of covariates
- No smoothing of data (deciding on what data to take, instead of feeding data to a model to estimate based on errors, etc.)
- Produce consistent trends and patterns
- Entire time series is revised in light of new empirical data
- Consideration of “local knowledge” (but only using empirical data to inform the estimates, e.g.: accepting decreases in coverage if info available on stock-outs, adverse events that affected confidence, etc.; not increasing coverage “only because a programme is making good efforts”)
- Assuming reported data “are innocent” unless evidence of otherwise (thresholds of 10% to challenge reported data)
- Reported and survey data are “visible”
- Natural language documentation of working group decisions (decisions are stored as text in the WUENIC database)

¹³ With the one small exception of the observed relationship from countries with survey data for DTP1 and DTP3 to help inform the production of DTP1 estimates in the absence of reported DTP1 data or reported DTP1 coverage that is greater than that for DTP3.

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WHO - WUENIC

Modelling Approaches to Produce Estimates of National Immunization Coverage

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Abbreviations

AIC	Akaike Information Criterion
BID	Better Immunization Data (Initiative)
BMGF	Bill and Melinda Gates Foundation
CI	Confidence interval
CSO	Civil Society Organisation
DHS	Demographic and health survey
DHIS	District health information system
DTP	Diphtheria Tetanus Pertussis
EPI	Expanded Programme on Immunization
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GVAP	Global Vaccine Action Plan
HIC	High-income country
HMIS	Health management information system
IHME	Institute of Health Metrics and Evaluation
IHMR	Institute of Health Management Research
IQR	Interquartile range
IVB	Immunization, Vaccines and Biologicals (Department)
IVIR-AC	Immunization and vaccines related implementation research advisory committee
JRF	Joint Reporting Form
LMIC	Low- and middle-income country
MAE	Mean Absolute Error
MCV	Meningococcal conjugate vaccine
MICS	Multiple indicator cluster survey
NGO	Non-Governmental Organisation
NITAG	National immunisation technical advisory group
PATH	Program for Appropriate Technology in Health
PCV	Pneumococcal conjugate vaccine
RITAG	Regional immunisation technical advisory group
RMSE	Root Mean Square Error
SAGE	Strategic Advisory Group of Experts
SCIH	Swiss Centre for International Health (of Swiss TPH)
SDI	Socio-demographic index
Swiss TPH	Swiss Tropical and Public Health Institute
UNDP	United Nations Population Division
UNICEF	United Nations Children's Fund
VPD	Vaccine-preventable disease
WAIC	Widely Applicable Information Criterion
WHO	World Health Organization
WUENIC	WHO/UNICEF estimates of national immunization coverage

1 Introduction

National estimates of vaccination coverage are crucial to inform countries and international organisations about the performance and equity of vaccination programmes. In 2018, the WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) were evaluated against the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) [9]. The WUENIC process met most criteria except those relating to formal model comparison and measuring of uncertainty. Together with the the development of new statistical methodologies, this underpins the case for revising the WUENIC methodology. This report is a response to the resulting call for new modelling approaches for national-level immunization coverage estimates issued by WHO in early 2019.

We believe that any attempt to improve a method to produce vaccination coverage estimates has to consider at its core the issues determining the credibility of the estimates produced, including the subjective perspectives of users. In other words, the impact of a new statistical approach or data sources will be reduced unless WHO, UNICEF, Gavi, countries' programme managers and other stakeholders are convinced that the outputs of the new method are worthwhile to use. The well-documented data quality issues affecting administrative and survey estimates [10] leading to their cautious and narrow use by the above-mentioned stakeholder groups illustrate this dynamic.

The issue of credibility can be faced in three different ways: by understanding the key factors that increase credibility among users (e.g. timeliness of the estimates, a sense of accuracy); by taking into account users' perspectives in the design of statistical models (e.g. incorporating variables that are important to users); by accompanying the estimates with user-friendly explanatory materials that make the estimates more transparent and understandable by users. In this work we develop and combine these strands.

The three components of this project are: (i) a survey to understand the stakeholders' perceptions and expectations regarding models and estimates of vaccination coverage ; (ii) development of two novel models to estimate coverage; and (iii) a survey to understand how stakeholders use the existing estimates, including their views on data quality. Taken together, these components contribute to achieving the goal of credible worldwide vaccination coverage estimates. Accompanying the report is a set of estimates and graphs for each country, and the code.

2 Survey approach and dissemination

2.1 Stakeholders surveys

There were two stakeholder surveys. The first aimed to inform the development of a model to estimate vaccine coverage, and the second contained components on data quality and decision-making. The survey content is detailed in the following sections. The questionnaires were designed iteratively with feedback from WHO and piloted among members of Swiss TPH for clarity and technical issues.

2.1.1 Stakeholder identification and survey dissemination process

The process of stakeholder identification and dissemination comprised several steps, each building on the other to achieve the greatest reach:

- 1. Identification of primary immunization stakeholders and events.** Topic specific newsletters (e.g., Global Immunization News) were screened and Google searches conducted to identify relevant stakeholders.
- 2. Use of professional networks (personal and institutional).** Contacts within networks were approached to seek direction on reaching diverse stakeholders across organisations (e.g., NESI, Sabin, John Hopkins, European Vaccine Initiative, PATH, BMGF, MCC, Save the Children). In the first instance, personal emails were sent, followed by snowballing actions depending on responses. Requests were also made for contacts to disseminate the surveys within their own organisations and across professional networks at their discretion.
- 3. Liaison with project sponsors (WHO and UNICEF).** To give greater weight to the request to complete the surveys, an introduction letter, endorsed by WHO and UNICEF, accompanied the survey links as an attachment. Further, given the sponsors access to global stakeholders and leadership role at key meetings (i.e., SAGE, GVAP, IVIR-AC, IHMR), it was agreed that sponsor channels would be most appropriate to support dissemination to some stakeholders (i.e., Gavi, WHO and UNICEF). This was particularly important for reaching key stakeholders working more at the implementation level such as EPI managers and national and regional immunisation technical advisory groups (NITAG / RITAG). Accordingly, the sponsors highlighted the existence of the surveys and primed attendees to receive it. Additionally, the Director of the IVB sent out a request for action from her personal account.
- 4. Use of online media platforms.** The surveys were posted on several immunization-specific sites (i.e., BID, Technet-21) as well as personal (LinkedIn) and organizational (Swiss TPH) platforms. It also featured in the *Immunization Economics* newsletter (Dec 2019).
- 5. Survey design.** The first survey included an option for respondents to be contacted again about the project. This served as a considerate way of establishing an immediate access point with consent to support the dissemination of the second survey and for any future work requiring direct contact for specific enquiry (e.g., expert interviews).

2.1.2 Circulation dates

The first survey, comprising component 1 with a focus on modelling, was launched on 17th October 2019 and remained open until 31 January 2020.

The second survey, comprising components 2 (data quality) and 3 (decision making), was launched on 16th December 2019 and remained open until 31 January 2020.

2.1.3 Total number of responses

At 31 January 2020 the response rates were as follows: survey 1: 84, and survey2: 512.

3 Findings from survey 1 to inform modelling

This survey focused on understanding users' perspectives on key components of the credibility of estimates, data sources and their perception of the underlying methods. This information was then fed into the development of a model with the aim of producing credible, transparent, straightforward and objective vaccine coverage estimates.

There were four areas: (i) a sense of who the users are and their knowledge of statistical methods (ii) how they use estimates and what characteristics are important for them, (iii) how credible they find estimates and whether specific changes to methods or data sources would improve or decrease credibility, and (iv) responses to a plot of data sources and estimates for 2000-2017 for a specific country which they know well. The country-specific questions were aimed at eliciting more concrete feedback and included items about specific changes to current practice. We included options to leave comments throughout the survey.

3.1 Responses

There were 84 respondents by 31 January 2020 working in a range of roles including health programme managers, NGO/CSO, aid organizations and academia (Table 1). The most common focus was national (n=26, 31%), with a range from districts/municipality to worldwide. The majority reported that they focused on LMICs (n=68, 81%), and could understand proportions or regression models.

Table 1. Characteristics of the respondents of the modelling component of the stakeholder questionnaire.

<i>Which role best describes your current work related to vaccination?</i>		
Health care practitioner	6	7%
Health programme manager	14	17%
Policy/decision maker	7	8%
NGO/ CSO	13	15%
Bilateral aid/Multilateral organization	12	14%
Academia	17	20%
I do not work directly in vaccination	8	10%
<i>Other:</i>		
Consultant	3	4%
Accountability & integrity in use of funds	1	1%
Private foundation/philanthropy	1	1%
US government	1	1%
Private for-profit entity	1	1%
<i>What is the geographical scope that best describes your current work related to vaccination?</i>		
District/municipality	13	15%
Region within a country	13	15%
National	26	31%
Multi-country	15	18%
Worldwide	15	18%
I don't work in vaccination/None	2	2%
<i>Which of these country categories best describes your current work?</i>		
Low and middle income countries	68	81%
High income countries	6	7%
Worldwide	10	12%
<i>How would you rate your understanding of statistics?</i>		
None – I have no statistics training	0	0%
Basic – I understand proportions	31	37%
Intermediate – I understand regression models	46	55%
Advanced – I understand machine learning	7	8%

The most commonly stated reason for using vaccine coverage estimates was to assess vaccine programme performance (n=71, 85%) (Table 2), followed by decisions on implementing interventions for vaccine coverage.

Table 2. Reason for using vaccination coverage estimates.

<i>What are the most common reasons for you to use national vaccination coverage estimates? (choose up to three)</i>		
<i>Percentage is percentage of respondents stating item</i>		
To make decisions on implementing (or to stop) interventions to increase vaccine coverage	51	61%
To make decisions on funding or providing resources (or stop) at any level of the system	25	30%
To assess vaccination programme performance	71	85%
To assess health systems performance	29	35%
To assess equity in vaccination	26	31%
To describe time or geographical trends	34	40%
I don't use vaccine coverage estimates	1	1%

The most frequently stated trusted sources were DHS surveys (75%) and WUENIC estimates (73%), followed by MICS and EPI surveys (Table 3). If an estimate had not been trusted, the most frequent response was to use local knowledge (51%), although a combination of local knowledge and estimates was also reported. The most common reasons for not trusting a vaccine estimate were unreliable data (61%), followed by uncertainty in the estimate and lack of transparency in the method. Several comments were articulated for this question covering the lack of objectivity of expert opinion, the quality of denominators and sudden changes in the coverage that could not be explained.

Table 3. Trust in vaccine coverage estimates.

<i>Which source(s) of national vaccination coverage estimates do you trust? (if specific reports, articles or papers, please use the 'other' option to provide reference to them) choose all that apply (Percentage is percentage of respondents ticking each box)</i>		
WUENIC (WHO/UNICEF estimates of national immunization coverage)	61	73%
Administrative (health management information system – HMIS)	28	33%
Demographic and health surveys (DHS)	63	75%
Multiple indicator cluster surveys (MICS)	50	60%
Extended programme on immunization surveys (EPI)	49	58%
Other surveys	10	12%
Published papers	12	14%
Grey literature	1	1%
Other:-IHME	1	1%
I don't trust any	1	1%
I am not sure	1	1%
<i>If there was an occasion when you did not trust an estimate, what did you do? (percentage of those who did not trust an estimate)</i>		
Made a decision based on local knowledge or my own experience	36	51%
Made a decision based on any estimate, hoping that it is more or less right	12	17%
Assumed the correct value is somewhere between the two extremes	16	23%
This has never happened to me	14	-
search for other estimates/contact the source	4	6%
other	2	3%
<i>Think of the last time you did not trust a national vaccine estimate. Why did you not? (percentage of those who did not trust an estimate)</i>		
Because I could not check it against local knowledge	12	17%
The method to produce the estimate was not explained	15	21%
The method to produce the estimate was explained but it was too complicated	6	9%
The data sources were not reliable/not available	43	61%
The estimate was uncertain (there was a wide range of likely values)	19	27%
There has never been a time when I did not trust the available estimate(s)	14	-
Other	8	10%

The estimates used by the respondents were chosen most commonly because they used reliable data sources (Table 4), but also because they were official, accurate and the methods appropriate. Timeliness, user-friendliness and availability were less common reasons given. Comments for this question indicated that estimates which are presented in the same way for all countries can facilitate

comparisons, and that the choice can depend on the context, with existing national data sometimes preferred for in-county planning due to political considerations. The most important characteristics of the estimates themselves were accuracy (81%) and timeliness (71%), followed by completeness, precision and user-friendliness (between 40 and 50%) (Table 4). While timeliness was considered an important characteristic, it was not a common decider on which estimates to use. The respondents reported that they required a high level of accuracy. This suggests a need for a measure of uncertainty for the estimates. The most frequently stated important characteristics of the statistical methods were that they could be understood (61%) and done by an international organization (60%). Using the most sophisticated methods was less frequently mentioned (n=10, 12%). Comments included concerns that the estimates should allow sudden increases or decreases rather than being too smooth, that the source was less important than credibility and rigour, that the surveys should have been analysed using best practices, and that the method for estimates should be reproducible and reflect the limitations of the input data.

Table 4. Characteristics of estimates and methods.

<i>Why do you choose the estimates that you use? (choose up to three)</i>		
<i>Percentage is percentage of respondents stating item</i>		
They are the most 'official'	43	51%
They are the most widely available	25	30%
They are produced in a timely manner	15	18%
They are the most accurate ones	39	46%
The methods used are appropriate	41	49%
They use reliable data sources	53	63%
They are very user-friendly	9	11%
<i>Which of the following criteria for estimates of vaccine coverage are the most important to you? (choose up to three) – number & percentage of respondents choosing each item</i>		
Completeness (there is no missing data in the sources used)	41	49%
Precision (range of likely values is not too wide)	35	42%
Accuracy (estimates are close to the real values)	68	81%
Timeliness (estimates are available when decisions need to be made)	60	71%
User-friendliness (method is easy to understand)	34	40%
<i>How accurate (close to the true value) do you need the estimates to be in practice?</i>		
I need a rough idea of the coverage	9	11%
I need the estimate to be within 10% of the true value	15	18%
I need the estimate to be within 5% of the true value	28	33%
It depends how close the estimate is to a threshold	30	36%
Other: depends on use	2	2%
<i>What is most important to you for the statistical methods to estimate national vaccine coverage estimates? (choose up to three) number & percentages of respondents choosing item</i>		
That it has been done by an academic institution	28	33%
That it has been done by technical staff from the countries	29	35%
That it has been done by an international organization (eg WHO, UNICEF)	50	60%
That I can understand the details of the method used	51	61%
That the most sophisticated methods have been used	10	12%
Other	-	-

The administrative data was most commonly considered to be of some use as a data source with few saying that it was either the best source (20%) or of little use (10%) (Table 5). It was stated that it could reflect sudden changes in coverage due to interventions by 46% of respondents. Comments indicated that administrative data was often used especially when there were no surveys, that it depended on the country context, and that it had challenges in both numerator and denominator at different levels. The most frequent response to a way to reconcile administrative and survey data was to adjust administrative data using both survey data and country characteristics (n=39, 46%). Comments to this question indicated that the degree of discrepancy gave a feel for accuracy, that further triangulation with stock-out data or outbreaks may be possible, and that the best method may depend on what it was needed for.

Table 5. Use of administrative data.

What are your views on using administrative data (HMIS) to get national vaccination coverage estimates for LMICS? (choose up to two) percentage of respondents choosing item		
It is the best source for vaccination estimates	17	20%
It is an acceptable source of vaccination coverage data	50	60%
It can be used if adjusted using statistical methods	39	46%
It can reflect changes due to specific interventions to increase coverage	39	46%
It is generally of little use	8	10%
I don't know	6	7%
Administrative data from the HMIS tend to differ from surveys (eg DHS, MICS). What approach to reconcile these data sources seems most credible to you?		
Use administrative data and then adjust it using survey data	17	20%
Use administrative data and adjust it using country characteristics	10	12%
A combination of the previous two	39	46%
Just show the data from different sources for the users to choose	13	15%
I don't know	1	1%
Other	4	5%

For the remaining questions, the respondents chose a country from the list available that they knew well. They were then presented with a graph of the administrative data, WUENIC estimates, survey data, and estimates from a series of simple models with differences in data sources and model structure. The countries chosen were in Africa, Asia and Eastern Europe (Table 6).

Table 6. Choice of country for country-specific questions.

<i>Choose a country that you are familiar with</i>			
Burkina Faso	2	Indonesia	1
Congo DRC	2	India	9
Cote d'Ivoire	5	Lao People's Democratic Republic	3
Guinea	1	Nepal	3
Lesotho	1	Pakistan	1
Liberia	3	Serbia	2
Kenya	2	Ukraine	23
Malawi	1	I am not familiar with any of the listed countries	
Mozambique	2		
Nigeria	15		
South Africa	2		
Tanzania	2		
Uganda	3		

Some questions had the majority of respondents answering in the same way, and others were divided (Table 7). Clearer majorities were found for including country characteristics in the model, for including admin data in the model and for using subnational data. Respondents were divided over whether to use UN denominators, to restrict survey data to DHS and MICS only and to use stock-out data. A comment suggested that a composite measure was seen as being generally better.

The range of scores for the credibility of WUENIC estimates on a scale of 1 to 5 was 2 to 5, with the most frequent responses of 4 (52%) and 3 (26%). Comments indicated that the availability of surveys, time trends and dispersion were used as criteria for judging credibility. A further comment said that historically adjusting WUENIC using the latest survey estimates had led to a decrease in credibility in the past.

Table 7. Feedback on a specific country.

<i>In your view, does using UN denominators represent an improvement over the administrative denominators? (n=55)</i>			
	Yes	34	56%
	No	19	31%
	I don't know	8	13%
<i>In your view, is restricting the survey data used to DHS and MICS an improvement?</i>			
	Yes	28	46%
	No	29	48%
	I don't know	4	7%
<i>In your view, is including data on stock-outs an improvement over the base model?</i>			
	Yes	36	59%
	No	20	33%
	I don't know	5	8%
<i>In your view, is the omission of country characteristics an improvement over the base model?</i>			
	Yes	12	20%
	No	42	69%
	I don't know	7	11%
<i>In your view, is the omission of administrative data an improvement over the base model?</i>			
	Yes	8	13%
	No	48	79%
	I don't know	5	8%
<i>How credible do you find the WUENIC estimates for your country?</i>			
	1 (low credibility)	0	0%
	2	7	11%
	3	16	26%
	4	32	52%
	5 (high credibility)	6	10%
<i>Would the use of subnational (disaggregated) data improve coverage estimates?</i>			
	Yes	47	77%
	No	5	8%
	I don't know	9	15%

Respondents suggested additional data sources (Table 8). These included national and sub-national sources of denominator data and variables which inform the numerator.

Table 8. Additional data sources.

Are there any other data sources that should be included (please specify)?

Surveillance and outbreak data

Health data in DHIS

Product consumption, stock data

Published information and desk reviews

Provincial level data (maybe unreliable if few HW at lower levels)

Specific country surveys (eg SANDoH, LSIS)

Field surveys by institutes

Sub-national survey data

Documented doses rather than recall-based surveys

Local denominator estimates, migration and displacement data, school attendance data

Private sector

Comments indicated that the quality of surveys can change from year to year.

3.2 Implications for the model development

The survey results suggested that:

There was a wide-range of survey respondents with different views. Estimates were most commonly but not only used for assessing vaccination programme performance. Trends as well as year-specific vaccination coverage were used.

Reliable data sources were considered important for credibility. No data source was universally trusted but DHS surveys were the most frequently trusted source. Including more types of data sources was perceived to lead to better estimates in general: there was a majority for including country characteristics, administrative and survey data in the model. Respondents were divided over whether to use UN denominators, to restrict survey data to DHS and MICS only and to use stockout data.

Accuracy was considered desirable. The reported required accuracy was greater than is likely to be possible with available data, underscoring the need for a measure of uncertainty.

Appropriate methods were considered important for credibility. Respondents wanted to understand the methods but use of the most sophisticated methods was not desired. The majority of respondents reported that they had basic or intermediate statistics knowledge (understanding proportions or regression). Distrust was due to perceived political motivation and lack of transparency or objectivity. The time trends should not be 'too smoothed'.

4 Modelling vaccination coverage

4.1 Overall approach to modelling and major design choices

4.1.1 Choice of statistical framework

The respondents to the modelling component of the stakeholder survey prioritized transparency over sophistication when it comes to the method of producing vaccination coverage estimates. The

majority rated their statistical expertise as intermediate, which was defined as understanding regression models. Accordingly, we have based our modelling on the regression framework. It is an established and extensively studied method for relating a dependent variable to a set of predictor variables by means of an explicit equation. Estimates of uncertainty of the predictions, a requirement of the project, are easily extracted from regression models in the form of confidence intervals. Because the stakeholders identified surveys as the most reliable source of vaccination coverage estimates, we used survey estimates as the dependent variable in our models.

Machine learning techniques are a credible alternative to regression modelling for complex predictive tasks. Indeed, they have been used to generate estimates of vaccination coverage at a subnational level [1]. They are particularly adept at discovering non-linear effects and interactions between variables, which in regression models have to be pre-specified by the modeller. The downside of machine learning is that the model predictions lack transparency, in the sense that it is difficult and sometimes impossible to investigate how a given prediction was built from the input variables. In addition, few machine learning algorithms produce robust and easily interpretable estimates of the uncertainty of the predictions. We have therefore decided against using machine learning except for a single, narrow task: analysis of the Joint Reporting Form data (Section 4.5).

4.1.2 Selection of predictor variables

Given the requirement to generate estimates for all WHO member states, we considered only the predictor variables that are available for an overwhelming majority of the 195 countries for the 2000-2017 period. This restriction prevented us from using promising variables measuring socioeconomic development and health system functioning, such as Gross Domestic Income or Ante-Natal Care coverage, and many other variables previously associated to vaccination coverage [2]. One possibility to still include them would be to use multiple imputation, a standard method for dealing with missing data. We have ultimately decided against it because there would still be countries where all variables are missing and imputation is not possible, and because we expected the distribution of missing values to be highly non-random, which adversely impacts the quality of imputation [3].

4.1.3 Model evaluation

Throughout model development, we used graphs to understand how the estimates were responding to different data inputs. To choose between competing models in an objective manner we relied on formal measures of fit. Our primary measure was the Akaike Information Criterion (AIC), which balances predictive performance against model complexity, and its Bayesian analogue, the Widely Applicable Information Criterion (WAIC). Where appropriate, we corroborated our decision with secondary goodness-of-fit measures such as the Root Mean Square Error (RMSE), Mean Absolute Error (MAE) and pseudo- R^2 . Occasionally we selected a less well-fitting model if we judged that doing otherwise would introduce undesirable artefacts that threatened the credibility of estimates. Section 4.5 contains an example of this type of reasoning.

4.1.4 Two sets of estimates

The first model we built is the base regression model. This model combines data from all countries and uses general relationships between predictor variables and coverage surveys to produce estimates of vaccination coverage. The main advantage of the base model is that all the available data can be used at once and thus countries ‘borrow strength’ from each other. However, this model also has the disadvantage that when predicting coverage and characterizing uncertainty for a specific country and year, surveys from that country do not carry any more weight than surveys from another country and in other years. To address this issue, we devised a second set of estimates (the “focal” estimates), by combining the surveys for the specific country with the predictions of the first model refitted without the surveys in question. In this way, the focal model adds more weight to the country-specific surveys but the general predictor-survey relationships still guide estimation where the surveys do not exist or have substantial variability between them.

4.1.5 Data sources

As our source of survey estimates, we used the dataset compiled by the WUENIC working group and published on the WHO webpage^a. We applied similar inclusion criteria as the working group, described in **Annex 1**.

We identified three major sources of potential predictor variables which meet our requirement of availability for almost all countries since 2000. The first is the above-mentioned WHO webpage, from which we obtained the coverage reported by countries (website sections 4.1 and 4.2), the Joint Reporting Forms (JRF; section 5.1) containing multiple immunization-related indicators, and the years of vaccine introduction (section 6.2).

The second source of data is the Institute of Health Metrics and Evaluation (IHME), and in particular the 2017 Global Burden of Disease (GBD) study^b. From GBD 2017 we obtained estimates of infant mortality rates, which are both a proxy for the overall development and functioning of the health system and directly related to vaccination since they include deaths from vaccine-preventable diseases. We downloaded also the estimates of mortality from conflict and terrorism, identified by previous work [4] as a significant predictor of vaccination coverage. A third variable we sourced from IHME is the Socio-Demographic Index, which is a composite measure of socioeconomic development subsuming income, schooling and fertility of the country’s population. The IHME variables are not available for eight WHO member countries: Cook Islands, Monaco, Nauru, Niue, Palau, St. Kitts & Nevis, San Marino and Tuvalu.

From the World Population Prospects produced by the United Nations Population Division (UNPD)^c we collected the estimated total population, population density, urbanisation and live births time series. The latter in combination with the infant mortality rates from IHME allowed us to derive the number of surviving infants, which we used as an alternative target population (“UN denominator”)

^a https://www.who.int/immunization/monitoring_surveillance/data/en/ (section 4.7)

^b <https://ghdx.healthdata.org/>

^c <https://population.un.org/wpp/>

when analysing the administrative coverage data. We also used UNPD's classification of countries into six continents.

Data cleaning and pre-processing procedures are described in detail in Annex 1.

4.1.6 Computing tools

Our main requirements regarding computing environment were mature support for Bayesian computation, ease of data manipulation and visualisation and reproducibility. For these reasons we used Stan^a v2.17, a state-of-the-art, open-source Bayesian computation platform, and R 3.5.1^b, a freely available statistical programming language. We relied on the following additional R packages: brms 2.7.0 and rstan 2.17, front-ends to Stan; tidyverse 1.2.1 for data manipulation and graphics; glmmTMB 0.2.3, implementing beta regression in the faster frequentist framework, which we used for rapid model prototyping; randomForest v4.6.14, implementing the machine learning algorithm that we used to analyse the Joint Reporting Form data; and countrycode v1.1.0 to translate between different country coding and naming schemes. Parallel computations were performed at the sciCORE cluster of the University of Basel^c.

The readme.txt file included in the code repository contains guidelines to help reproduce our work as well as a snapshot of our computing environment.

4.2 The base model

Our main model is a beta regression. We chose the beta distribution as a flexible, general approach to modelling of proportions [5]. Another natural choice is the binomial distribution, but we found it to be overly confident in the precision of survey estimates (cf. Section 4.6: Recommendations and lessons learnt). We considered all vaccines together in a single model in order to better estimate the intrinsic survey and country effects, and especially the strength of agreement between the administrative data and survey estimates in each country.

The dependent variable in our model were the coverage estimates from surveys; Table 9 below gives the independent variables (predictors). Using AIC, we determined that replacing administrative denominators with those from UNPD results in a better-fitting model. This agrees with the perception of 59% of survey respondents who thought that UNDP denominators would be an improvement. We have also compared alternative country groupings: WHO regions and the GBD regions, but we found the UN-based classification of countries into six continents to be the most predictive. We decided *a priori* to use the administrative data instead of official government estimates for better comparability to WUENIC, the possibility of swapping denominators and because the published official data is artificially converted to 0-100%. This choice was vindicated in the sense that the equivalent model built on official data exhibited worse fit.

^a <https://mc-stan.org/>

^b <https://www.r-project.org/>

^c <https://scicore.unibas.ch>

Table 9. Predictor variables included in the base model.

Variable	Values	Source
survey type	categorical: DHS, MICS, EPI, other	WHO/UNICEF
continent	categorical: Africa, Asia, Australia, Europe, North America, South America	UN PD
vaccine	categorical: DTP1, DTP3, MCV1, MCV2, PCV3	WHO/UNICEF
years since introduction	integer 0-4, with 4 standing for "4 or more"	WHO/UNICEF
logarithm of population density	continuous, positive	UN PD
percentage of population living in urban areas	continuous, 0-100	UN PD
socio-demographic index (SDI)	continuous, 0-1	IHME
under-1 mortality rate	continuous, positive	IHME
mortality from conflict and terrorism over the last 10 years	discrete 0-10, with 1-10 denoting the decile among the country-years with conflict and terrorism mortality	IHME
reported coverage (reported numerator / UNPD denominator)	continuous, positive	WHO/UNICEF
reported DTP1-3 dropout (based on UN denominator-corrected DTP1 and DTP3 coverage as above)	continuous, positive	WHO/UNICEF

For all continuous variables except the reported coverage we tested using AIC whether including a square term improved the model, which would be an indication of a curved non-linear relationship. Square terms were retained for infant mortality and SDI. We tested also interactions between the continent and most other variables to allow for regional differences in the associations; interactions with the vaccine, logarithm of population density and urbanization were retained. We modelled between-country and between-survey differences not captured by the predictor variables as random effects.

The administrative coverage enters the model as a predictor whose strength varies by country. In countries that show good agreement between survey and administrative data, the administrative data becomes a strong predictor, and the model predictions are sensitive to changes in administrative data. In contrast, where the agreement of survey and administrative data is weak, the model reacts weakly to changes administrative data when generating predictions or ignores them altogether. For eight countries^a, an inverted relationship was found, meaning that the predicted coverage decreases with growing administrative coverage. In each of these cases the effect was of negligible magnitude and statistically insignificant.

The inclusion of the category of survey (DHS, MICS, EPI and "other") in the model revealed that EPI and "other" surveys report higher coverage on average than DHS and MICS. It is possible that these surveys are conducted in countries or times of higher coverage more often than DHS or MICS. Nevertheless, in light of this difference, we decided to calibrate model predictions to DHS level. We

^a From more to less strongly inverted: Sudan, Djibouti, Zimbabwe, Ethiopia, South Africa, Cameroon, Chad and Afghanistan.

chose DHS rather than MICS because the stakeholders perceived DHS as the most reliable data source, but in fact we found no meaningful statistical differences between MICS and DHS in any of our models and analyses.

Lastly, we found that the variability of survey estimates differs between countries. In order for this variability to be accounted for during fitting and reflected in the confidence intervals, we modelled it by specifying a separate equation for the precision parameter of the beta distribution. The predictors used in this part are the vaccine in question, its administrative coverage, the survey category and the continent. A random effect for each country was also included.

4.3 The focal model

The base model described above produces transparent and credible coverage estimates by relating survey estimates to predictor variables across all countries. This approach has the drawback that coverage estimates of a particular vaccine from a survey in a particular country are not prioritized when producing model estimates for that country and vaccine. As a result, the confidence interval around the base model estimate may be wide even when a reliable survey such as a DHS exists for that country-vaccine combination in the given or neighbouring year.

To address this, we devised a Bayesian procedure for combining the predictions from the base model with surveys for a specific country and vaccine, resulting in a second set of estimates, which we term the focal estimates. The approach was as follows: for every country-vaccine combination with at least one survey estimate between 2000 and 2017, we first refitted the base model omitting these surveys. We then took the predictions from this refitted base model as our prior belief about coverage and combined it with the omitted survey estimates by applying the Bayes rule. Each previously omitted survey entered this computation together with an estimate of its own precision, which was also taken from the refitted base model. The refitting step is essential to avoid using survey estimates twice in the process, which would lead to an artificial narrowing of the confidence intervals.

Each survey in a given year is also informative for the neighbouring years for the same country-vaccine combination. To propagate information back and forward in time when generating the focal estimates, we used the exponential decay covariance structure. We also tested the first-order autoregressive (AR1) structure as an alternative, obtaining near-identical results.

4.4 Estimates of vaccination coverage

Our models were built on a dataset of 1809 survey estimates from 468 individual eligible surveys in 119 countries. We generated base model estimates for 761 country-vaccine combinations and focal estimates for 417 combinations. The estimates were produced for every year between 2000 to 2017 if the vaccine was introduced in the whole country before 2000. For vaccines introduced after 2000, estimates were produced for the year of introduction and every year thereafter. The complete dataset of estimates as well as country-vaccine specific plots are included with this report. We only provide here a high-level overview of results and guidelines for interpretation.

4.4.1 Interpreting both sets of estimates: DTP1 in Niger and MCV1 in Azerbaijan

Using DTP1 coverage in Niger and MCV1 in Azerbaijan, we illustrate the features of both models, introduce our country graph and give an example of how to interpret both sets of estimates. The graphs in Figure 1 and Figure 2 contain four lines: the solid black line shows the administrative coverage reported by the country; the dotted black line is the WUENIC estimate (2018 revision); the green line is the base model estimate and the red one is the focal one. 95% confidence intervals are shown for both models, and the existing survey estimates are plotted indicating the type of survey.

Figure 1. Example of country output: Niger.

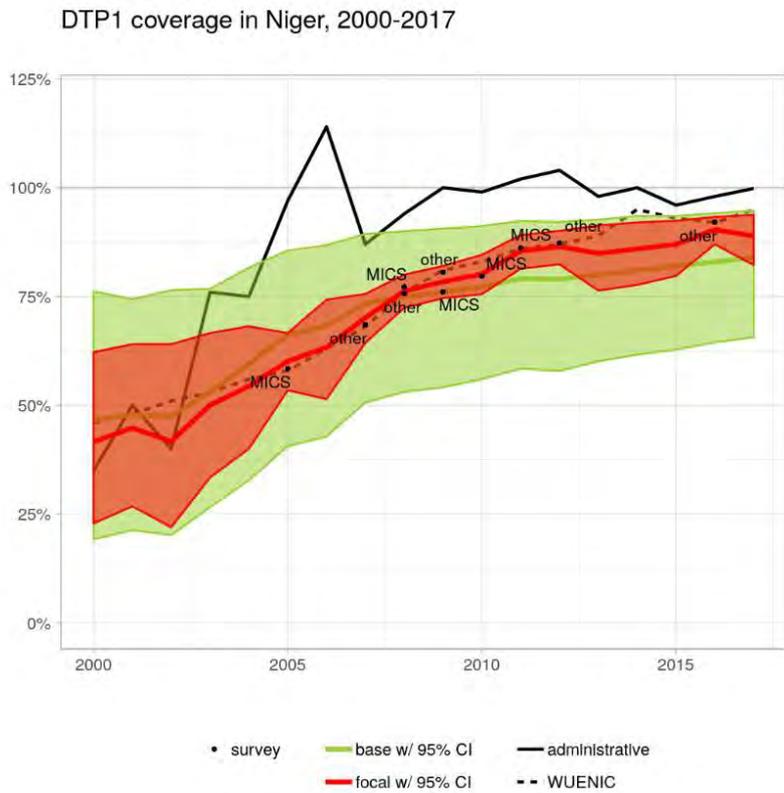
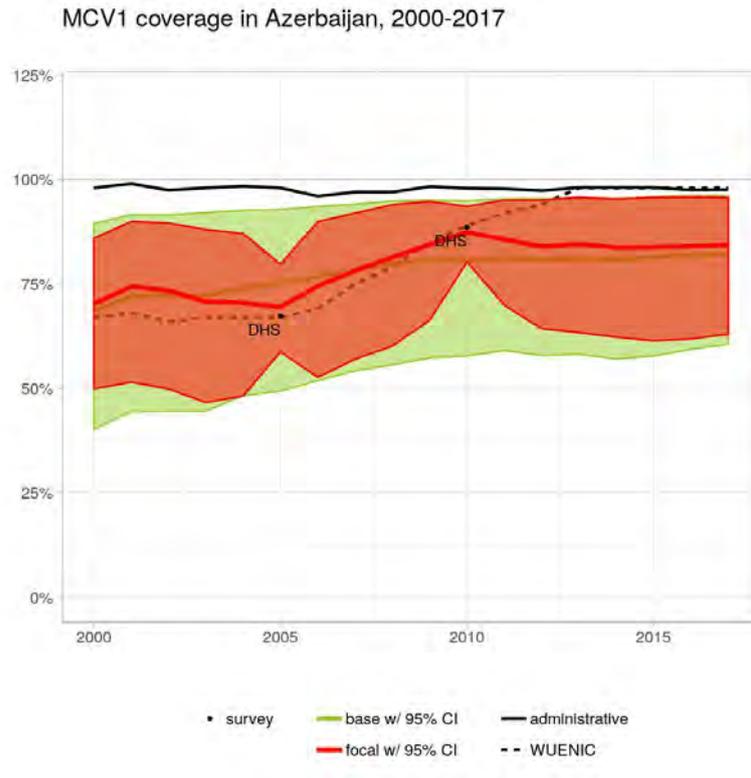


Figure 2. Example of country output: Azerbaijan.



The base estimates form a relatively smooth time trend and have a relatively large uncertainty. The focal estimates follow the surveys closely and the resulting trend is more jagged. The confidence band of the focal estimate is narrower, but the uncertainty grows in the periods without surveys. These features, shared by our estimates for most country-vaccine combinations, are direct consequences of the design of both models. The considerable uncertainty of the base model reflects our limited ability to predict vaccination coverage only from administrative data and country-level indicators when taking all countries together. The smoothness of the trend stems from small year-on-year changes in most of these variables. The focal estimates can change sharply if survey evidence does.

4.4.2 Most improved countries and comparison to WUENIC

Table 10 and

Table 11 show the five countries with the greatest increase in the coverage of each vaccine over the modelled period according to both models, with the WUENIC estimates included for comparison. As expected, the most improved countries according to our models are also recognised as such by WUENIC. A notable exception is the case of DTP1 coverage in Somalia, which has grown by over 34 percentage points between 2000 and 2017 according to the focal model but decreased by 5 points according to WUENIC. Our models disagree with WUENIC also about the magnitude of improvement in the coverage of MCV2 and PCV3 in a number of countries, with our models being generally more optimistic about the coverage in the introduction year.

Figure 3 and Figure 4 show all DTP3 estimates plotted against WUENIC, with the outlying country-years labelled. Our estimates tend to be lower than WUENIC, with the greater mass of points below the diagonal of the plot. This is partly a result of our models' calibration to DHS. Another reason is the WUENIC rule of accepting the administrative coverage if it is supported by another source within 10 percentage points. When this supporting source is a survey, it is often lower than the administrative coverage.

The DTP3 figures highlight a group of countries where our models perform poorly: the island nations of Western Pacific. As mentioned above, we do not have predictors available for several WHO member states from this region. This makes it hard for the model to capture how their unique geographical, demographic and socioeconomic circumstances interact with vaccination coverage. The dearth of reliable surveys in the region exacerbates the problem. Another notable disagreement with WUENIC is Syria, where our models seem to underestimate the potential effects of conflict in the country.

Table 10. Most-improved countries according to the base model.

Vaccine	Country	Period	Est. change (base model)	Est. change (WUENIC)
DTP1	Angola	2000-2017	+38.1 (41.1-79.1)	+17 (44-61)
	Niger	2000-2017	+37.3 (46.6-83.9)	+49 (46-95)
	Liberia	2000-2017	+35.1 (55.1-90.2)	+19 (80-99)
	Ethiopia	2000-2017	+33.7 (50.5-84.2)	+38 (47-85)
	Uganda	2000-2017	+33.0 (60.7-93.7)	+19 (80-99)
	Uganda	2000-2017	+51.8 (33.1-84.9)	+42 (52-94)
DTP3	Senegal	2000-2017	+44.5 (45.9-90.4)	+41 (52-93)
	Liberia	2000-2017	+42.4 (36.4-78.8)	+40 (46-86)
	Niger	2000-2017	+41.8 (26.6-68.4)	+51 (34-85)
	Sierra Leone	2000-2017	+39.3 (47.7-87.0)	+46 (44-90)
	Uganda	2000-2017	+47.6 (35.1-82.6)	+22 (57-79)
MCV1	Sierra Leone	2000-2017	+45.6 (41.0-86.6)	+43 (37-80)
	Senegal	2000-2017	+43.8 (46.3-90.1)	+42 (48-90)
	Niger	2000-2017	+38.7 (30.4-69.1)	+45 (37-82)
	Ethiopia	2000-2017	+38.3 (32.9-71.2)	+29 (36-65)
	Bangladesh	2012-2017	+60.9 (26.8-87.7)	+52 (41-93)
MCV2	Malawi	2015-2017	+35.8 (37.0-72.7)	+59 (8-67)
	Senegal	2014-2017	+35.5 (34.2-69.7)	+57 (13-70)
	Burkina Faso	2014-2017	+32.6 (35.8-68.5)	+48 (17-65)
	India	2011-2017	+29.8 (26.7-56.5)	+53 (27-80)
	Mauritania	2013-2017	+33.1 (45.7-78.8)	+76 (1-77)
PCV3	Liberia	2014-2017	+32.2 (42.2-74.4)	+41 (45-86)
	Togo	2014-2017	+31.3 (50.4-81.7)	+56 (34-90)
	Bangladesh	2015-2017	+31.1 (61.3-92.4)	+49 (48-97)
	Congo - Kinshasa	2013-2017	+29.0 (44.1-73.1)	+48 (31-79)

Table 11. Most improved countries according to the focal model.

Vaccine	Country	Period	Est. change (focal model)	Est. change (WUENIC)
DTP1	Niger	2000-2017	+47.3 (41.6-88.9)	+49 (46-95)
	Congo - Kinshasa	2000-2017	+36.9 (54.2-91.1)	+33 (49-82)
	Liberia	2000-2017	+36.8 (53.2-90.0)	+19 (80-99)
	Somalia	2000-2017	+34.6 (27.7-62.3)	-5 (57-52)
	Afghanistan	2000-2017	+32.3 (41.0-73.4)	+25 (48-73)
DTP3	Niger	2000-2017	+52.0 (23.9-75.9)	+51 (34-85)
	Senegal	2000-2017	+50.5 (41.6-92.1)	+41 (52-93)
	Uganda	2000-2017	+48.8 (35.3-84.1)	+42 (52-94)
	Comoros	2000-2017	+44.5 (39.8-84.4)	+21 (70-91)
	Liberia	2000-2017	+43.6 (36.4-80.0)	+40 (46-86)
MCV1	Sierra Leone	2000-2017	+48.1 (38.8-86.9)	+43 (37-80)
	Niger	2000-2017	+47.7 (26.9-74.6)	+45 (37-82)
	Uganda	2000-2017	+45.0 (37.4-82.3)	+22 (57-79)
	Guinea-Bissau	2000-2017	+42.9 (41.4-84.2)	+15 (71-86)
	Liberia	2000-2017	+40.8 (38.8-79.6)	+24 (63-87)
MCV2	Bangladesh	2012-2017	+47.9 (42.5-90.4)	+52 (41-93)
	Tanzania	2014-2017	+45.6 (35.8-81.4)	+50 (29-79)
	Philippines	2010-2017	+34.2 (37.1-71.3)	+36 (10-46)
	Burundi	2013-2017	+32.5 (51.3-83.8)	+24 (51-75)
	Belize	2005-2017	+26.5 (49.7-76.2)	+1 (87-88)
PCV3	Zimbabwe	2012-2017	+73.0 (12.3-85.3)	+68 (21-89)
	Ethiopia	2011-2017	+48.2 (20.7-68.9)	+56 (12-68)
	Nepal	2015-2017	+41.8 (48.1-89.9)	+75 (5-80)
	Ghana	2012-2017	+31.0 (64.1-95.2)	+56 (43-99)
	Côte d'Ivoire	2014-2017	+30.3 (47.7-78.0)	+80 (2-82)

Figure 3. Comparison of base DTP3 estimates to WUENIC.

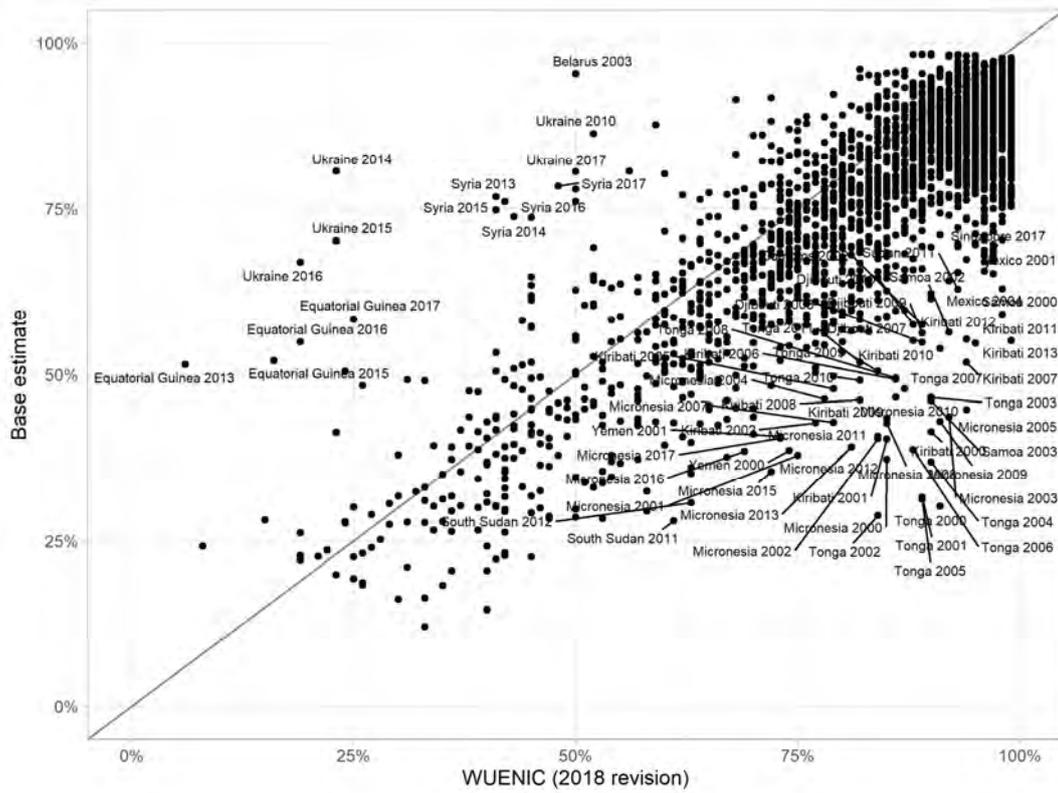
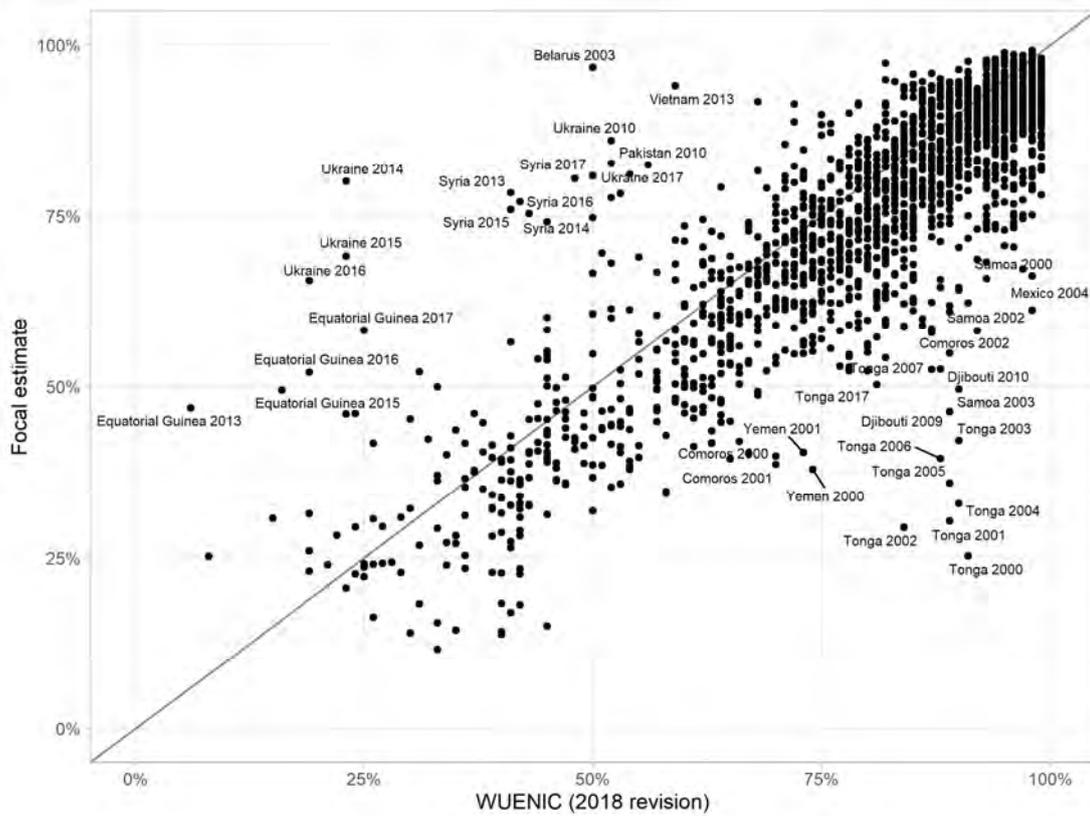


Figure 4. Comparison of focal DTP3 estimates to WUENIC



4.4.3 Countries without model estimates

We did not produce estimates for the following countries or categories of countries:

High Income Countries without administrative DTP1 data. Seventeen High Income Countries (HICs) did not report the administrative coverage of the first dose the DTP vaccine in the 2000-2017 period, and a further five reported in only one year^a. When administrative DTP1 coverage is undefined then so is the administrative DTP1-3 dropout, which is an important predictor in the base model. Model estimates can still be generated for these countries if DTP1 data is imputed, for example based on the DTP3 value. We did not do perform this step because it would bring no additional value to the overall goal of estimating coverage. In the countries in question, DTP1 coverage is very high, and the administrative data for the remaining vaccines seems reliable. In contrast, estimates from our base model would necessarily introduce considerable uncertainty for most of them due to the absence of surveys. We thus recommend basing the DTP1 estimate on the DTP3 coverage, and the coverage of the other vaccines on the administrative data.

Country-years without administrative PCV3 or MCV2 data. There are several countries where the administrative data for the recently introduced PCV3 or MCV2 vaccines is available for one year only or not at all. In these cases, we produced estimates only for the years where data exists. The affected countries are Algeria, Austria, Kyrgyzstan, Lebanon and Portugal (PCV3), and Cyprus and Djibouti (MCV2).

Countries with missing IHME predictors. The eight countries for which IHME-sourced predictor variables (i.e. SDI, infant mortality and mortality from conflict and terrorism) are not available are Cook Islands, Monaco, Nauru, Niue, Palau, St. Kitts & Nevis, San Marino and Tuvalu. We suggest treating San Marino and Monaco in the same way as the other HICs discussed above. The lack of data for the remaining six island nations is a genuine limitation and has the knock-on effect of weakening model performance for similar countries.

Thailand. Thailand does not report administrative DTP1 coverage. Estimates can be generated if this data is imputed, likely based on the official government estimates.

4.5 Analysis of JRF indicators

The indicators reported annually by member countries to WHO/UNICEF in Joint Reporting Forms (JRFs) are a potentially valuable source of information with which to improve the predictive performance of our model. The number of variables, the high degree of missing entries and the differences in reporting practices between countries are significant challenges that need to be overcome before this data can be used. To tackle them, we decided to use a machine learning algorithm to select the most promising indicators for inclusion in the base model. We chose random forests for this task due to the in-built notion of “variable importance” [6]. The measure of variable importance that we used was “percent increase in MSE”, which is the decrease in model

^a This section includes also Romania and Russia, which are not considered high-income countries currently, but to which our reasoning still applies.

accuracy when the values of the variable are permuted so as to destroy the association with the outcome.

Our JRF indicator scan procedure was as follows: first, we pre-selected 67 indicators which could plausibly measure strong determinants or correlates of vaccination coverage, and which have a consistent interpretation for all countries. Of these indicators, 24 were binary (yes/no) in nature and the rest were numerical, and most belonged to the “Vaccine supply” and “System performance” categories. To deal with missing entries, we discretized binary indicators into three categories: “missing”, “yes” and “no”, and numerical indicators into “missing”, “low” (bottom 50% of country-years) and “high” (top 50%). We then trained a random forest on these discretised indicators in addition to the same variables as the base model. Table 12 gives the 20 most important variables identified by the algorithm.

Table 12. The most important variables identified by the random forest.

Variable name	Variable meaning	Variable importance
U1M	infant mortality rate	0.540
dropout_un	reported DTP1-3 dropout, using UN denominators	0.470
vaccine	the vaccine in question (DTP1, DTP3, MCV1, MCV2 or PCV3)	0.302
admin_un	administrative coverage, using UN denominators	0.291
SDI	Socio-Demographic Index (IHME)	0.239
logPOP	logarithm of population (UN PD)	0.164
GSA_02155	DTP1-3 dropout rate	0.159
GSA_02148	% of districts with DTP1-3 dropout > 10%points	0.152
CAT10decile	mortality from conflict and terrorism over the last 10 years, discretised (IHME)	0.152
continent	the continent where the country in question is located (UN PD)	0.128
logDEN	logarithm of population density	0.121
GSA_02012	% of districts with DTP3 coverage less than 50%	0.119
URB	% of population living in an urban area (UN PD)	0.118
GSA_02018	% of districts with DTP3 coverage greater than 80%	0.094
GSA_02058	% of districts with MCV1 coverage less than 50%	0.079
survey_type	the survey category (DHS, MICS, EPI, other)	0.077
CATdecile	mortality from conflict and terrorism in the given year (IHME)	0.058
GSA_02070	% of districts with MCV1 coverage > 90%	0.054
GSA_02014	% of districts with DTP3 coverage between 50% and 80%	0.049
GSA_02024	% of districts with DTP3 coverage > 90%	0.046

We chose to investigate further the GSA_02012 (% of districts with DTP3 coverage below 50%) and GSA_02058 (same but for MCV1) indicators. The reason was their clear interpretation and direct relation to coverage, and the fact that the other indicators highlighted by the random forest related to DTP1-3 dropout, for which we had a direct measurement. As expected, the inclusion of these variables in the base model substantially improved the goodness-of-fit measures. However, the visual inspection of the estimates generated from this extended model revealed that in many cases

where a JRF entry was missing for a particular country-year, the model estimate of coverage would drop significantly. We decided that it was simply not credible to reduce a coverage estimate by several percentage points compared to neighbouring years due to what in many cases would be a clerical omission. We have therefore excluded the JRF indicators from modelling entirely. See Section 4.6 below for a discussion of this exercise.

4.6 Recommendations and lessons learnt

Base and focal perspectives are complementary. The base model relates administrative coverage and country characteristics to survey coverage by combining data from all countries. By borrowing strength across time and space like this it is possible to produce estimates for countries and years where coverage surveys are not available. However, while transparent and credible, the base estimates exhibit high statistical uncertainty. This uncertainty reflects the difficulty of predicting vaccination coverage from administrative data and socioeconomic indices. When surveys for the given country and vaccine exist, the focal model can deliver more confident estimates by putting these surveys in the context of the base model predictions. In addition, these estimates can be more responsive to sudden changes in coverage, for example after implementing a campaign or an intervention, provided that such sharp change is attested to by a survey or reliable administrative data. But the central role of surveys in the focal model means also that the quality of its estimates can suffer in countries with particularly unreliable surveys, whereas the base estimates are not easily swayed by outliers.

It is essential to characterize surveys and model their precision. In the course of data preparation and model development we have identified many surveys reporting implausible levels of coverage. There are also multiple instances of surveys of the same vaccine in the same country-year which disagree beyond what is possible due only to survey design. It follows that surveys are subject to additional sources of error, especially non-representativeness. We have dealt with this issue by calibrating our predictions to DHS surveys and by modelling survey precision directly in our beta regression framework. The latter approach can be significantly strengthened, and estimates improved, if more information were available on the methodology and execution of surveys. The ongoing effort by the WUENIC working group to produce a survey checklist is an essential step in this direction. We recommend that this checklist serves not as a set of inclusion criteria, but is used to weigh survey evidence in a formal statistical setting.

Stakeholder input helps in model development, especially if timed well. The modelling component of the stakeholder survey provided specific inputs that were incorporated, especially the importance of using both administrative data and country characteristics in the model, the value of UN denominators, and the reliability of DHS surveys. General perceptions and expectations of stakeholders, such as the desire to understand the models, distrust of subjective processes, and no real appetite for the most sophisticated techniques were taken into account as well. In our questionnaire, we included also preliminary models to generate specific feedback for a country that the respondent knew well. However, as our final models differ substantially from the preliminary ones, it may be useful to repeat this process.

Recall bias is hard to model and its importance remains unclear. When a child's vaccination status is assessed during a survey by asking the caregiver, a bias of unknown magnitude and direction may be introduced to the overall estimate. A recent review of recall bias studies summarises the difficulties of assessing recall bias and recommends the continued use of estimates derived partly through recall [7]. In the case of surveys of coverage of multi-dose vaccines, an adjustment to the estimate of the latter dose may be applied [8], but this approach rests on the strong assumption of equal dropout in the subpopulations with and without cards. Our original strategy for addressing recall bias was to perform a sensitivity analysis, which is also one of the recommendations of the above-cited article. Unfortunately, we were unable to do so due to the gaps and inconsistencies in the survey dataset, as well as the prohibitive computational cost of refitting the focal model. To the extent that it is possible, modelling of recall bias should be part of a comprehensive effort to model survey precision as recommended above. However, unless significant new evidence from dedicated recall bias studies becomes available, sensitivity analyses may remain the most tractable way of addressing the issue.

Region-specific models may be a better way forward. The kind, quality and availability of data relating to vaccination coverage varies across regions of the world. The same is true about socio-economic indices and other potential correlates of coverage. And, of course, what has the greatest influence on coverage varies from region to region and country to country. We accounted for the regional differences by using interaction terms in the base model. However, our difficulties in modelling the nations in Oceania suggest that the interaction-driven approach is not flexible enough and that models built at a continental or regional level may deliver more precise estimates.

The JRF indicators are a potentially valuable source of data for vaccination coverage modelling. Hoping to improve the predictive performance of our model, we performed variable selection on the dataset of immunization-related indicators reported to WHO/UNICEF on the Joint Reporting Forms. Two of the indicators highlighted by this analysis substantially improved the formal fit measures of our base model. Although we decided not to use them in the final version because of credibility concerns, our conclusion is that JRF data can inform further long-term efforts in vaccination coverage modelling. At present, the high degree of missing entries and the heterogeneity of reporting practices reduce its value considerably. If these issues were addressed in the future, or if the patterns of missing values were characterized sufficiently well to perform good imputation, then JRF data could become an important part of a formal vaccination coverage estimation process.

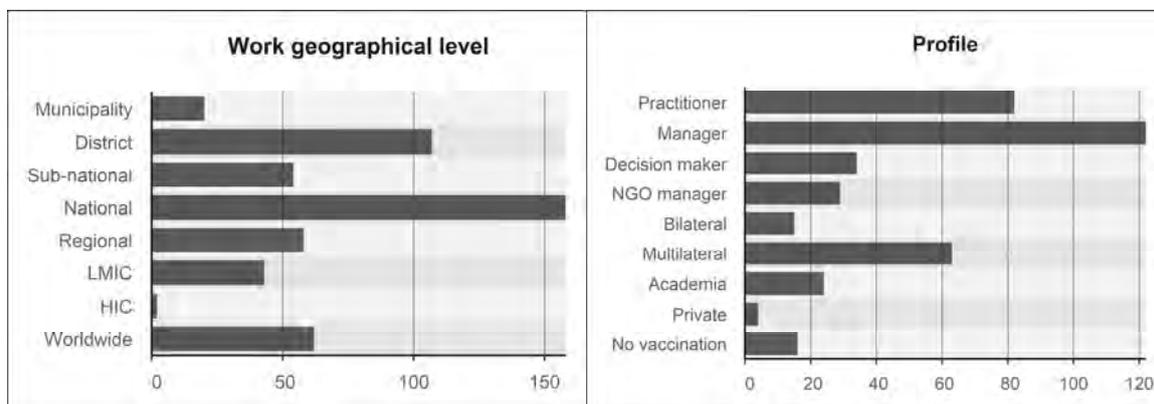
5 Second component stakeholders survey

5.1 Sample description: respondents were typically vaccination managers practitioners and from multilateral organisations, working at national or district levels in Africa and experts in management and VPD (and mostly male)

A total of 512 people responded to the questionnaire (1st February 2020).

- Respondent employment profiles (High to low frequency; %): The majority of respondents were programme managers (122; 24%), followed by 82 (16%) vaccination practitioners (82; 16%) and members of multilateral organisations (63; 12%), Fewer respondents were decision or policy makers, NGO managers, academics, people considered not to be vaccination experts, members of bilateral organisations and professionals in the private-for-profit vaccination field.
- Geographical level where the vaccination related job of respondents usually takes place (High to low frequency; %): Most respondents worked at the (159; 31%) and district (107; 21%) levels followed by those working at worldwide (62; 12%), regional (58; 11%) and other sub-national (54; 11%) levels. Less frequently reported workplaces were LMIC in general, municipality level and HIC in general (2, 0.4%). Eight respondents (1.2%) did not answer this question.
- Geographical regions where vaccination work was reported to be related to (High to low frequency; %): More than half of the respondents vaccination work linked to Africa (298, 58%). The other four regions were represented by the remaining respondents - South East Asia (51, 10%), Eastern Mediterranean region (45, 9%), Americas (16, 3%) and Western Pacific (12, 2%). 67 (13%) respondents did not answer this question. The scope of countries reported was extremely wide, including all continents; particularly Nigeria (at least 62 respondents), Ghana (39), Pakistan (23), India (19), Ethiopia (17) and Cameroon (12).
- Vaccination areas of expertise (High to low frequency; %): VPD (137; 27%) VPD, management (102; 20%), epidemiology (90; 18%); and less than 7% across? policy-making, communications, cold chain and supplies. A relatively high number of respondents left this question blank.
- The mean number of reported years of experience in the vaccination field was 11.4 years (SD = 8.4); median of 10 years (IQR = 5 to 15 years).
- Two thirds of respondents reported being males (332, 65%) and one third females (158, 31%); 22 (4%) respondents did not state their gender.

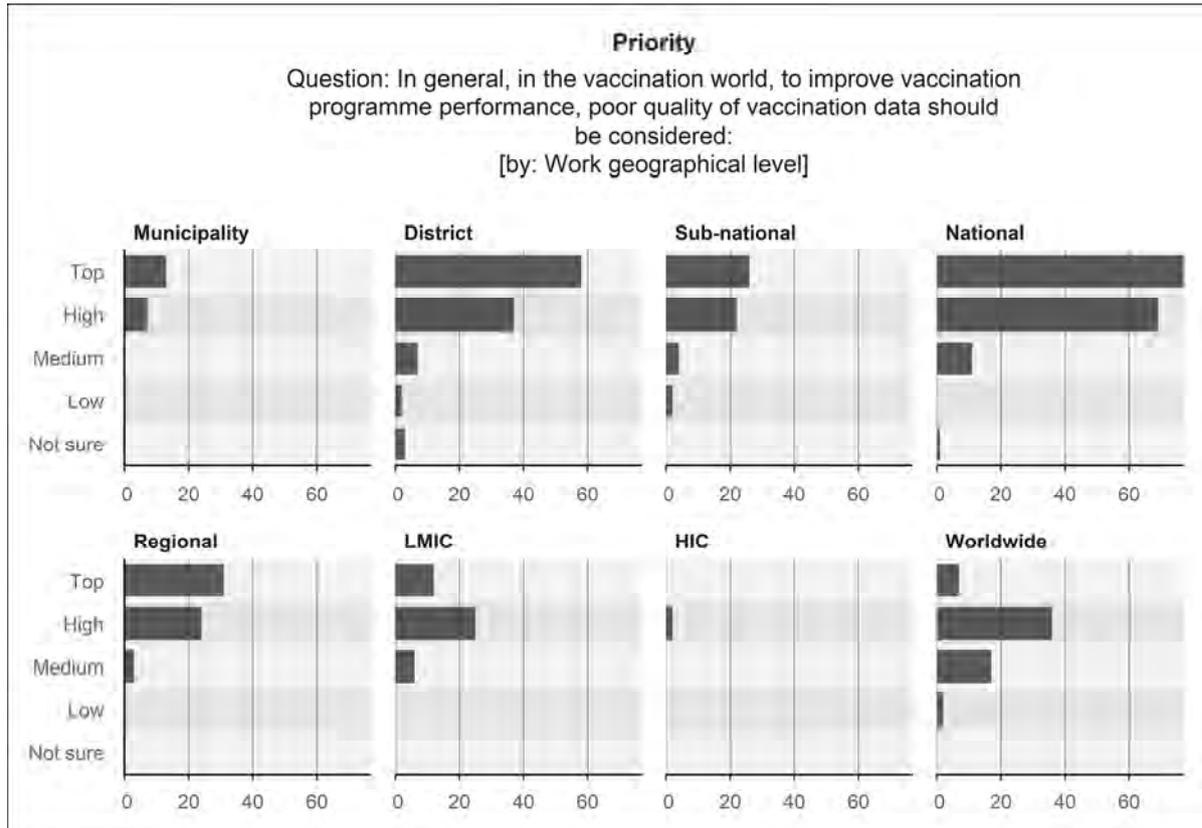
Figure 5. Respondents profile: work geographical level (a) and profile (b).



5.2 Data quality: data quality is an important problem, perceived to be (exclusively) rooted in the frontline of the system

- Data quality is considered to be a ‘top’ or ‘high’ priority by almost 90% respondents.
- There seems to be slight differences between subgroups. Practitioners and managers (as opposed to more ‘international’ profiles) reported data quality as a ‘top’ priority as did regional, national and subnational levels (as opposed to those working in LMIC and worldwide). Differences among vaccination expertise field were less prominent.

Figure 6. Degree of priority of the ‘data problem’, by work geographical level of respondents.

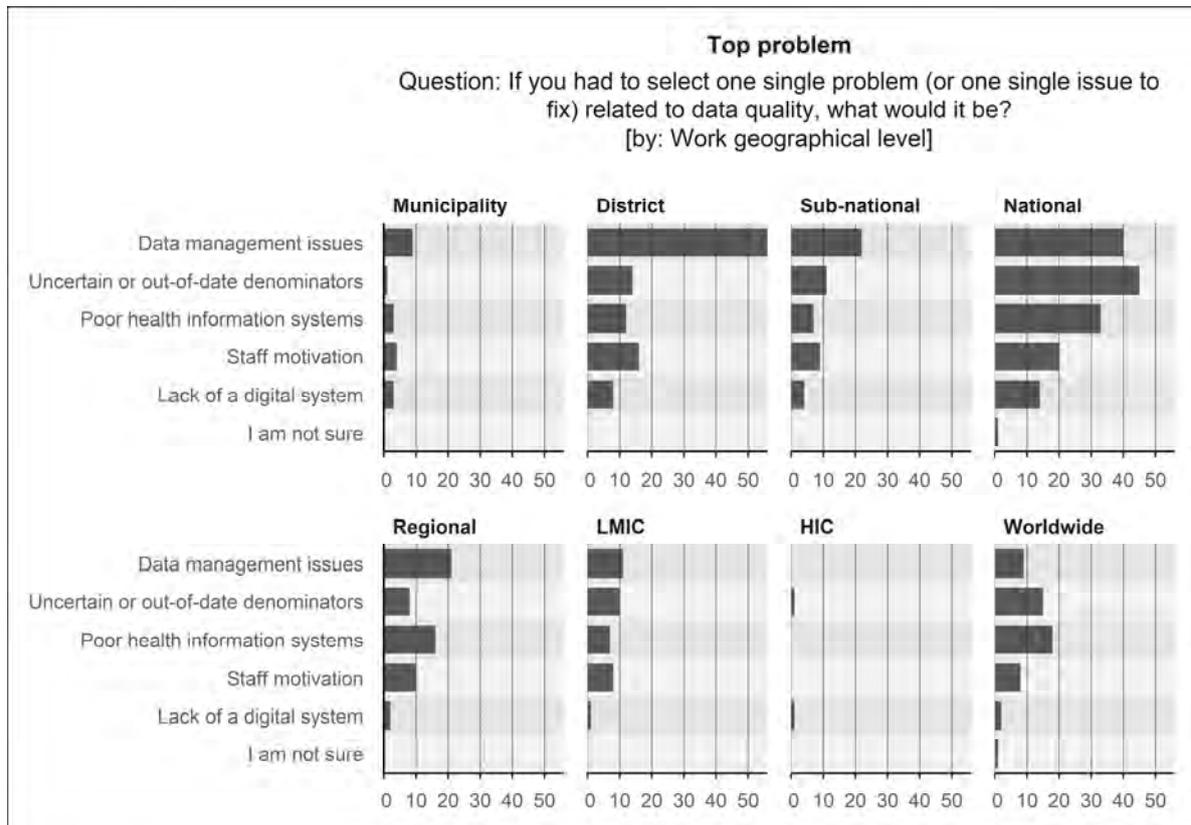


- There seems to be consistency across all working profiles, geographical levels and vaccination expertise in placing the responsibility of the problems of data quality on the frontline of the system and, in decreasing frequency, on intermediate management, national management and policy making levels. Very few respondents were ‘not sure’.
- Free text responses in the ‘Other’ category to indicate where in the system root causes of data quality issues stem from were inconclusive, either pointing at ‘all’ levels or giving vague or conditional responses (see Annex 2).

Note: respondents were asked to mark up to three options, hence in this case the total number of responses was 1,210.

- In terms of data management **processes** considered most related to data quality, the top three responses were ‘recording’ (28%), ‘tallying’ (17%) and ‘reporting’ (16%). Of note, these processes are typically carried out at peripheral level. The other process options were selected less frequently (i.e. ‘counting’, ‘adding’, ‘copying’, ‘sending’, ‘aggregating’ and ‘analysing’). In the subgroup of multilateral organisations, the second most frequent processes cited were, with small differences, ‘aggregating’ (15%) , ‘analysing’ (15%) and ‘reporting’ (14%). Similar responses were found across vaccination field of expertise; interestingly, ‘reporting’ was marginally more cited than ‘recording’ by ‘communication’ experts, albeit the number of responses was smaller than in other groups.
- Respondents could also use the ‘other’ option to offer a free narrative of their views on the critical processes in data quality. These can be grouped under several themes:
- At the workplace location level, when asked to indicate a **single problem** that they would prioritise to address data quality issues, all respondents, except those working at ‘national’ and ‘worldwide’ levels, would address ‘data management issues’. In contrast, experts working at the ‘national’ level would address the ‘problem of denominators’ and those working worldwide, ‘health information systems’. This divergence could also be seen when looking at different working profiles, where ‘data management issues’ would be indicated by practitioners and managers, and ‘health information systems’ by decision-makers, multilaterals and academia. There were hardly any differences between vaccination expertise fields.
- Other problems highlighted in the free text options are included in Annex 2.

Figure 7. Most important ‘single data quality problem’, by workplace location of respondents.



- Across all workplace locations, the most frequently mentioned potential **causes** that could influence (national) vaccination estimates were consistently across working geographical level- denominator (33%) and numerator (23%) issues. Other less frequently cited issues included: differences between districts, vaccine stock-outs (mentioned more amongst practitioners and programme managers), urban-rural mix, population growth and level of infant mortality. The GINI index and GDP options were rarely selected.
- Other potential issues impacting national vaccination coverage estimates noted in the free-text option are included in Annex 2.

Note: respondents were asked to mark up to three options, hence in this case the total number of responses was 1,247.

- Finally, we explored the perceived relationship between **data quality and performance**, in terms of vaccination coverage.
Most respondents stated that high vaccination coverage could ‘possibly’ lead to better data quality; a smaller number suggested that this was sure, or likely or unlikely. The answers varied across profiles, working geographical level and vaccination field of expertise.
In contrast, most respondents agreed that good quality data may contribute to higher vaccination coverage with 70% selecting either ‘agree’ (the most frequent response) or ‘likely’. However, this response was not consistent across respondent categories. For those working at LMIC level the most frequent response was ‘possibly’ (30%); and ‘likely’ for those working at the global level (48%), and for respondents from bilateral (7 out of 15 responses) and multilateral (38%) organisations.

5.3 Indicators: the most relevant indicators are Penta-3 and drop-out rate

We asked about the most important vaccination coverage indicators at different levels (i.e. frontline health workers, intermediate managers and the international level).

- Overall, at frontline level Penta-3 and Penta-13 drop-out rates were considered the most important indicators (18% and 19%, respectively);
- At the intermediate and international levels, the most important indicator selected was fully immunized (19% and 21%, respectively), followed by Penta-3 (18%) and Penta-13 drop-out (16%) rates in the intermediate level, and not-vaccinated and Penta-3 (17%, both) at international level.
- The least selected indicators were ‘coverage differences’, at frontline level (2%) and Penta-1 coverage at intermediate and international levels (4% and 3%, respectively).
- The other indicators also selected included: not vaccinated (14%, 15% and 17%, respectively), missed opportunities (14%, 15% and 17%, respectively) and wastage (8%, 9% and 8%, respectively).
- Responses were uniform across the different subgroups (geographical level, profile or vaccine expertise). Detailed below are some more exceptional cases:

- for respondents working ‘worldwide’ the most important indicator for frontline health workers was missed opportunities (and the least important, ‘coverage differences’) and for intermediate managers and at the international level, ‘not vaccinated’;
- the most important indicator for the intermediate and international levels, according to respondents working ‘worldwide’ was ‘not vaccinated’; the same for respondents working in LMIC for the intermediate level;
- for experts in the communication field, the indicator ‘missed opportunities’ was considered the most important for frontline health workers and for the international level, with modest differences with the other indicators mentioned.

Note: respondents were asked to mark up to three options, hence in this case the total number of responses ranged from 1,316 up to 1,338.

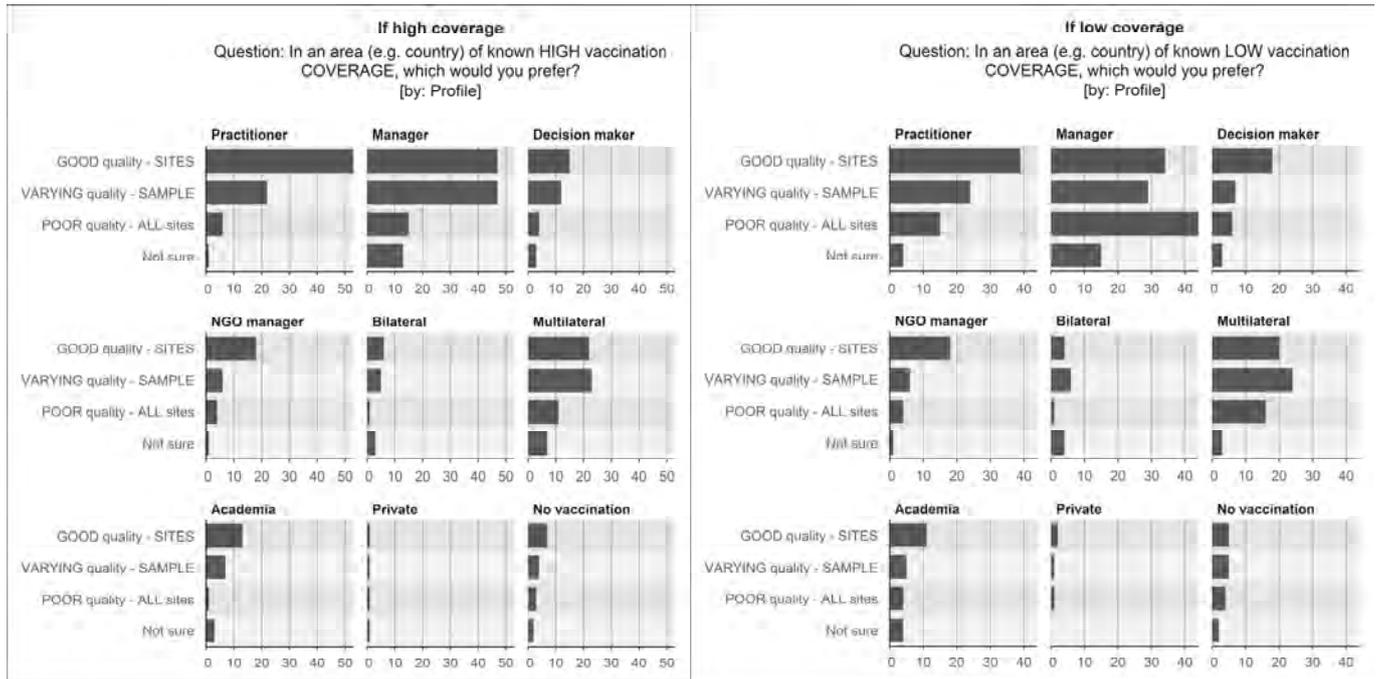
5.4 Quality criteria: the most important criterion was ‘accuracy’ and the least ‘user friendliness’; ‘accuracy’ is preferred to ‘representativeness’ and ‘timeliness’ (not always)

- The most important quality criteria selected by respondents were (high to low): accuracy (24% of responses), completeness (23%), timeliness (19%), availability (15%), comprehensiveness (7%), precision (5%), simplicity (5%) and user-friendliness (2%).
- These findings were similar across the different workplace locations with occasional small variation. For example, ‘Timeliness’ was selected more frequently than ‘completeness’ by respondents working in LMIC or worldwide, as well as by academics and policy-makers (i.e. small number of responses).
- Furthermore, we proposed some scenarios to assess the perceived relative importance of quality (in this case, mainly ‘accuracy’, as seen in the previous paragraphs) and ‘comprehensiveness’ (presented in terms of the representativeness of sites to gather data from). The options to choose from were to have: (i) data of good quality from sentinel sites; (ii) data of varying quality from a representative sample of site; and (iii) data of poor quality from all sites; both in the contexts of low and high coverage.

Everyone preferred to have accuracy at the expense of representativeness, in both low- and high-coverage scenarios. There were only a few exceptions to these:

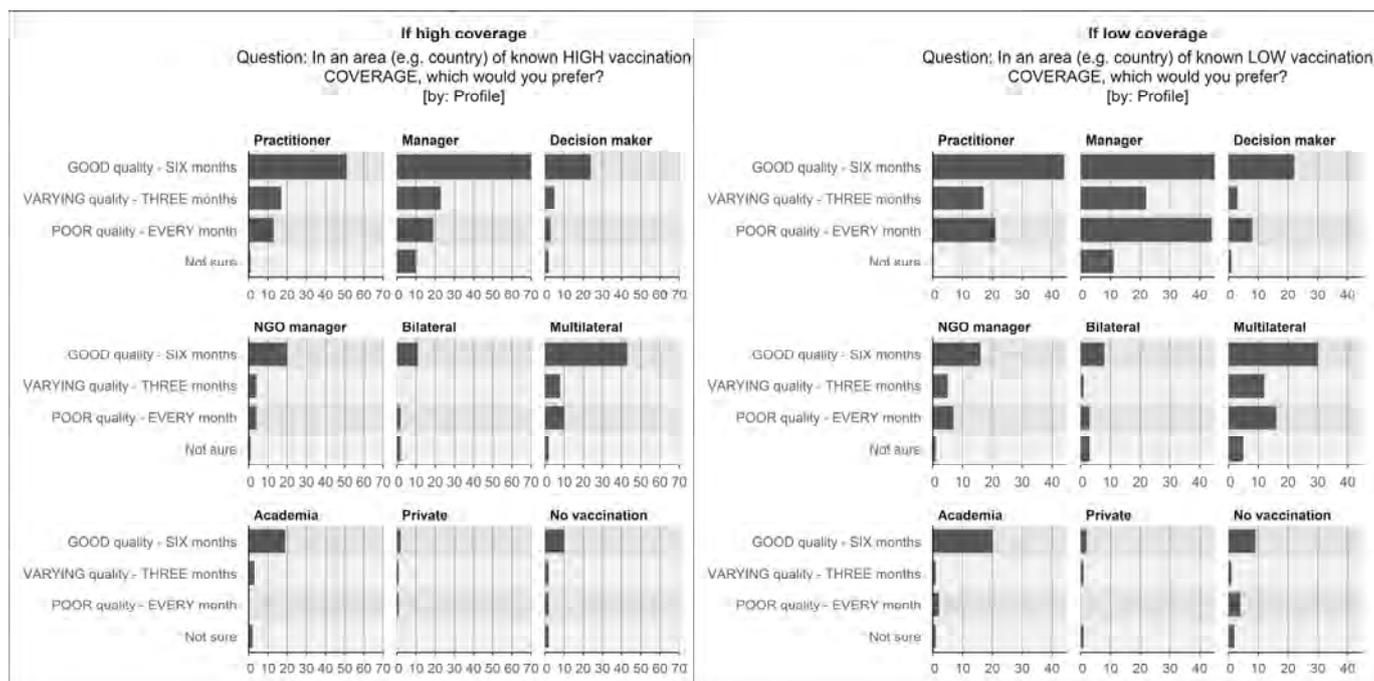
- respondents working at sub-national level (only low-coverage scenario) and respondents from multilateral organisations (preferred varying quality from a representative sample of sites), statisticians (only low coverage scenario) (preferred poor quality data from all sites; relatively large difference);
- managers in the high coverage scenario equally preferred good quality from selected sites and varying quality from a representative sample of sites; in the low coverage scenario, they seemed to prefer poor quality from all sites.

Figure 8. Preferences in relation to the quality of data and its representativeness (high- and low-coverage contexts).



- Finally, we proposed some more scenarios to assess the perceived relative importance of quality (i.e. ‘accuracy’) and ‘timeliness’. The options to choose from were to have: (i) data of good quality every six months; (ii) data of varying quality every three months and (iii) data of poor quality every month; both in the contexts of low and high coverage.

The predominant preference was to have good quality data even if this implied longer timelines (i.e. data every six months). There was only one exception to this: the respondent profile of managers who almost equally selected to have data of good quality every six months or data of poor quality every month.

Figure 9. Preferences in relation to the quality of data and timeliness (high- and low-coverage contexts).

5.5 Interventions to improve quality: the scope of interventions is limited and not evidence-based and stakeholders are prepared to spend on data quality; triangulation is preferred when data is of known poor quality

- We assessed the level of (lack of) accuracy required to trigger a data improvement plan. Most stakeholders would advocate for a data improvement plan when observed estimates of vaccination coverage would be $\pm 5\%$ of the true values (34% of respondents); followed by the option $\pm 10\%$ (26%). Differences between stakeholders seemed minor in all few observed cases. Less frequent options were: $\pm 1\%$ and $\pm 3\%$.
- We enquired about potential interventions to improve the quality of data in rural and in urban contexts and gave options for this.
- For the rural context, most of the subgroups consistently selected (by order of frequency): supervision (26%), training (23%), and improvement of paper systems (21%) and much less frequently (below 10%): electronic systems, a parallel HIS, reducing indicators, increasing frontline staff and increasing data management staff. There were no remarkable differences between the subgroups of respondents.
- In the free-text option, several interventions were suggested (arranged thematically) in Annex 2.
- In urban contexts, the most frequent interventions selected were: the use of electronic information systems (25%), followed by supervision (24%) and then training (17%). Less frequently (below 10%) were: parallel HIS, improvement of paper tools, increase frontline staff, increase data management staff and, lastly, reduce the number of indicators. There were no remarkable differences between subgroups of respondents, except possibly for the national level respondents who indicated a reduction of indicators as the fourth most frequent intervention.

Note: respondents were asked to mark up to three options, hence in this case the total number of responses ranged from 1,350 up to 1,353.

- When enquiring about the target of training, most of the respondents selected the frontline level and less frequently the intermediate level. Hardly any respondents selected the national or policy-makers levels.
- Respondents were asked to choose between three strategies to address data quality issues once data have already been collected: A) triangulate data sources, B) obtain an alternative better quality estimate or C) discuss the issue in meetings. This was proposed in three different scenarios: (i) low Penta-3 coverage; (ii) high Penta-3 coverage and (iii) measles coverage of 89%. All stakeholders across all scenarios most frequently selected (A) 'triangulation' (43%, 54% and 51% in the three scenarios, respectively), (B) better estimate (16%, 23% and 28%, respectively) and (C) 'meetings' (40%, 20% and 20%, respectively). Of note, only in the situation of low vaccination coverage were (C) 'meetings' preferred to a(B) better estimate. No remarkable differences were found between stakeholders with a large number of responses; except for the national level and the respondents from multilateral organisations, in the scenario of low Penta coverage, where meetings (50%) were preferred to the other strategies.
- In the free-text option, respondents could also propose alternative strategies; none were radically new.
- In terms of the proportion of the vaccination programme budget that could be dedicated to improve data quality, most of the respondents selected the option of 5% to 10% of the budget (27% of respondents) and less frequently the options 11 to 20% (23%), 21 to 39% and more than 30% (17% respondents each) and less than 5% (4% of respondents).
- The types of stakeholders advocating for a higher proportion of the budget to be dedicated to data quality were district staff and practitioners; and for the lowest, members of multilateral organisations.

Data showing the values of the variables in the questionnaire of the second survey, by geographical level of respondent's place of working is shown in Table 13, Annex 3.

5.6 Interpretation

Vaccination coverage data – who's responsible?

There is some consistency in placing the 'data quality' problem at peripheral level, both when directly asked about the level as well as when asked about the processes mostly affected by data quality. It seemed striking to us that all non-routine, non-operational parts of the system (e.g. design of the system, availability of tools, coordination with processes of care, to give few examples) fell outside the more prevalent perception of problems and where they exist.

Does data quality play an important role?

There is an optimistic view that better data leads to better programme performance. Despite the fact that this sounds logical, to our knowledge there is hardly any robust evidence to support this statement. Interestingly, respondents working at national or subnational levels seemed more optimistic than those working globally or in LMIC.

Data quality – what matters and to whom?

The questions about indicators tried to ascertain which data items respondents cared for the most i.e. what are the items that would eventually require good quality data to populate them. The findings point at some potential differences between what respondents considered important depending on the level of the system where indicators would be meant to be used. Overall, responses, seemed to follow current practices that focus on Penta-3 and also on drop-out rates as

key indicators. Variations in responses according to subgroups, and even remarkable differences in what is considered important, seems to reflect different priorities in the vaccination world at different levels. It is striking that equity related indicators (e.g. not vaccinated or coverage differences) have been mentioned quite less frequently in some instances.

The perception of data quality is quite 'numerical', as suggested by the prominence of 'accuracy' and other quantitative criteria, as opposed to simplicity and user-friendliness. This would have been a monolithic findings hadn't we investigated scenarios close to real-life situations. There respondents still seemed reluctant to compromise 'accuracy'; but, interestingly, they seemed prepared to compromise 'representativeness' and 'timeliness'. A second remarkable finding in this section was that managers are prepared to compromise accuracy in favour of representativeness and timeliness, in a context of low vaccination coverage. The relevance of this findings is not only this particular 'choice' or the arguable reasonability of this preference; but the fact that managers seem to portray themselves as a quite unique group of stakeholders, which clearly distinct preferences in several of the issues explored.

In situations of poor data quality, triangulation was generally preferred to obtaining better estimates. This is somehow surprising when considering that often alternative better estimates (e.g. from surveys) are the first choice when challenging the quality of routine data sources. There were no substantial alternative strategies to the one proposed. Top interventions to improve data quality differed between urban and rural contexts. Respondents seemed to assume that urban context are more ready for IT solutions. The level of accuracy to trigger a data improvement plan seemed reasonable. It was somehow shocking, though, that supervision and training were so frequently selected as preferred actions, despite the weak evidence supporting the effects of those interventions on programme performance. Training needs consistently focused on frontline health workers, which parallels with the general perception that data quality problems were rooted in the most peripheral (i.e. frontline) level of the system. Other interventions freely suggested by respondents were not radically different to those proposed in the questionnaire. Also, the stakeholders more in favour of spending higher proportions of the budget on data quality were those closer to the frontline system level (i.e. district staff and practitioners).

Limitations of the stakeholder survey

The results of this survey are based on voluntary responses to an online version of the questionnaire and are not representative of any stakeholder groups.

We cannot be sure that the understanding of the concepts in the questions was homogeneous across all respondents. Actually, we limited the amount of explanations in the questions to make the questionnaire more agile, which may not have helped to remove ambiguities or misunderstandings of some of the concepts, such as 'triangulation' or 'accuracy', to give two examples.

The pre-eminence of respondents from Africa and much less frequently from the Americas and other regions may be related to the fact that the questionnaire was only available in English. This can also reflect, though, the areas of the world where vaccination is considered a high priority and where many efforts are concentrated.

5.7 Conclusions and implications

1. **One size does not fit all.** Despite the overall similar patterns across different types of stakeholders, observed differences do not seem anecdotal, are consistent with the interests of a specific stakeholders and large enough to suggest the possibility of true particularities.
2. **Frontline health workers are the ones to blame.** There seems to be a common understanding on where the data problems lie. However, it does not seem reasonable to ignore the influence of other system components, such as the design of the systems, tools, processes, coordination and leadership; as if those were not integral parts of the system and, therefore, of the problem.
3. **There are potentially substantial differences on what is considered important to measure** (i.e. indicators) by different types of stakeholders. This should be taken into account when producing estimates at each level of the system.
4. **Stakeholders do not seem to value criteria which can be paramount for data use;** simplicity and user-friendliness.
5. If **stakeholders are ready to compromise timeliness and representativeness** for getting accuracy, it should be considered how this can be translated into real life situations; i.e. considering decreasing reporting periods and/or establishing special reporting only from sentinel sites.
6. **Managers seem to be a particular and specific group of stakeholders,** across several of the issues explored in the questionnaire. Members of multilateral organisations somehow as well. This would support stakeholder-specific approaches to data issues and, more importantly, to decision making.
7. The scope of interventions to improve data quality is limited and hardly supported by available evidence.

ANNEXES

Annex 1. Data preparation

In our data preparation, we followed similar logic and procedures as the WUENIC working group, as described in the WUENIC GATHER checklist[9]. One notable difference is that we included surveys even when the proportion of cards was not reported. We performed all adjustments and corrections through programming code, so that our work is fully reproducible.

Survey estimates. Our starting point was the dataset of surveys compiled by WHO/UNICEF^a. We excluded surveys reporting valid rather than crude coverage, and surveys where the sample size was less than 300 or was not given at all. Surveys where the target cohort year was before 2000 were also excluded. We classified the surveys into four categories: DHS, MICS, EPI and other, based on the survey names. Where a single survey provided multiple estimates for a given vaccine and year, we selected the estimate corresponding to the single year cohort.

Given the important role of DHS surveys in our approach, we checked the survey list manually against the DHS website^b to identify surveys that followed the DHS methodology but were branded differently. This exercise led to reassignment of 9 surveys from the “other” category to DHS. We excluded the 2011 Northeast Zone Somalia MICS, since the very name indicated that it was not nationally representative. In the interest of objectivity, we made no other arbitrary exclusions, even in the cases where the survey estimates were clearly not plausible. The file `wrangle-surveys.R` contains the code applying the above procedures.

Administrative data. We downloaded the administrative coverage time series from the above-mentioned WHO website. Where the data was missing, we used linear interpolation between the nearest years with available data. Where the reported coverage spiked or dropped in a single year by more than 10 percentage points before returning close to the previous levels, we also replaced it by linear interpolation from the neighbouring years. Where no data was reported for the initial few years after 2000, we imputed the value from the first available year. In the rare cases where the administrative coverage was reported for just one year, we did not extrapolate this value to the whole period of interest and retained the missing entries.

During the course of model development, we identified many records where the administrative data was clearly incorrect. In a few cases upon inspection of the original dataset the intended value was obvious. In these cases we corrected the error. The file `wrangle-admin.R` documents these corrections.

Predictive variables. We rescaled most of our numerical predictors to zero mean and unit variance. Where a variable spanned multiple orders of magnitude, we took a logarithmic transformation. We plotted the data and checked for obvious errors and outliers. The file `wrangle-covariates.R` contains the code for assembling the time series of predictors for model development.

^a http://www.who.int/immunization/monitoring_surveillance/data/Coverage_survey_data.xls

^b <https://dhsprogram.com>

Annex 2. 'Free text' responses to the stakeholder survey - 2

Issue: critical processes compromising data quality

- Performance related / perverse incentives:
 - bad intentions to show over reporting as their performance against the real data coverage;
 - data manipulation;
 - manipulating data to fit in management expectations and performance criteria;
 - pressure to report high coverage;
 - inappropriate incentives
- Data limitations / contamination
 - in Lebanon there is limited reporting on vaccination coverage from the private sector this impacts the National coverage estimation on all antigens;
 - counting those who live in a different community outside their facility, so the facility personnel are not sure how to count them (and there is not clear policy and/or no proper training);
 - incomplete data, multiple sources of recording and reporting;
 - insufficient validation steps for the data
 - participation rates and bias;
 - there is no updated census in the country to provide accurate or even close estimate of denominator (population targeted under EPI);
- Human Resources / Skills
 - in understanding the how data are used - this applies in multiple places;
 - insufficient human resources (time) to do the job correctly;
 - insufficient knowledge of what to do,
 - ownership / responsibility
- Digitalisation
 - computerizing;
 - forms and/or digital systems that are not user friendly
- Population characteristics
 - sometimes the poor quality of data is an outcome not of data management practices but of the complexity of a population-based service, i.e., population movement, choices on care seeking based on initial experience of care. E.g., in some instances a negative dropout rate may not represent poor data quality but rather the actual situation on use of services.
- Features of the vaccination schedule
 - vaccination schedule in itself is a barrier to good quality data.

Issue: Problems of data quality

- HIS design
 - HMIS tools designed for data reporting, not on the spot decision making;
- Health system capacity / culture
 - accountability;
 - technical issues related to reporting;
 - our understanding and appreciation of how users at all levels of the health system utilize data and data tools to manage their work;
 - weak global technical leadership;
- Data availability
 - denominator definitions;
 - willingness to share and show subnational and national data.

- Human resources / skills
 - human resource capacity - vaccinators are very busy and have lots of responsibilities;
 - lack of time and skills of health workers to collect and use data;
 - lack of understanding of the data element;
 - weak supervision.

Issue: causes of data quality problems.

- Data availability and contamination
 - data accessibility and validation;
 - lack of reporting tools such as registers;
 - paper-based recording;
 - technical issues related to reporting;
 - availability of data from fee-based immunization services;
 - availability of vaccination records;
 - data manipulations to meet admin targets;
 - falsification of the data (for performance based incentives in programmes);
 - ownership / accountability;
- Human Resources / skills
 - competency of data manager at all levels of the health system;
 - staff motivation;
 - [need for] systematic and frequent in-depth analyses of data by the program;
 - use (or lack of use) of data for decision making by budget allocators;
- Health System capacity
 - difficulty in conducting high quality surveys including sampling methods that are likely to miss the most disadvantaged groups;
 - district directors not providing mobility/vehicle to vaccination teams;
 - frequency and robustness of coverage surveys;
 - lacking commitment;
 - conflicts;
 - weakness of the health system in developing countries.
- Population characteristics
 - continuous movement of displaced populations;
- Vaccination procedures
 - multi-vial policy to be minimized;
 - wastage rates.

Issue: interventions to improve quality – rural context

- Human Resources / skills
 - address perverse incentives
 - helping the frontline worker understand / use the data
 - incentives to frontline and district staff related to data timeliness, quality, and completeness from the remote rural area;
 - motivate staff;
 - on the job mentorship/training of frontline vaccination staff, not just more training;
- Health system capacity
 - strengthening existing HMIS system or integrating with other powerful tools;
 - studying the region and system dynamics first ahead of selecting and implementing a single solution;
 - use of data at all levels;

- Digitalisation (including skills)
 - install internet, where there is network coverage;
 - technology adoption and monitoring in real time manner with built in accountability;
 - training plus EIS;
 - use of mobile device to report immunisation data.
- Community level
 - community leaders involved in new-born / defaulter tracking.

Issue: interventions to improve quality – urban context

- Digitalisation
 - E-immunization system, but only if it is fully integrated with the HMIS and includes individual health records;
 - technology adoption and monitoring in real time manner with built in accountability;
 - training plus EIS;
 - use of data at all levels.
- Human Resources / Skills
 - helping the frontline worker understand / use the data;
 - incentives to frontline and district staff related to data timeliness, quality, and completeness from the remote rural area;
- Health system capacity
 - studying the region and system dynamics first ahead of selecting and implementing a single solution.

Annex 3. Data table of responses from survey component – 2

Table 13. Frequency and proportions (with 95% confidence intervals) of responses in the survey component-2, by geographical level of respondents' working scope.

	Total		Municipality		District		Sub-national		National		Regional		LMIC		HIC		Worldwide	
Top	224	44% (40 to 49)	13	65% (41 to 84)	58	54% (44 to 64)	26	48% (35 to 62)	77	49% (41 to 57)	31	53% (40 to 66)	12	28% (16 to 44)	0	7	11% (5 to 22)	
High	222	44% (40 to 49)	7	35% (16 to 59)	37	35% (26 to 44)	22	41% (28 to 55)	69	44% (36 to 52)	24	41% (29 to 55)	25	58% (42 to 73)	2	Y1 (20 to 100)	36	58% (45 to 70)
Medium	48	10% (7 to 13)	0	7%	7	7% (3 to 13)	4	7% (2 to 19)	11	7% (4 to 12)	3	5% (1 to 15)	6	14% (6 to 29)	0	17	27% (17 to 40)	
Low	6	1% (.48 to 3)	0	2%	2	2% (.32 to 7)	2	4% (1 to 14)	0	0	0	0	0	0	0	2	3% (1 to 12)	
Not sure	4	1% (.25 to 2)	0	3%	3	3% (1 to 9)	0	1%	1	1% (.03 to 4)	0	0	0	0	0	0	0	
Totals Priority	504	100%	20	4% (3 to 6)	107	21% (18 to 25)	54	11% (8 to 14)	158	31% (27 to 36)	58	12% (9 to 15)	43	9% (6 to 11)	2	.4% (.07 to 2)	62	12% (10 to 16)
Frontline	303	64% (60 to 68)	14	70% (46 to 87)	83	80% (71 to 87)	36	68% (54 to 80)	98	64% (56 to 72)	37	66% (52 to 78)	16	48% (31 to 66)	1	50% (9 to 91)	18	35% (23 to 50)
Intermediate management	95	20% (17 to 24)	5	25% (10 to 49)	12	12% (6 to 20)	12	23% (13 to 37)	37	24% (18 to 32)	8	14% (7 to 27)	9	27% (14 to 46)	0	12	24% (13 to 38)	
National management	44	9% (7 to 12)	1	5% (.26 to 27)	6	6% (2 to 13)	4	8% (2 to 19)	12	8% (4 to 14)	5	9% (3 to 20)	5	15% (6 to 33)	0	11	22% (12 to 36)	
Policy making	18	4% (2 to 6)	0	2%	2	2% (.33 to 7)	1	2% (.1 to 11)	4	3% (1 to 7)	4	7% (2 to 18)	3	9% (2 to 25)	1	50% (9 to 91)	3	6% (2 to 17)
Not sure	12	3% (1 to 5)	0	1%	1	1% (.05 to 6)	0	1%	2	1% (.23 to 5)	2	4% (1 to 13)	0	0	0	7	14% (6 to 27)	

	Total		Municipality		District		Sub-national		National		Regional		LMIC		HIC		Worldwide	
Totals Causes	472	100%	20	4% (3 to 7)	104	22% (18 to 26)	53	11% (9 to 15)	153	32% (28 to 37)	56	12% (9 to 15)	33	7% (5 to 10)	2	.4% (.07 to 2)	51	11% (8 to 14)
Data management issues	168	35% (31 to 39)	9	45% (24 to 68)	56	53% (43 to 63)	22	42% (28 to 56)	40	26% (20 to 34)	21	37% (25 to 51)	11	30% (16 to 47)	0		9	17% (9 to 30)
Uncertain or out-of-date denominators	105	22% (18 to 26)	1	5% (.26 to 27)	14	13% (8 to 22)	11	21% (11 to 34)	45	29% (22 to 37)	8	14% (7 to 26)	10	27% (14 to 44)	1	50% (9 to 91)	15	28% (17 to 43)
Poor health information systems	96	20% (17 to 24)	3	15% (4 to 39)	12	11% (6 to 19)	7	13% (6 to 26)	33	22% (16 to 29)	16	28% (17 to 42)	7	19% (9 to 36)	0		18	34% (22 to 48)
Lack of a digital system	35	7% (5 to 10)	3	15% (4 to 39)	8	8% (4 to 15)	4	8% (2 to 19)	14	9% (5 to 15)	2	4% (1 to 13)	1	3% (.14 to 16)	1	50% (9 to 91)	2	4% (1 to 14)
Staff motivation	75	16% (13 to 19)	4	20% (7 to 44)	16	15% (9 to 24)	9	17% (9 to 30)	20	13% (8 to 20)	10	18% (9 to 30)	8	22% (10 to 39)	0		8	15% (7 to 28)
I am not sure	2	.4% (.07 to 2)	0		0		0		1	1% (.03 to 4)	0		0		0		1	2% (.1 to 11)
Totals Prob	481	100%	20	4% (3 to 6)	106	22% (18 to 26)	53	11% (8 to 14)	153	32% (28 to 36)	57	12% (9 to 15)	37	8% (6 to 11)	2	.4% (.07 to 2)	53	11% (8 to 14)
Agree (evidence)	68	13% (11 to 17)	5	25% (10 to 49)	17	16% (10 to 25)	5	9% (3 to 21)	26	16% (11 to 23)	7	12% (5 to 24)	2	5% (1 to 17)	1	50% (9 to 91)	5	8% (3 to 19)
Likely	87	17% (14 to 21)	1	5% (.26 to 27)	26	24% (17 to 34)	8	15% (7 to 28)	21	13% (9 to 20)	12	21% (12 to 34)	5	12% (4 to 26)	0		14	23% (13 to 35)
Possibly	164	33% (28 to 37)	3	15% (4 to 39)	31	29% (21 to 39)	16	30% (18 to 44)	54	34% (27 to 42)	13	22% (13 to 36)	21	49% (34 to 64)	1	50% (9 to 91)	25	40% (28 to 54)
Unlikely	139	28% (24 to 32)	9	45% (24 to 68)	27	25% (18 to 35)	24	44% (31 to 59)	40	25% (19 to 33)	17	29% (18 to 43)	8	19% (9 to 34)	0		14	23% (13 to 35)

	Total		Municipality		District		Sub-national		National		Regional		LMIC		HIC		Worldwide	
I am not sure	46	9% (7 to 12)	2	10% (2 to 33)	6	6% (2 to 12)	1	2% (.1 to 11)	17	11% (7 to 17)	9	16% (8 to 28)	7	16% (7 to 31)	0	4	6% (2 to 16)	
Totals QualCov1	504	100%	20	4% (3 to 6)	107	21% (18 to 25)	54	11% (8 to 14)	158	31% (27 to 36)	58	12% (9 to 15)	43	9% (6 to 11)	2	.4% (.07 to 2)	62	12% (10 to 16)
Agree (evidence)	204	40% (36 to 45)	6	30% (13 to 54)	48	45% (35 to 55)	25	46% (33 to 60)	66	42% (34 to 50)	27	47% (34 to 60)	13	30% (18 to 46)	1	50% (9 to 91)	18	29% (19 to 42)
Likely	150	30% (26 to 34)	5	25% (10 to 49)	30	28% (20 to 38)	18	33% (21 to 48)	38	24% (18 to 32)	20	34% (23 to 48)	8	19% (9 to 34)	1	50% (9 to 91)	30	48% (36 to 61)
Possibly	108	21% (18 to 25)	5	25% (10 to 49)	21	20% (13 to 29)	7	13% (6 to 26)	38	24% (18 to 32)	6	10% (4 to 22)	18	42% (27 to 58)	0	13	21% (12 to 34)	
Unlikely	32	6% (4 to 9)	4	20% (7 to 44)	7	7% (3 to 13)	4	7% (2 to 19)	9	6% (3 to 11)	5	9% (3 to 20)	3	7% (2 to 20)	0	0	0	
I am not sure	10	2% (1 to 4)	0	1%	1	(.05 to 6)	0	4%	7	(2 to 9)	0	2%	1	(.12 to 14)	0	1	2% (.08 to 10)	
Totals QualCov2	504	100%	20	4% (3 to 6)	107	21% (18 to 25)	54	11% (8 to 14)	158	31% (27 to 36)	58	12% (9 to 15)	43	9% (6 to 11)	2	.4% (.07 to 2)	62	12% (10 to 16)
GOOD quality - SITES	195	39% (34 to 43)	10	50% (30 to 70)	45	42% (33 to 52)	18	33% (21 to 48)	61	39% (31 to 47)	22	38% (26 to 52)	18	42% (27 to 58)	1	50% (9 to 91)	20	32% (21 to 45)
VARYING quality - SAMPLE	137	27% (23 to 31)	1	5% (.26 to 27)	28	26% (18 to 36)	20	37% (25 to 51)	38	24% (18 to 32)	18	31% (20 to 45)	14	33% (20 to 49)	1	50% (9 to 91)	17	27% (17 to 40)
POOR quality - ALL sites	127	25% (22 to 29)	7	35% (16 to 59)	29	27% (19 to 37)	14	26% (15 to 40)	43	27% (21 to 35)	17	29% (18 to 43)	6	14% (6 to 29)	0	11	18% (10 to 30)	
Not sure	45	9% (7 to 12)	2	10% (2 to 33)	5	5% (2 to 11)	2	4% (1 to 14)	16	10% (6 to 16)	1	2% (.09 to 10)	5	12% (4 to 26)	0	14	23% (13 to 35)	

	Total		Municipality		District		Sub-national		National		Regional		LMIC		HIC		Worldwide	
Totals AccSites1	504	100%	20	4% (3 to 6)	107	21% (18 to 25)	54	11% (8 to 14)	158	31% (27 to 36)	58	12% (9 to 15)	43	9% (6 to 11)	2	.4% (.07 to 2)	62	12% (10 to 16)
GOOD quality - SITES	230	46% (41 to 50)	12	60% (36 to 80)	56	52% (43 to 62)	29	54% (40 to 67)	63	40% (32 to 48)	26	45% (32 to 58)	20	47% (31 to 62)	2	1 (20 to 100)	22	35% (24 to 49)
VARYING quality - SAMPLE	161	32% (28 to 36)	6	30% (13 to 54)	35	33% (24 to 43)	16	30% (18 to 44)	55	35% (28 to 43)	20	34% (23 to 48)	12	28% (16 to 44)	0		17	27% (17 to 40)
POOR quality - ALL sites	64	13% (10 to 16)	2	10% (2 to 33)	12	11% (6 to 19)	6	11% (5 to 23)	22	14% (9 to 21)	11	19% (10 to 32)	4	9% (3 to 23)	0		7	11% (5 to 22)
Not sure	49	10% (7 to 13)	0		4	4% (1 to 10)	3	6% (1 to 16)	18	11% (7 to 18)	1	2% (.09 to 10)	7	16% (7 to 31)	0		16	26% (16 to 39)
Totals AccSites2	504	100%	20	4% (3 to 6)	107	21% (18 to 25)	54	11% (8 to 14)	158	31% (27 to 36)	58	12% (9 to 15)	43	9% (6 to 11)	2	.4% (.07 to 2)	62	12% (10 to 16)
GOOD quality - SIX months	253	50% (46 to 55)	9	45% (24 to 68)	47	44% (34 to 54)	27	50% (37 to 63)	76	48% (40 to 56)	24	41% (29 to 55)	30	70% (54 to 82)	1	50% (9 to 91)	39	63% (50 to 75)
VARYING quality - THREE months	79	16% (13 to 19)	1	5% (.26 to 27)	21	20% (13 to 29)	10	19% (10 to 32)	25	16% (11 to 23)	12	21% (12 to 34)	4	9% (3 to 23)	1	50% (9 to 91)	5	8% (3 to 19)
POOR quality - EVERY month	142	28% (24 to 32)	9	45% (24 to 68)	37	35% (26 to 44)	15	28% (17 to 42)	45	28% (22 to 36)	20	34% (23 to 48)	7	16% (7 to 31)	0		9	15% (7 to 26)
Not sure	30	6% (4 to 8)	1	5% (.26 to 27)	2	2% (.32 to 7)	2	4% (1 to 14)	12	8% (4 to 13)	2	3% (1 to 13)	2	5% (1 to 17)	0		9	15% (7 to 26)
Totals AccTime1	504	100%	20	4% (3 to 6)	107	21% (18 to 25)	54	11% (8 to 14)	158	31% (27 to 36)	58	12% (9 to 15)	43	9% (6 to 11)	2	.4% (.07 to 2)	62	12% (10 to 16)
GOOD quality - SIX months	320	63% (59 to 68)	13	65% (41 to 84)	63	59% (49 to 68)	29	54% (40 to 67)	103	65% (57 to 72)	34	59% (45 to 71)	34	79% (64 to 89)	2	1 (20 to 100)	42	68% (55 to 79)

	Total		Municipality		District		Sub-national		National		Regional		LMIC		HIC		Worldwide	
VARYING quality - THREE months	84	17% (14 to 20)	5	25% (10 to 49)	22	21% (14 to 30)	15	28% (17 to 42)	23	15% (10 to 21)	11	19% (10 to 32)	4	9% (3 to 23)	0	4	6% (2 to 16)	
POOR quality - EVERY month	73	14% (12 to 18)	2	10% (2 to 33)	19	18% (11 to 27)	9	17% (8 to 30)	22	14% (9 to 21)	12	21% (12 to 34)	4	9% (3 to 23)	0	5	8% (3 to 19)	
Not sure	27	5% (4 to 8)	0	3% (1 to 9)	3	3% (1 to 9)	1	2% (.1 to 11)	10	6% (3 to 12)	1	2% (.09 to 10)	1	2% (.12 to 14)	0	11	18% (10 to 30)	
Totals AccTime2	504	100%	20	4% (3 to 6)	107	21% (18 to 25)	54	11% (8 to 14)	158	31% (27 to 36)	58	12% (9 to 15)	43	9% (6 to 11)	2	.4% (.07 to 2)	62	12% (10 to 16)
Frontline	345	70% (65 to 74)	18	90% (67 to 98)	79	75% (65 to 82)	46	85% (72 to 93)	116	75% (67 to 81)	41	71% (57 to 82)	19	45% (30 to 61)	0	26	44% (31 to 58)	
Intermediate	127	26% (22 to 30)	1	5% (.26 to 27)	25	24% (16 to 33)	7	13% (6 to 26)	31	20% (14 to 27)	14	24% (14 to 37)	20	48% (32 to 63)	1	28	47% (34 to 61)	
National	12	2% (1 to 4)	1	5% (.26 to 27)	1	1% (.05 to 6)	0	1% (.05 to 6)	5	3% (1 to 8)	1	2% (.09 to 10)	1	2% (.12 to 14)	0	3	5% (1 to 15)	
Policy makers	8	2% (1 to 3)	0	1% (.05 to 6)	1	1% (.05 to 6)	1	2% (.1 to 11)	3	2% (1 to 6)	1	2% (.09 to 10)	1	2% (.12 to 14)	0	1	2% (.09 to 10)	
I am not sure	4	1% (.26 to 2)	0	0	0	0	0	0	0	0	1	2% (.09 to 10)	1	2% (.12 to 14)	1	1	2% (.09 to 10)	
Totals IntTraining	496	100%	20	4% (3 to 6)	106	21% (18 to 25)	54	11% (8 to 14)	155	31% (27 to 36)	58	12% (9 to 15)	42	8% (6 to 11)	2	.4% (.07 to 2)	59	12% (9 to 15)
< 5%	17	3% (2 to 5)	0	2%	2	2% (.32 to 7)	1	2% (.1 to 11)	5	3% (1 to 8)	1	2% (.09 to 10)	0	0	0	8	13% (6 to 24)	
5% to 10%	138	27% (24 to 32)	1	5% (.26 to 27)	21	20% (13 to 29)	10	19% (10 to 32)	47	30% (23 to 38)	16	28% (17 to 41)	19	44% (29 to 60)	1	23	37% (25 to 50)	

	Total	Municipality	District	Sub-national	National	Regional	LMIC	HIC	Worldwide									
11% to 20%	114	23% (19 to 27)	5	25% (10 to 49)	20	19% (12 to 28)	16	30% (18 to 44)	43	27% (21 to 35)	14	24% (14 to 37)	8	19% (9 to 34)	1	50% (9 to 91)	7	11% (5 to 22)
21% to 30%	85	17% (14 to 20)	7	35% (16 to 59)	21	20% (13 to 29)	12	22% (12 to 36)	25	16% (11 to 23)	12	21% (12 to 34)	3	7% (2 to 20)	0		5	8% (3 to 19)
> 30%	88	17% (14 to 21)	6	30% (13 to 54)	36	34% (25 to 44)	11	20% (11 to 34)	24	15% (10 to 22)	7	12% (5 to 24)	3	7% (2 to 20)	0		1	2% (.08 to 10)
I am not sure	62	12% (10 to 16)	1	5% (.26 to 27)	7	7% (3 to 13)	4	7% (2 to 19)	14	9% (5 to 15)	8	14% (7 to 26)	10	23% (12 to 39)	0		18	29% (19 to 42)
Totals IntBudget	504	100%	20	4% (3 to 6)	107	21% (18 to 25)	54	11% (8 to 14)	158	31% (27 to 36)	58	12% (9 to 15)	43	9% (6 to 11)	2	.4% (.07 to 2)	62	12% (10 to 16)
± 1% of the true value	46	9% (7 to 12)	5	25% (10 to 49)	15	14% (8 to 22)	5	9% (3 to 21)	11	7% (4 to 12)	9	16% (8 to 28)	1	2% (.12 to 14)	0		0	
± 3% of the true value	42	8% (6 to 11)	2	10% (2 to 33)	16	15% (9 to 23)	3	6% (1 to 16)	10	6% (3 to 12)	5	9% (3 to 20)	4	9% (3 to 23)	0		2	3% (1 to 12)
± 5% of the true value	174	35% (30 to 39)	3	15% (4 to 39)	34	32% (23 to 42)	22	41% (28 to 55)	61	39% (31 to 47)	14	24% (14 to 37)	15	35% (21 to 51)	1	50% (9 to 91)	24	39% (27 to 52)
± 10% of the true value	133	26% (23 to 31)	4	20% (7 to 44)	19	18% (11 to 27)	12	22% (12 to 36)	50	32% (25 to 40)	20	34% (23 to 48)	11	26% (14 to 41)	0		17	27% (17 to 40)
It does not matter	30	6% (4 to 8)	0		4	4% (1 to 10)	2	4% (1 to 14)	8	5% (2 to 10)	0		6	14% (6 to 29)	0		10	16% (8 to 28)
I am not sure	79	16% (13 to 19)	6	30% (13 to 54)	19	18% (11 to 27)	10	19% (10 to 32)	18	11% (7 to 18)	10	17% (9 to 30)	6	14% (6 to 29)	1	50% (9 to 91)	9	15% (7 to 26)
Totals ThresholdPlan	504	100%	20	4% (3 to 6)	107	21% (18 to 25)	54	11% (8 to 14)	158	31% (27 to 36)	58	12% (9 to 15)	43	9% (6 to 11)	2	.4% (.07 to 2)	62	12% (10 to 16)

	Total	Municipality	District	Sub-national	National	Regional	LMIC	HIC	Worldwide									
Better quality estimate	77	15% (12 to 19)	2	10% (2 to 33)	20	19% (12 to 28)	8	15% (7 to 28)	28	18% (12 to 25)	8	14% (7 to 26)	5	12% (4 to 26)	1	50% (9 to 91)	5	8% (3 to 19)
Triangulate sources	213	43% (38 to 47)	7	35% (16 to 59)	46	43% (34 to 53)	31	57% (43 to 70)	50	32% (25 to 40)	29	50% (38 to 62)	20	48% (32 to 63)	1	50% (9 to 91)	29	48% (35 to 61)
Meetings	206	41% (37 to 46)	11	55% (32 to 76)	41	38% (29 to 48)	15	28% (17 to 42)	78	50% (42 to 58)	20	34% (23 to 48)	17	40% (26 to 57)	0		24	40% (28 to 53)
I am not sure	4	1% (.26 to 2)	0		0		0		1	1% (.03 to 4)	1	2% (.09 to 10)	0		0		2	3% (1 to 13)
Totals ScePentaLow	500	100%	20	4% (3 to 6)	107	21% (18 to 25)	54	11% (8 to 14)	157	31% (27 to 36)	58	12% (9 to 15)	42	8% (6 to 11)	2	.4% (.07 to 2)	60	12% (9 to 15)
Better quality estimate	120	24% (20 to 28)	2	10% (2 to 33)	35	33% (24 to 43)	24	44% (31 to 59)	32	20% (14 to 28)	11	19% (10 to 32)	9	21% (11 to 37)	0		7	12% (5 to 23)
Triangulate sources	273	54% (50 to 59)	16	80% (56 to 93)	53	50% (40 to 59)	22	41% (28 to 55)	90	57% (49 to 65)	32	55% (42 to 68)	21	50% (36 to 64)	1	50% (9 to 91)	38	63% (50 to 75)
Meetings	102	20% (17 to 24)	2	10% (2 to 33)	18	17% (11 to 26)	8	15% (7 to 28)	34	22% (16 to 29)	14	24% (14 to 37)	11	26% (14 to 42)	1	50% (9 to 91)	14	23% (14 to 36)
I am not sure	6	1% (.49 to 3)	0		1	1% (.05 to 6)	0		2	1% (.22 to 5)	1	2% (.09 to 10)	1	2% (.12 to 14)	0		1	2% (.09 to 10)
Total ScePentaHigh	501	100%	20	4% (3 to 6)	107	21% (18 to 25)	54	11% (8 to 14)	158	32% (28 to 36)	58	12% (9 to 15)	42	8% (6 to 11)	2	.4% (.07 to 2)	60	12% (9 to 15)
Better quality estimate	142	29% (25 to 33)	6	30% (13 to 54)	40	38% (29 to 48)	14	26% (15 to 40)	48	30% (23 to 38)	18	31% (20 to 45)	8	20% (9 to 35)	0		8	14% (6 to 26)
Triangulate sources	253	51% (46 to 55)	9	45% (24 to 68)	48	45% (36 to 55)	30	56% (41 to 69)	78	49% (41 to 57)	26	45% (32 to 58)	23	56% (40 to 71)	2	1 (20 to 100)	37	63% (49 to 75)

	Total		Municipality		District		Sub-national		National		Regional		LMIC		HIC		Worldwide	
Meetings	97	19% (16 to 23)	5	25% (10 to 49)	18	17% (11 to 26)	10	19% (10 to 32)	29	18% (13 to 25)	13	22% (13 to 36)	9	22% (11 to 38)	0	13	22% (13 to 35)	
I am not sure	6	1% (.49 to 3)	0		0		0		3	2% (.49 to 6)	1	2% (.09 to 10)	1	2% (.13 to 14)	0	1	2% (.09 to 10)	
Totals SceMeaHigh	498	100%	20	4% (3 to 6)	106	21% (18 to 25)	54	11% (8 to 14)	158	32% (28 to 36)	58	12% (9 to 15)	41	8% (6 to 11)	2	.4% (.07 to 2)	59	12% (9 to 15)
Adding	38	3% (2 to 4)	3	5% (1 to 16)	10	4% (2 to 7)	6	5% (2 to 10)	13	4% (2 to 6)	3	2% (1 to 7)	2	2% (.35 to 8)	0	1	1% (.04 to 5)	
Aggregating	144	12% (10 to 14)	4	7% (2 to 18)	23	8% (5 to 12)	8	6% (3 to 12)	48	13% (10 to 17)	21	15% (10 to 23)	18	18% (11 to 27)	1	33% (2 to 87)	21	15% (10 to 22)
Analysing	101	8% (7 to 10)	1	2% (.09 to 11)	20	7% (5 to 11)	11	8% (5 to 15)	22	6% (4 to 9)	12	9% (5 to 15)	16	16% (10 to 25)	0	19	14% (9 to 21)	
Copying	58	5% (4 to 6)	3	5% (1 to 16)	10	4% (2 to 7)	8	6% (3 to 12)	20	5% (3 to 8)	6	4% (2 to 10)	3	3% (1 to 9)	0	8	6% (3 to 11)	
Counting	95	8% (6 to 10)	8	15% (7 to 27)	24	9% (6 to 13)	9	7% (3 to 13)	32	9% (6 to 12)	11	8% (4 to 14)	2	2% (.35 to 8)	1	33% (2 to 87)	8	6% (3 to 11)
Not sure	15	1% (1 to 2)	0		2	1% (.13 to 3)	0		1	.3% (.01 to 2)	3	2% (1 to 7)	1	1% (.05 to 6)	0	8	6% (3 to 11)	
Recording	342	28% (26 to 31)	16	29% (18 to 43)	81	29% (24 to 35)	38	29% (22 to 38)	106	29% (24 to 34)	38	28% (21 to 36)	26	26% (18 to 36)	1	33% (2 to 87)	36	26% (19 to 34)
Reporting	191	16% (14 to 18)	8	15% (7 to 27)	53	19% (15 to 24)	21	16% (10 to 24)	65	18% (14 to 22)	15	11% (7 to 18)	13	13% (7 to 22)	0	16	11% (7 to 18)	
Sending	23	2% (1 to 3)	0		7	3% (1 to 5)	2	2% (.27 to 6)	5	1% (.5 to 3)	3	2% (1 to 7)	3	3% (1 to 9)	0	3	2% (1 to 7)	

	Total		Municipality		District		Sub-national		National		Regional		LMIC		HIC		Worldwide	
Tallying	203	17% (15 to 19)	12	22% (12 to 35)	46	17% (13 to 22)	27	21% (14 to 29)	58	16% (12 to 20)	24	18% (12 to 25)	16	16% (10 to 25)	0		20	14% (9 to 21)
Totals Mech	1210	100%	55	5% (3 to 6)	276	23% (20 to 25)	130	11% (9 to 13)	370	31% (28 to 33)	136	11% (10 to 13)	100	8% (7 to 10)	3	.2% (.06 to 1)	140	12% (10 to 14)
Denominators	406	33% (30 to 35)	17	31% (20 to 46)	74	27% (22 to 33)	46	33% (25 to 42)	133	34% (30 to 39)	46	34% (26 to 42)	39	35% (26 to 45)	0		51	35% (28 to 44)
District differences	120	10% (8 to 11)	7	13% (6 to 26)	32	12% (8 to 16)	15	11% (6 to 17)	39	10% (7 to 14)	11	8% (4 to 14)	6	5% (2 to 12)	0		10	7% (4 to 13)
I am not sure	8	1% (.3 to 1)	0		1	.4% (.02 to 2)	1	1% (.04 to 5)	0		1	1% (.04 to 5)	1	1% (.05 to 6)	1	1 (5 to 100)	3	2% (1 to 6)
Level of infant mortality	21	2% (1 to 3)	2	4% (1 to 14)	5	2% (1 to 4)	2	1% (.25 to 6)	6	2% (1 to 4)	4	3% (1 to 8)	0		0		2	1% (.24 to 5)
Numerators	293	23% (21 to 26)	11	20% (11 to 34)	51	19% (14 to 24)	31	22% (16 to 30)	101	26% (22 to 31)	36	26% (19 to 35)	25	23% (15 to 32)	0		38	26% (20 to 35)
Political instability	116	9% (8 to 11)	3	6% (1 to 16)	28	10% (7 to 15)	13	9% (5 to 16)	33	9% (6 to 12)	11	8% (4 to 14)	13	12% (7 to 20)	0		15	10% (6 to 17)
Population growth	90	7% (6 to 9)	6	11% (5 to 23)	25	9% (6 to 13)	9	6% (3 to 12)	20	5% (3 to 8)	9	7% (3 to 12)	10	9% (5 to 16)	0		11	8% (4 to 14)
Stock outs of vaccines	122	10% (8 to 12)	6	11% (5 to 23)	39	14% (10 to 19)	15	11% (6 to 17)	36	9% (7 to 13)	12	9% (5 to 15)	8	7% (3 to 14)	0		6	4% (2 to 9)
The GINI index	6	.5% (.2 to 1)	0		1	.4% (.02 to 2)	2	1% (.25 to 6)	1	.3% (.01 to 2)	1	1% (.04 to 5)	1	1% (.05 to 6)	0		0	
The Gross Domestic Product (GDP)	7	1% (.25 to 1)	0		3	1% (.28 to 3)	0		2	1% (.09 to 2)	0		2	2% (.31 to 7)	0		0	

	Total		Municipality		District		Sub-national		National		Regional		LMIC		HIC		Worldwide	
Urban-rural mix	58	5% (4 to 6)	2	4% (1 to 14)	14	5% (3 to 9)	5	4% (1 to 9)	17	4% (3 to 7)	6	4% (2 to 10)	6	5% (2 to 12)	0	8	6% (3 to 11)	
Totals QuaNat	1247	100%	54	4% (3 to 6)	273	22% (20 to 24)	139	11% (9 to 13)	388	31% (29 to 34)	137	11% (9 to 13)	111	9% (7 to 11)	1	.1% (. to 1)	144	12% (10 to 13)
Coverage differences	21	2% (1 to 2)	2	4% (1 to 13)	3	1% (.28 to 3)	3	2% (1 to 6)	6	1% (1 to 3)	4	3% (1 to 7)	2	2% (.32 to 7)	0	1	1% (.03 to 4)	
Fully immunised	209	16% (14 to 18)	10	18% (9 to 31)	45	16% (12 to 21)	24	17% (11 to 24)	77	18% (15 to 22)	21	14% (9 to 21)	14	13% (8 to 21)	0	18	12% (7 to 18)	
I am not sure	5	.4% (.14 to 1)	0		0		0		1	.2% (.01 to 2)	1	1% (.04 to 4)	0		1	25% (1 to 78)	2	1% (.23 to 5)
Missed opportunities	192	15% (13 to 17)	8	14% (7 to 27)	45	16% (12 to 21)	18	12% (8 to 19)	50	12% (9 to 15)	20	14% (9 to 20)	14	13% (8 to 21)	1	25% (1 to 78)	36	24% (17 to 31)
Not vaccinated	194	15% (13 to 17)	3	5% (1 to 16)	39	14% (10 to 19)	17	12% (7 to 18)	60	14% (11 to 18)	29	20% (14 to 27)	18	17% (10 to 25)	0	28	18% (13 to 26)	
Penta-1 coverage	94	7% (6 to 9)	6	11% (4 to 23)	17	6% (4 to 10)	11	8% (4 to 13)	35	8% (6 to 11)	10	7% (3 to 12)	6	6% (2 to 12)	0	9	6% (3 to 11)	
Penta-3 coverage	254	19% (17 to 22)	14	25% (15 to 39)	50	18% (14 to 23)	31	21% (15 to 29)	94	22% (18 to 26)	25	17% (11 to 24)	18	17% (10 to 25)	1	25% (1 to 78)	21	14% (9 to 21)
Penta1-3 dropout rate	241	18% (16 to 21)	11	20% (11 to 33)	57	21% (16 to 26)	29	20% (14 to 28)	70	16% (13 to 20)	27	18% (13 to 26)	22	20% (13 to 29)	1	25% (1 to 78)	24	16% (11 to 23)
Wastage	106	8% (7 to 10)	2	4% (1 to 13)	19	7% (4 to 11)	12	8% (5 to 14)	35	8% (6 to 11)	11	7% (4 to 13)	14	13% (8 to 21)	0	13	9% (5 to 14)	
Totals IndHW	1316	100%	56	4% (3 to 6)	275	21% (19 to 23)	145	11% (9 to 13)	428	33% (30 to 35)	148	11% (10 to 13)	108	8% (7 to 10)	4	.3% (.1 to 1)	152	12% (10 to 13)

	Total	Municipality	District	Sub-national	National	Regional	LMIC	HIC	Worldwide									
Coverage differences	74	6% (4 to 7)	2	3% (1 to 13)	14	5% (3 to 8)	9	6% (3 to 11)	23	5% (4 to 8)	11	8% (4 to 14)	7	6% (3 to 13)	0	8	5% (2 to 10)	
Fully immunised	263	20% (18 to 22)	14	23% (14 to 36)	55	19% (15 to 24)	28	19% (13 to 26)	87	21% (17 to 25)	31	22% (16 to 31)	19	17% (10 to 25)	1	25% (1 to 78)	28	18% (12 to 25)
I am not sure	6	.5% (.18 to 1)	0	0	0	0	0	0	0	1	1%	1	1% (.04 to 5)	1	25% (1 to 78)	3	2% (.49 to 6)	
Missed opportunities	162	12% (10 to 14)	7	12% (5 to 23)	41	14% (10 to 19)	12	8% (4 to 14)	50	12% (9 to 16)	20	14% (9 to 22)	12	10% (6 to 18)	0	20	13% (8 to 19)	
Not vaccinated	200	15% (13 to 17)	6	10% (4 to 21)	41	14% (10 to 19)	24	16% (11 to 23)	64	15% (12 to 19)	17	12% (8 to 19)	17	15% (9 to 23)	1	25% (1 to 78)	30	19% (13 to 26)
Penta-1 coverage	62	5% (4 to 6)	3	5% (1 to 15)	15	5% (3 to 9)	5	3% (1 to 8)	17	4% (2 to 7)	7	5% (2 to 11)	8	7% (3 to 14)	0	7	4% (2 to 9)	
Penta-3 coverage	235	18% (16 to 20)	11	18% (10 to 31)	50	17% (13 to 22)	25	17% (11 to 24)	82	20% (16 to 24)	20	14% (9 to 22)	24	21% (14 to 30)	0	23	15% (10 to 21)	
Penta1-3 dropout rate	212	16% (14 to 18)	12	20% (11 to 33)	53	18% (14 to 23)	33	22% (16 to 30)	58	14% (11 to 18)	13	9% (5 to 16)	18	16% (10 to 24)	1	25% (1 to 78)	24	15% (10 to 22)
Wastage	119	9% (7 to 11)	5	8% (3 to 19)	22	8% (5 to 11)	13	9% (5 to 15)	38	9% (7 to 12)	18	13% (8 to 20)	9	8% (4 to 15)	0	14	9% (5 to 15)	
Totals IndSub	1333	100%	60	5% (3 to 6)	291	22% (20 to 24)	149	11% (10 to 13)	419	31% (29 to 34)	138	10% (9 to 12)	115	9% (7 to 10)	4	.3% (.1 to 1)	157	12% (10 to 14)
Coverage differences	132	10% (8 to 12)	2	4% (1 to 14)	17	6% (4 to 10)	14	10% (6 to 16)	44	10% (8 to 14)	19	12% (8 to 19)	16	13% (8 to 21)	0	20	13% (8 to 20)	
Fully immunised	280	21% (19 to 23)	9	17% (8 to 30)	62	22% (17 to 27)	32	22% (16 to 30)	80	19% (15 to 23)	40	26% (19 to 33)	22	18% (12 to 26)	2	50% (15 to 85)	33	22% (16 to 29)

	Total		Municipality		District		Sub-national		National		Regional		LMIC		HIC		Worldwide	
I am not sure	5	.4% (.14 to 1)	1	2% (.1 to 11)	0	0	0	0	0	1	1% (.03 to 4)	2	2% (.29 to 6)	0	1	1% (.03 to 4)		
Missed opportunities	141	11% (9 to 12)	8	15% (7 to 28)	33	12% (8 to 16)	13	9% (5 to 15)	47	11% (8 to 15)	17	11% (7 to 17)	10	8% (4 to 15)	0	13	9% (5 to 15)	
Not vaccinated	237	18% (16 to 20)	9	17% (8 to 30)	44	15% (12 to 20)	20	14% (9 to 21)	74	18% (14 to 22)	23	15% (10 to 22)	28	23% (16 to 32)	1	25% (1 to 78)	38	25% (19 to 33)
Other	1	.1% (. to .48)	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1% (.03 to 4)	
Penta-1 coverage	41	3% (2 to 4)	3	6% (1 to 16)	7	2% (1 to 5)	4	3% (1 to 7)	17	4% (2 to 7)	5	3% (1 to 8)	2	2% (.29 to 6)	0	3	2% (1 to 6)	
Penta-3 coverage	230	17% (15 to 19)	10	19% (10 to 32)	46	16% (12 to 21)	23	16% (10 to 23)	78	19% (15 to 23)	26	17% (11 to 24)	18	15% (9 to 23)	0	29	19% (13 to 27)	
Penta1-3 dropout rate	164	12% (11 to 14)	8	15% (7 to 28)	48	17% (13 to 22)	20	14% (9 to 21)	52	12% (9 to 16)	12	8% (4 to 13)	14	12% (7 to 19)	1	25% (1 to 78)	9	6% (3 to 11)
Wastage	107	8% (7 to 10)	4	7% (2 to 19)	28	10% (7 to 14)	20	14% (9 to 21)	29	7% (5 to 10)	13	8% (5 to 14)	9	7% (4 to 14)	0	4	3% (1 to 7)	
Totals IndInt	1338	100%	54	4% (3 to 5)	285	21% (19 to 24)	146	11% (9 to 13)	421	31% (29 to 34)	156	12% (10 to 14)	121	9% (8 to 11)	4	.3% (.1 to 1)	151	11% (10 to 13)
Accuracy	331	24% (22 to 27)	15	26% (16 to 39)	71	25% (21 to 31)	36	24% (18 to 32)	96	22% (18 to 27)	37	23% (17 to 31)	29	24% (17 to 33)	1	1	29% (22 to 36)	
Availability	206	15% (13 to 17)	5	9% (3 to 20)	40	14% (11 to 19)	21	14% (9 to 21)	74	17% (14 to 21)	27	17% (12 to 24)	16	13% (8 to 21)	0	23	14% (9 to 21)	
Completeness	315	23% (21 to 26)	17	29% (18 to 43)	74	27% (22 to 32)	41	28% (21 to 36)	107	25% (21 to 29)	36	23% (17 to 30)	20	17% (11 to 25)	0	20	12% (8 to 19)	

	Total		Municipality		District		Sub-national		National		Regional		LMIC		HIC		Worldwide
Comprehensiveness	89	7% (5 to 8)	4	7% (2 to 18)	17	6% (4 to 10)	10	7% (3 to 12)	32	7% (5 to 10)	12	8% (4 to 13)	8	7% (3 to 13)	0	6	4% (2 to 8)
I am not sure	3	.2% (.06 to 1)	0		0		0		0		0		1	1% (.04 to 5)	0	2	1% (.22 to 5)
Precision	68	5% (4 to 6)	2	3% (1 to 13)	13	5% (3 to 8)	4	3% (1 to 7)	26	6% (4 to 9)	6	4% (2 to 8)	8	7% (3 to 13)	0	9	6% (3 to 11)
Simplicity	66	5% (4 to 6)	2	3% (1 to 13)	10	4% (2 to 7)	7	5% (2 to 10)	15	3% (2 to 6)	11	7% (4 to 12)	10	8% (4 to 15)	0	11	7% (4 to 12)
Timeliness	255	19% (17 to 21)	11	19% (10 to 32)	53	19% (15 to 24)	28	19% (13 to 26)	72	17% (13 to 21)	26	16% (11 to 23)	26	21% (15 to 30)	0	39	24% (18 to 32)
User friendliness	24	2% (1 to 3)	2	3% (1 to 13)	1	.4% (.02 to 2)	1	1% (.04 to 4)	9	2% (1 to 4)	3	2% (.49 to 6)	3	2% (1 to 8)	0	5	3% (1 to 7)
Totals Criteria	1357	100%	58	4% (3 to 6)	279	21% (18 to 23)	148	11% (9 to 13)	431	32% (29 to 34)	158	12% (10 to 13)	121	9% (7 to 11)	1	161	12% (10 to 14)
Electronic	132	10% (8 to 12)	3	5% (1 to 16)	27	9% (6 to 14)	11	8% (4 to 14)	52	12% (9 to 15)	16	11% (7 to 17)	12	10% (5 to 17)	1	10	6% (3 to 12)
I am not sure	4	.3% (.09 to 1)	0		0		0		1	.2% (.01 to 1)	0		0		0	3	2% (.49 to 6)
Improve paper	280	21% (19 to 23)	10	18% (9 to 30)	58	20% (16 to 26)	26	19% (13 to 26)	93	21% (18 to 25)	33	22% (16 to 30)	24	20% (13 to 28)	2	34	22% (16 to 29)
More data staff	42	3% (2 to 4)	1	2% (.09 to 11)	11	4% (2 to 7)	3	2% (1 to 7)	9	2% (1 to 4)	6	4% (2 to 9)	4	3% (1 to 9)	0	8	5% (2 to 10)
More frontline staff	69	5% (4 to 6)	6	11% (4 to 22)	14	5% (3 to 8)	6	4% (2 to 10)	13	3% (2 to 5)	6	4% (2 to 9)	7	6% (3 to 12)	0	17	11% (7 to 17)

	Total		Municipality		District		Sub-national		National		Regional		LMIC		HIC		Worldwide	
Parallel HIS	82	6%	5	9%	32	11%	12	9%	22	5%	4	3%	3	2%	1	20%	3	2%
		(5 to 8)		(3 to 20)		(8 to 16)		(5 to 15)		(3 to 8)		(1 to 7)		(1 to 8)		(1 to 70)		(.49 to 6)
Reducing indicators	79	6%	1	2%	8	3%	4	3%	25	6%	9	6%	16	13%	0		16	10%
		(5 to 7)		(.09 to 11)		(1 to 6)		(1 to 8)		(4 to 8)		(3 to 12)		(8 to 21)				(6 to 16)
Supervision	354	26%	16	28%	71	25%	41	29%	117	27%	37	25%	32	26%	0		40	25%
		(24 to 29)		(17 to 42)		(20 to 30)		(22 to 38)		(23 to 31)		(18 to 33)		(19 to 35)				(19 to 33)
Training	308	23%	15	26%	65	23%	36	26%	105	24%	37	25%	23	19%	1	20%	26	17%
		(21 to 25)		(16 to 40)		(18 to 28)		(19 to 34)		(20 to 28)		(18 to 33)		(13 to 27)		(1 to 70)		(11 to 24)
Totals IntRural	1350	100%	57	4%	286	21%	139	10%	437	32%	148	11%	121	9%	5	.4%	157	12%
				(3 to 5)		(19 to 23)		(9 to 12)		(30 to 35)		(9 to 13)		(8 to 11)		(.14 to 1)		(10 to 13)
Electronic	345	25%	12	20%	68	24%	41	27%	122	28%	40	28%	29	23%	2	33%	31	19%
		(23 to 28)		(11 to 33)		(20 to 30)		(21 to 35)		(24 to 33)		(21 to 36)		(16 to 32)		(6 to 76)		(14 to 27)
I am not sure	2	.1%	0		0		0		0		0		0		0		2	1%
		(.03 to 1)																(.22 to 5)
Improve paper	94	7%	2	3%	18	6%	10	7%	30	7%	9	6%	8	6%	0		17	11%
		(6 to 8)		(1 to 13)		(4 to 10)		(3 to 12)		(5 to 10)		(3 to 12)		(3 to 13)				(7 to 17)
More data staff	90	7%	4	7%	17	6%	7	5%	22	5%	9	6%	10	8%	2	33%	19	12%
		(5 to 8)		(2 to 17)		(4 to 10)		(2 to 10)		(3 to 8)		(3 to 12)		(4 to 15)		(6 to 76)		(8 to 18)
More frontline staff	91	7%	7	12%	20	7%	8	5%	25	6%	10	7%	9	7%	0		12	8%
		(5 to 8)		(5 to 23)		(5 to 11)		(3 to 11)		(4 to 9)		(4 to 13)		(4 to 14)				(4 to 13)
Parallel HIS	95	7%	3	5%	33	12%	15	10%	25	6%	6	4%	6	5%	2	33%	5	3%
		(6 to 9)		(1 to 15)		(8 to 16)		(6 to 16)		(4 to 9)		(2 to 9)		(2 to 11)		(6 to 76)		(1 to 8)
Reducing indicators	73	5%	0		6	2%	6	4%	32	7%	10	7%	10	8%	0		9	6%
		(4 to 7)				(1 to 5)		(2 to 9)		(5 to 10)		(4 to 13)		(4 to 15)				(3 to 11)

	Total		Municipality		District		Sub-national		National		Regional		LMIC		HIC		Worldwide	
Supervision	327	24% (22 to 27)	16	27% (16 to 40)	66	24% (19 to 29)	33	22% (16 to 30)	102	24% (20 to 28)	34	24% (17 to 32)	35	28% (21 to 37)	0		41	26% (19 to 33)
Training	236	17% (15 to 20)	16	27% (16 to 40)	51	18% (14 to 23)	30	20% (14 to 27)	74	17% (14 to 21)	25	17% (12 to 25)	17	14% (8 to 21)	0		23	14% (10 to 21)
Totals IntUrban	1353	100%	60	4% (3 to 6)	279	21% (19 to 23)	150	11% (9 to 13)	432	32% (29 to 34)	143	11% (9 to 12)	124	9% (8 to 11)	6	.4% (.18 to 1)	159	12% (10 to 14)

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Evaluation of coverage estimation methods

Paul Colrain, 19/06/2020

1 Introduction

In January 2019, the World Health Organization invited expressions of interest for *Modelling Approaches to Produce Estimates of National Immunization Coverage* to develop a modelling approach to produce annual estimates of vaccination coverage that satisfy the conditions:

- I. The model must produce national-level estimates for each of the 195 countries, for each of five vaccine-dose combinations (DTP1, DTP3, MCV1, MCV2, PCV3), for each year during 2000 to 2017.
- II. The modelled estimates must be reproducible
- III. The model must allow for annual updates of the vaccination coverage time-series for each Country
- IV. The model should have a measure of uncertainty around estimated coverage values.

Three institutions responded to the RFP:

1. Imperial College London (Dr. Alex de Figueired, 2020)
2. Swiss Tropical and Public Health Institute (Marek Kwiatkowski, 2020)
3. University of Southampton (Utazi C. E., 2020)

In addition, as part of the Global Burden of Disease Study (GBD), the Institute for Health Metrics and Evaluation (IHME) produces national-level estimates of vaccine coverage annually (Mosser, Quantifying routine vaccination coverage in 195 countries and territories from 1980 to 2017, 2019). All four methods use statistical frameworks to generate expected values with statistical uncertainties.

Here I summarise and compare the four methods from a statistics perspective. I review the data inputs, the data pre-processing steps, and the statistical frameworks used. I pay particular attention to the use of covariates and model parameters and their potential impact on the coverage estimates, both the expected values and their uncertainties. At the end, I take the liberty to make some recommendations.

I use the term “estimate” to mean expected value AND uncertainty, and I try to use consistent terminology across the methods to ease comparison.

The scope of, and the estimates produced by, the four methods have been summarised and compared to WUENIC elsewhere (Mosser, 2020) (Murphy, 2020), and will not be reviewed here. I also do not review the stated rationale for each method.

2 Description and evaluation of methods

2.1 WUENIC

2.1.1 Data

The following input data are used:

- Reported data: Administrative Coverage
- Survey data: Coverage; DHS, MICS, EPI and Other
- Covariates: None

The following pre-processing is carried out:

- Reported data:
 - Administrative coverage values greater than 99% are set to 99%.
- Survey data:
 - Cohort assignment: example – a survey conducted in 2004 and reporting on children aged 12–23 months are assigned a birth cohort of 2003.
 - Recall bias adjustment: multi-dose antigen survey coverage values are adjusted by applying the dropout observed in the documented data to the vaccination history recalled by the child's caretaker.

2.1.2 Method – Jargon-free, simplified description

For each country and each vaccine-dose combination, a set of “guiding principles”, combined with subjective judgement of experts, are applied to “estimate” the coverage time series. In essence, the estimation process consists of linear interpolation to estimate missing admin coverage values, and replacement of available admin coverage values with survey values if the admin values are inconsistent with nearby survey values.

In over-simplified terms, the process is:

- Missing administrative data:
 - linear interpolation (to fill gaps)
 - horizontal extrapolation (if last year missing)
- Administrative bias adjustment (adjusted admin = admin – bias):
If “consistent level [$<10\%$]”
 bias = 0
 (adjusted admin level = admin level, adjusted admin trend = admin trend)
else (bias \neq 0)
 if “consistent trend [subjective judgement]”
 bias = admin interpolation [between survey years] – survey interpolation
 (adjusted admin level = survey level, adjusted admin trend = admin trend)
 else
 bias = admin – survey interpolation
 (adjusted admin level = survey level, adjusted admin trend = survey trend)
 endif
endif

All rules are described in detail below.

2.1.3 Method – Technical details

The WUENIC coverage “estimation” process:

- If national data are available from a single source, the estimates are based solely on that source, with linear interpolation to impute missing values.

- If no data are available for the most recent estimation period, the estimate remains the same as the previous year's.
- If reported data are within ± 10 percentage points of the survey data, the estimates are based on reported data.
- If multiple survey points show a "fairly consistent" relationship with the trend in reported data and the survey data are "significantly different" from reported data, the estimates are based on reported data calibrated to the level established by the survey data.
- If survey data are "inconsistent" with reported data, the reported data show "no consistent relationship" with survey data and the survey data "appear more reliable", coverage estimates are based on survey data, with interpolation between survey data points for intervening years.
- If multiple data points are available for a given country, vaccine/dose, and year, data points are not averaged; instead, "potential biases" in each source are considered and an attempt is made to construct a consistent pattern over time from the data with "the least potential for bias" "consistent with" temporal trends and comparisons between vaccines.
- If coverage patterns are "inconsistent" with the vaccine and dose numbers given, an attempt to identify and adjust for possible biases is made.
- If "inconsistent" patterns are explained by programmatic (e.g. vaccine shortage) or contextual events (e.g. international incidents), the estimates reflect the impact of these events.
- When several estimates are possible, alternative explanations that appear to cover the observed data are constructed and treated as competing hypotheses. Local information is considered, potential biases in the data are identified and the more likely hypothesis is selected.

2.1.4 Comments

Methodology

The transparency of the rule-bound process is undermined by the subjectivity involved in judging "consistency" of trends and "reliability" of data. Couldn't the subjectivity be replaced by mathematical or statistical definitions of adjectives such as "consistent" and "reliable"?

The admin-survey difference 10% cut-off used to define administrative bias could be replaced by the survey coverage measurement uncertainty (eg. half-width of 95% confidence interval), being sure to include both the statistical uncertainty (i.e. sample size) and systematic uncertainties (eg. recall bias uncertainty).

Combination of survey data points:

If multiple data points are available for a given country, vaccine/dose, and year, data points are not averaged; instead, potential biases in each source are considered and an attempt is made to construct a consistent pattern over time from the data with the least potential for bias consistent with temporal trends and comparisons between vaccines.

Why not just combine available survey data points, taking into account their statistical and systematic uncertainties, thus removing one more layer of subjectivity?

Uncertainty

In overly simplistic terms, the WUENIC coverage value is given by:

- If no evidence of bias, WUENIC value = reported admin value
- If evidence of bias, WUENIC value = survey value (+interpolation)

Why not extend your trust in the reported admin values:

- If no evidence of bias:

- WUENIC value = reported admin value
- WUENIC uncertainty = 0
- If evidence of bias:
 - WUENIC value = survey value (+ interpolation)
 - WUENIC uncertainty = survey uncertainty (+ uncertainty from interpolation)

This way, WUENIC could provide a statistical uncertainty for all values.

Note that IHME coverage estimates will, or should, have zero uncertainty when, in their terms, there is no bias (admin=survey).

2.2 IHME

2.2.1 Data

The following input data are used:

- Reported data: Administrative Coverage
- Survey data: Coverage; DHS, MICS, EPI and Other
- Covariates:
 - Socio-demographic Index (SDI); covariate of administrative bias¹
 - Healthcare Access and Quality Index (HAQ); covariate of coverage¹
 - JRF stock-out; covariate of coverage²
 - Mortality rate due to war and terror; covariate of coverage²
- User inputs: None

The following pre-processing is carried out:

- Reported data:
 - Administrative coverage values are adjusted for bias. This is critical to the estimation process, so is described below in the Method sections.
- Survey data:
 - Where available, individual-level data are used to assign individuals to the correct birth cohort.
 - Survey coverage values for the same country, vaccine-dose and year are combined by weighting by sample size.

2.2.2 Method – Jargon-free, simplified description

For each country and each of the vaccine-dose combinations, BCG, DTP3, MCV1 and Polio3:

1. **Evaluate survey/admin ratio values**, for country-vaccine-dose-years for which both survey and admin coverage values are available.
2. **Estimate survey/admin ratio values**, for all other country-vaccine-dose-years, by “interpolating” the ratio values from available years for the same country-vaccine-dose, and/or by “borrowing” ratio values from countries with similar SDI values.
3. **Evaluate adjusted admin coverage values**, for all available admin coverage values, by multiplying the admin coverage value by the corresponding estimated survey/admin ratio.
4. **Estimate adjusted admin coverage values**, for all other country-vaccine-dose-years, by “interpolating” the coverage values from recent years for the same country-vaccine-dose if available, and/or by “borrowing” coverage values from countries with similar HAQ values.

For the other vaccine-doses (DTP1, HepB3, Hib3, PCV3, RotaC, MCV2, RCV1) there are 3 further steps:

5. **Evaluate admin/admin ratio values** (DTP1/DTP3, HepB3/DTP3, Hib3/DTP3, PCV3/DTP3, RotaC/DTP3, MCV2/MCV1, RCV1/MCV1), for country-vaccine-dose-years for which both numerator and denominator admin coverage values are available.
6. **Estimate admin/admin ratio values**, for all other country-vaccine-dose-years, by “interpolating” the ratio values from recent years for the same country-vaccine-dose if available, and/or by “borrowing” ratio values from countries with similar HAQ values.
7. **Evaluate adjusted admin coverage values**, by multiplying each estimated admin/admin ratio value by its denominator’s estimated coverage value from step 4.

¹ See IHME - Supplementary Information

² See WUENIC-IHME summary_differences

The technical details of the “interpolation” and “borrowing” are described below.

2.2.3 Method – Technical details

The three estimation steps (2, 4, 6) above are described here in more detail.

2. **Estimate survey/admin ratio values** (BCG, DTP3, MCV1, Polio3)
 - A Spatio-Temporal Gaussian Process Regression (ST-GPR) is used to estimate the logit of the survey/admin ratio.
 - The mean function is estimated as linear in the Socio-Demographic Index (SDI), no other details provided.
 - The covariance function – no details provided.
4. **Estimate adjusted admin coverage values** (BCG, DTP3, MCV1, Polio3)
 - A ST-GPR is used to estimate the logit of the adjusted administrative coverage
 - The mean function is estimated as linear in the Healthcare Access and Quality Index (HAQ), with country and region intercepts.
 - The residuals of the linear model were smoothed using a LOESS estimator, weighted across geography and time.
 - A Matern-Euclidean covariance function is used. The parameter priors are not presented.
6. **Estimate admin/admin ratio values** (DTP1, HepB3, Hib3, PCV3, RotaC, MCV2, RCV1)
 - A ST-GPR is used to estimate the logit of admin/admin ratio.
 - The mean function is estimated as linear in the Healthcare Access and Quality Index (HAQ), with country and region intercepts.
 - The residuals of the linear model were smoothed using a LOESS estimator, weighted across geography and time.
 - A Matern-Euclidean covariance function is used. The parameter priors are not presented.

The coverage estimates incorporate uncertainty from various sources:

- statistical uncertainty of the survey coverage values (sample size),
- uncertainty in the estimated administrative bias,
- bias introduced by the smoothing process.

2.2.4 Comments

Documents used

The description of the method is taken from three documents:

1. IHME - Quantifying routine vaccination coverage in 195 countries and ...
2. IHME - Supplemental Information - Quantifying routine vaccination coverage
3. WUENIC-IHME summary_differences

The description is incomplete and/or unclear in places:

- Document 1 seems to suggest that the survey data are used twice, firstly to estimate administrative bias, and then to estimate coverage. To be clarified.
- The covariance function parameter priors are not presented in document 2. And it is not clear if the administrative bias estimate covariance function is the same as that used in the coverage estimate.
- Document 3 talks about two covariates, “JRF stock-out” and “Mortality rate due to war and terror”. These covariates are not mentioned in the first two documents.
- The sensitivity of the final coverage estimates to the specifications of the mean and covariance functions (function specifications and parameter priors) is not discussed in the available documentation.

Data and pre-processing

Recall bias adjustment:

- A recall bias adjustment is not applied due to concerns that such adjustments may introduce systematic biases instead of resolving them.
- Do such adjustments introduce more bias than they remove?
- This question can only be answered empirically.
- Either way, the uncertainty in the recall bias should be reflected in the final coverage uncertainty. It appears not to be.

Methodology

Admin bias adjustment:

- Admin bias adjustment is always applied:
 - An admin bias adjustment is always applied, even when there is no evidence of bias, when admin and survey values are statistically consistent.
 - The implicit assumption/assertion is that any difference between survey and admin values is due to admin bias, and not survey sample error for example.
 - When there is no actual bias, this method systematically adds a bias given by the survey sampling error (the estimated “admin bias”).
 - Which estimate is least biased, WUENIC or IHME, depends on how often admin-survey coverage differences of less than 10% are due to actual admin bias (assuming surveys are unbiased).
 - This question can only be answered empirically.
- Admin bias is borrowed from countries with similar SDI:
 - The mean of the admin bias prior distribution is linearly regressed on one covariate, the SDI.
 - In years without survey data, the bias is determined partly by the country’s SDI, and partly by interpolating from the last and next available bias values.
 - A country with better than average data management (no or low admin bias), but with low socio-demographic development (low SDI), is more likely to have its admin coverage “adjusted” downward than upward, unless there is a recent survey (showing that it has no bias). This will cause disadvantage, or at best offence, to countries deserving the opposite.
 - Were other options for the admin bias mean function considered? For example, a constant mean equal to the actual mean bias value for each country-vaccine-dose, or a simple parameterization (eg. linear) of the actual time dependence of the bias (see Imperial). I am not convinced that the SDI is a strong enough covariate of admin bias, that it will provide significantly better estimates than those obtained without any covariates.
- Coverage is borrowed from countries with similar HAQ:
 - The mean of the coverage prior distribution is linearly regressed on one covariate, the HAQ.
 - Where there is missing admin coverage data, the coverage is determined partly by the country’s HAQ, and partly by interpolating from the last and next available admin coverage values.
 - In the absence of administrative coverage data for a period, a country with higher than average coverage, but with poor healthcare quality otherwise (low HAQ), is more likely to have its coverage underestimated than overestimated. This will cause disadvantage, or at best cause offence, to countries deserving the opposite.
 - In the absence of administrative coverage data for a period, if the coverage trend is upward before the period, but the HAQ did not change during the period, the estimate will want to follow the flat HAQ trend rather than the upward coverage trend.

- Were other options for the coverage mean function considered? For example, a constant mean equal to the actual mean coverage value for each country-vaccine-dose, or a simple parameterization (eg. linear) of the actual time dependence of the coverage (see Imperial). I am not convinced that the HAQ is a strong enough covariate of coverage, that it will provide significantly better estimates than those obtained without any covariates.
- This question can only be answered empirically.
- Smoothing:
 - The residuals from the linear prior are smoothed using a LOESS estimator, weighted across geography and time.
 - This appears to be done simply to make the final coverage curves look smoother.
 - This does not improve the individual country-vaccine-dose-year estimates, in fact it introduces a systematic bias in the estimates.
 - This is acknowledged by the inclusion of a systematic uncertainty based on the difference between the smoothed prior and the linear prior.

Uncertainty

- Sources of uncertainty included in the coverage estimates:
 - administrative bias estimation (includes survey statistical uncertainty [sample size])
 - coverage estimation
 - smoothing
- Not included or not presented:
 - Recall bias uncertainty
 - Administrative bias mean function and covariance function specification
 - Coverage mean function and covariance function specification
- The sensitivity of the final coverage estimates to the specifications of the mean and covariance functions (function specifications and parameter priors) should be discussed in the available documentation.

Complexity

- The method is complex.
- Would an EPI manager understand why her/his country's reported admin coverage had been reduced? No!
- Would WHO be able to explain why? Probably not.
- It would be difficult to disentangle the reason why a reported value has been adjusted by a certain amount.
- The estimation process has various steps, and would need to be conducted by technical experts, each time new data is available.
- I am not convinced the improvement in performance (bias and efficiency), if any, over much simpler methods such as WUENIC, warrants such complexity.
- This question can only be answered empirically.

2.3 Imperial College

2.3.1 Data

The following input data are used:

- Reported data:
 - Number of children immunized (number of doses administered)
 - Target population
- Survey data:
 - Survey sample size
 - Number of children immunised
 - DHS surveys only!
- Covariates: None
- User inputs:
 - Recall bias
 - Administrative bias

The following pre-processing steps are carried out:

Reported data:

- If the reported administrative coverage exceeds 99.5%, the numerator (doses administered) is adjusted to give a coverage of 99.5%.
- Six months is subtracted from the year of the reported data (e.g. 2016 becomes 2015.5)!

Survey data:

- Children aged 18-27 (27-36) months at the time of the survey are assigned an immunization date equal to the survey date minus 4.5 (13.5) months!

2.3.2 Method – Jargon-free, simplified description

For each state within a country and for each vaccine-dose:

- Select a value for the recall bias.
- Select a value for the administrative bias.
- Apply the user-selected recall bias adjustment to the DHS survey values of number of children immunized.
- Apply the user-selected administrative bias adjustment to the reported values of number of children immunized.
- Estimate the coverage for all years, by “interpolating” from available survey coverage values (recall bias adjusted number of children immunized/sample size) and available administrative coverage values (admin bias adjusted number of children immunized/target population), giving more weight to nearby coverage values, and to coverage values with larger denominators.
- Evaluate the national coverage as the denominator weighted average of the individual state estimated coverage values.

The technical details of the “interpolation” are described below.

2.3.3 Method – Technical details

- The number of children immunized each year (admin and survey numerators) is modelled using the Binomial distribution:
 - # successes = # children immunized; input,
 - # tries = target population or sample size (admin and survey denominators); input,
 - probability of success = probability of being immunized = coverage; to be estimated.
- A Gaussian Process Regression (GPR) is used to estimate (the logit of) the coverage.

- The prior distribution has a mean linear in time and an exponential covariance function; the priors of the parameters of the mean function and covariance function are clearly specified.

2.3.4 Comments

Documents used

- The description of the method is taken from: Gaussian Process Estimates of National Immunisation Coverage (GPENIC); Dr. Alex de Figueiredo & Dr. Nick Jones, Imperial College London; 31 January 2020

Data and pre-processing

- Survey data:
 - Only DHS survey data is used. No explanation given. There are plans to use MICS data. No mention of EPI and other surveys.
 - Subtraction of 4.5 and 13.5 months from survey date. Shouldn't it be 18+4.5 and 18+13.5 months? And children should be assigned to an annual cohort, not a point in time.
- Admin data:
 - Subtraction of 6 months from year of report?

Methodology

- Recall bias:
 - The recall bias is a user input!
 - The recall bias correction can be applied to all vaccine-doses (eg. DTP1 and DTP3).
 - I assume it can be applied to each vaccine-dose separately, and to each country separately. This is not clear.
 - The final coverage estimation solution should be a turn-key solution, ready to be used when new coverage data is available.
 - So, ideally, the recall bias should be determined from within the data itself.
 - So, the method would have to be extended to first estimate the recall bias (expected value and uncertainty for each country and vaccine-dose) within the data, and then use the recall bias estimate as an input to the coverage estimate.
- Admin bias:
 - The admin bias is a user input!
 - I assume it can be applied to each vaccine-dose separately, and to each country separately. This is not clear.
 - The final coverage estimation solution should be a turn-key solution, ready to be used when new coverage data is available.
 - So, ideally, the admin bias should be determined from within the data itself.
 - So, the method would have to be extended to first estimate the admin bias (expected value and uncertainty for each country and vaccine-dose) within the data, and then use the admin bias estimate as an input to the coverage estimate.
 - The admin bias is set to 1 (no bias) in the analysis presented. So, the survey and admin coverage values remain inconsistent. This is evident in the charts.
 - The admin bias correction is applied to the reported numerator (# children immunized), not to the reported admin coverage. Implicit assertion is that its is the numerator that is biased.
 - Given that the source of the admin bias is not known (numerator or denominator), it seems more appropriate, and convenient, to apply the admin bias correction to the estimated coverage rather than the input numerator.
- Mean function:
 - The prior mean function is a linear function of time.

- Seems reasonable for the prior, but where data is missing for an extended period (eg. >2 years), the estimate will want to follow the overall linear mean trend, which may not reflect the local trend before or after the period.
- Downscaling:
 - To address the denominator scale difference between admin and survey coverage values, the admin data is "downscaled" so that it is on the same order of magnitude. No "downscaling" details are given.
 - If the absence of any admin bias, the admin values WOULD and SHOULD dominate over survey values, as they represent the whole population, whereas the survey values represent a small sample.
 - But we do have admin bias, and we need to use the survey data to estimate the bias. As such, the admin bias corrections are uncertain to a level determined by the sample sizes of the surveys used to calculate them.
 - The issue with this method, is that the admin bias adjustment is applied without any uncertainty, and the admin and survey values enter the estimation calculation on equal terms.
- Weighting to get national estimates:
 - The national coverage each year is given logically by the denominator weighted sum of the estimated state coverage values.
 - The weights are actually obtained through a multinomial regression.
 - I'm not convinced of the logic on first reading. Needs more thought/explanation.

Uncertainty

- Sources of uncertainty included in the coverage estimates:
 - survey statistical uncertainty [sample size]
 - inflated admin statistical uncertainty (downscaling)
- Not included or not presented:
 - Recall bias uncertainty
 - Admin bias uncertainty

Complexity

- Simple and elegant in principle, without covariates.
- But add-ons to address initial over-sights, reduce elegance, and increase complexity.
- If this method is to provide the turn-key solution that is required, it would need to be still more complex (handle recall and admin bias internally).

2.4 Swiss-TPH

2.4.1 Data

The following input data are used:

- Reported data:

- Administrative coverage
- Target population (replaced by UNPD value)
- Survey data:
 - Coverage
 - DHS, MICS, EPI and Other surveys
- Target population data:
 - UNPD Target population (births and surviving infants (replaces Reported value))
- Covariates:
 - Introduction year (WHO/UNICEF)
 - DTP1-3 dropout (WHO/UNICEF)
 - Infant mortality rate (IHME)
 - Mortality from conflict and terrorism in last 10 years (IHME)
 - Socio-Demographic Index (IHME)
 - Population density (UNPD)
 - Urbanisation (UNPD)
- User inputs: None

Data are pre-processed using procedures similar to those used by the WUENIC working group, in addition to the following steps.

- Reported data:
 - Missing administrative coverage values are estimated using linear interpolation between the last and next available values.
 - Where the reported administrative coverage spikes or drops in a single year by more than 10 percentage points before returning close to the previous levels, it is replaced by linear interpolation from the neighbouring years.
 - Administrative coverage is re-evaluated using the UNPD denominator.
- Survey data:
 - Inclusion criteria: crude only, sample size greater than 300, target cohort year > 1999.

2.4.2 Method – Jargon-free, simplified description

For a given country and vaccine-dose (focal model):

1. **Remove the given country-vaccine-dose survey data** from the data set of all survey coverage values (all survey types, all countries, all vaccine-doses, all years).
2. **Rough-estimate the “survey coverage”** for each year of the given country-vaccine-dose series, by “borrowing” survey coverage values from countries with similar administrative coverage, similar demography, at similar times since introduction.
3. **Estimate the final “survey coverage”** for each year of the given country-vaccine-dose series, by combining the rough estimates from the previous step with the survey coverage values omitted in step 1.

The technical details of the estimation steps are described below.

2.4.3 Method – Technical details

The two estimation steps (2, 3) above are described here in more detail.

2. Rough-estimate the “survey coverage”

For all countries and vaccine-doses together (minus the country-vaccine-dose being estimated), the survey coverage is beta-regressed on the listed covariates:

- linear terms for administrative coverage and all other covariates

- squared terms for infant mortality and SDI
- continent interactions with vaccine, logarithm of population density and urbanization
- random effects for country and survey type

The precision parameter of the beta distribution is estimated separately by regressing the variance of the survey estimates for a given country-vaccine-dose-year on administrative coverage, continent, country (random effect), vaccine and survey type.

3. Estimate the final “survey coverage”

The final coverage values are given by the posterior distribution formed from:

- the prior distribution: The time-series of rough estimates for the given country-vaccine-dose, combined with an exponential decay covariance function
- the survey coverage values of the country-vaccine-dose in question

2.4.4 Comments

Documents used

- The description of the method is taken from: Modelling Approaches to Produce Estimates of National Immunization Coverage, Swiss Tropical and Public Health Institute
- I review only the "focus" model. The "base" model is not considered for the same reason stated in the text – a country’s own surveys hold no more weight in its coverage estimation than surveys of other countries.
- Some mathematical details, such as the covariance function specification and parameter priors, are missing.

Data and pre-processing

- Recall bias adjustment:
 - No recall bias adjustment is made to the survey coverage values.
 - And the final coverage estimates’ uncertainties do not account for the uncertainty in recall bias.
- Admin coverage:
 - “Where the reported coverage spiked or dropped in a single year by more than 10 percentage points before returning close to the previous levels, we replaced it by linear interpolation from the neighbouring years.”
 - The implication is that such drops are always data errors, that coverage never drops for just one year.
 - What if the survey coverage does experience the same real shock? This may dilute the power of admin coverage to explain survey coverage.

Methodology

- Survey coverage is regressed on administrative coverage:
 - This is an interesting way to avoid having to explicitly evaluate administrative bias.
 - However, it assumes administrative coverage explains survey coverage in a consistent way, at least across time within a given country.
 - Given that administrative bias is known to vary across countries, the specification should include interactions between country and administrative coverage. It does not appear to do so.
 - In the absence of survey data, countries will “borrow” survey coverage values from countries with similar administrative coverage. Given the heterogeneity of administrative bias, some countries with high coverage will borrow low coverage, and vice versa.
- Calibrate estimates to DHS level:
 - “EPI and “other” surveys report higher coverage on average than DHS and MICS ... so we calibrate model predictions to DHS level.”

- This is not clear. Seems ad hoc.

Uncertainty

- Sources of uncertainty included in the coverage estimates:
 - uncertainty from rough estimation process
 - covariance matrix parameter priors (not described)
 - survey statistical uncertainty (sample size)
- Not included or not presented:
 - Recall bias uncertainty (not included in survey coverage estimates)

Complexity

- The method is complex.
- Would an EPI manager understand why her/his country's reported admin coverage had been reduced? No!
- Would WHO be able to explain why? Probably not.
- It would difficult to disentangle the reason why a reported value has been adjusted by a certain amount.
- The estimation process has various steps, and would need to be conducted by technical experts, each time new data is available.
- I am not convinced the improvement in performance (bias and efficiency), if any, over much simpler methods such as WUENIC, warrants such complexity.
- This question can only be answered empirically.

2.5 Southampton University

2.5.1 Data

The following input data are used:

- Reported data:
 - Doses administered (divided by UNPD Target population to give adjusted Admin coverage)
 - Official coverage
- Survey data:
 - Coverage
 - DHS, MICS, EPI and Other surveys
- Target population data:
 - UNPD Target population (births and surviving infants (replaces Reported value))
- Covariates: None
- User inputs: None

The following pre-processing is carried out:

- Survey data:
 - use survey if its sample size is greater than 300 or if the survey is labelled valid
 - use Card+History if available, rather than Card
 - if multiple survey values available, use that with largest sample size
 - recall bias adjustment - same as WUENIC
- Reported data:
 - replace admin denominator with that from UNPD
 - if denominator adjusted admin < 100%, use it, otherwise use official; if no official, mark as missing
 - Admin bias adjustment: if difference between adjusted admin and survey is < 10%, use adjusted admin, otherwise use survey

2.5.2 Method – Jargon-free, simplified description

For each country and vaccine-dose (model 2):

1. estimate the mean and variance of the available coverage values (adjusted admin), and the correlation between the values and their predecessors, using the available values,
2. estimate the missing coverage values, using the estimated mean and variance, the last available and next available value, and the estimated correlation between neighbouring values.

2.5.3 Method – Technical details

For each country and vaccine-dose (model 2), a Bayesian framework is used to estimate the parameters of a first-order auto-regression of the coverage values (adjusted admin). The steps are:

- choose appropriate prior distributions for the coverage intercept and variance, and the auto-regressive parameter and variance of the latent process,
- estimate the marginal posterior distribution of the parameters using the available coverage values,
- calculate the expected values and the uncertainties of any missing coverage values, using the posterior parameter distributions.

2.5.4 Comments

Documents used

- The description of the method is taken from: Bayesian time series regression methods for estimating national immunization coverage; Utazi C. E., Sahu S. K. and Tatem A. J., University of Southampton, UK
- I review only model 2, in which each country-vaccine-dose is estimated separately.

Data and pre-processing

- Admin bias adjustment: if difference between adjusted admin and survey is $< 10\%$, use adjusted admin, otherwise use survey.
- This seems overly simplistic. More detail needed.
- Appears admin replaced by survey only in years with survey values.
- Charts seem to confirm this – zig-zag!
- So, survey values are only used if they disagree with corresponding admin values.

Methodology

- The AR(1) does not follow an underlying trend, so in periods without admin coverage values, the estimate will want to return to the mean admin coverage.

Uncertainty

- The AR(1) parameter priors are presented.
- But there is no discussion of uncertainty due to admin bias adjustment (survey statistics) or recall bias adjustment.

Complexity

- Simple, one-step, logical model, without covariates.
- But overly-simplistic treatment of admin-bias adjustment.

3 Overview of the methods

3.1 Administrative bias treatment

It is worth noting that if administrative coverage figures were not biased, we would not be having this conversation. We would use the administrative coverage figures as they are. We would not tweak them or smooth them. We would just fill any gaps.

So, administrative bias is THE problem. Missing administrative data is also an issue but much more easily resolved. And given that we need to correct for administrative bias using survey data, the fact that survey coverage figures may suffer from recall bias is another problem.

So how is administrative bias treated in each method? In over-simplified terms:

- WUENIC; for each country and vaccine-dose:
 - Calculate admin-survey difference (where survey available)
 - Interpolate admin-survey difference (where survey not available; linear interpolate)
 - Evaluate bias: if difference < 10%, bias = 0, bias = difference
 - Apply bias adjustment: adjusted admin = admin – bias
 - Interpolate adjusted admin (where admin not available; interpolate)
- IHME; for each vaccine-dose:
 - Calculate admin-survey difference (where survey available)
 - Interpolate, borrow, and smooth admin-survey difference
 - Evaluate bias: bias = difference
 - Apply bias adjustment: adjusted admin = admin – bias
 - Interpolate, borrow, and smooth adjusted admin
- Imperial; for each country and vaccine-dose:
 - Apply bias adjustment: adjusted admin = admin – user defined bias
 - Interpolate and smooth adjusted admin and survey together
- Swiss-TPH:
 - Not applicable – admin coverage is not adjusted for bias, as it is not estimated, but used as a covariate of survey coverage.
- Southampton: for each country and vaccine-dose:
 - Calculate admin-survey difference (where survey available)
 - Evaluate bias: if difference < 10%, bias = 0, bias = difference (where survey available)
 - Apply bias adjustment: adjusted admin = admin – bias (ONLY where survey available!)
 - Interpolate and smooth adjusted admin (where admin not available)

The key differences between WUENIC and IHME in the treatment of administrative bias are:

- Country specific:
 - WUENIC: yes
 - IHME: no, assumes countries with similar SDI have similar admin bias
- Evaluation of admin-survey difference:
 - WUENIC: difference is calculated where survey available, linear interpolated across time where not
 - IHME: difference is estimated statistically across time and across countries
- Definition of bias:
 - WUENIC: bias = 0 if calculated difference < 10%, otherwise bias = difference
 - IHME: bias = estimated difference; effectively assumes all admin values are biased!

3.2 Gaussian processes

Why use them?

- Gaussian Process regressions are “sophisticated smoothing devices”.
- Measurement uncertainties can be propagated through to the estimate uncertainties. The uncertainties (confidence intervals) of the estimates are provided by the posterior distribution.
- Understanding of the context can be used to define appropriate prior mean functions and covariance functions.
- However, the choice of prior mean functions and covariance functions will influence the expected values and uncertainties of the estimates. So, one must take care to cover all reasonable functional forms and parameter values when generating the prior distributions.

Prior mean specification

- Where there are missing coverage values, the estimates move towards the specified prior mean function (at a rate determined by the covariance function).
- Temporal trend:
 - Ideally, the prior mean function should follow the evident temporal trend (eg. moving average).
 - If the mean function does not follow the temporal trend evident in the coverage data, estimates of missing coverage values will stray from that trend.
- Covariates:
 - It might be useful to use other covariates in addition to time, to refine the estimates when temporal gaps in the data are large.
 - However, if estimates stray from the evident temporal trend, a simple and convincing justification should be available.
 - Complicated specifications with many covariates, or covariates with little predictive power, should be avoided.
 - The 195 countries are not anonymous random draws from a large population of countries. Each country is conscious of its reported administrative data. We should avoid at all costs causing disadvantage to a country by estimating its coverage to be lower than reported without a simple and convincing explanation (eg. a recent survey).

3.3 Uncertainty

The mere presence of an uncertainty might add credibility to an estimate, but every effort should be made to include all sources of uncertainty, statistical and systematic, in the final coverage estimate uncertainty. If the coverage estimate uncertainty does not include, for example, the recall bias uncertainty, the estimate lacks credibility.

The final coverage estimate uncertainty should include uncertainty due to:

1. Administrative bias estimate uncertainty
 - a. Survey coverage uncertainty:
 - I. Statistical uncertainty (sample size)
 - II. Systematic uncertainty (Recall bias uncertainty)
 - b. Uncertainty from administrative bias estimation process
 - I. Statistical uncertainty
 - II. Systematic uncertainty (eg. prior specification uncertainty)
2. Coverage estimate uncertainty
 - I. Statistical uncertainty
 - II. Systematic uncertainty (eg. prior specification uncertainty)

Although it is not always explicitly stated, it appears that the systematic uncertainties arising from any estimation steps (eg. GPR) are taken into account. The statistical uncertainty is generated by the estimation process itself.

However, it appears that none of the four methods evaluate and propagate the recall bias uncertainty through to the coverage estimate uncertainty, and it is not always apparent that the survey sample size uncertainty is taken into account.

3.4 Complexity

The complexity of each method may be reviewed according to simple criteria:

- Would an EPI manager understand why her/his country's reported admin coverage had been reduced or increased?
- Would WHO be able to provide a simple and convincing explanation?
- Would WHO be able to run the estimation each year when new data are available, without technical assistance from the institution?
- Assuming a method provides significantly better estimates (less biased, more efficient) than WUENIC, does the improvement justify the added complexity? Of course, this question can only be answered using Monte Carlo simulation.

I suspect the answer to each question is in the negative for all 4 methods, especially those that use covariates.

3.5 Brief summary of key issues

The strengths of each method are clearly stated by each institution. Here I highlight what I believe are the key issues with each method.

- WUENIC:
 - Subjectivity in judgements of reliability and consistency of levels and trends
 - Ad hoc 10% cut-off in definition of admin bias
 - No uncertainty on estimates
- IHME:
 - Highly complex, use of covariates to borrow from other countries
 - No recall bias adjustment or systematic uncertainty
 - Survey values are used in place of admin, even when no evidence of admin bias.
 - Borrowing: missing coverage values will be underestimated when a country has higher than average coverage but lower than average HAQ values, and vice versa.
- Imperial:
 - Uses DHS survey data only.
 - Not a complete turn-key solution, recall and admin bias input by user, not extracted from the data.
 - Admin bias correction of numerator only.
- Swiss-TPH:
 - Highly complex, use of many covariates to borrow from other countries
 - No recall bias adjustment or systematic uncertainty.
 - Admin coverage demoted to an explanatory variable of survey coverage => survey values used in place of admin, even when no evidence of admin bias.
 - Borrowing: missing coverage values will be underestimated for countries with higher than average coverage.
- Southampton:

- Overly simplistic administrative bias adjustment
- Survey data only used if admin and survey values are inconsistent (difference > 10%)

4 Recommendations

4.1 Break the problem down

4.1.1 The problem

The data have the following problems:

- Admin data:
 - Missing data
 - Measurement error: numerator and/or denominator (admin bias)
- Survey data:
 - Measurement error: numerator (recall bias)

4.1.2 The solution

Principles

Any solution should respect the following principles:

1. For each *available* admin coverage value:
 - a. if there is no *evidence* of bias, the value should not be adjusted,
 - b. if there is *evidence* of bias, the value should be adjusted by the evident bias.
2. For each *missing* admin coverage value, the value should be estimated in a *simple* and *transparent* manner.

To clarify point 1.a, we should not smooth or replace available data with trends. Shocks, such as floods, wars, supply shortages should be reflected in the coverage values. We should only be correcting measurement errors (1.b) and estimating coverage where there are missing data (2). Finding and explaining underlying trends are separate tasks.

On point 2, missing coverage values may be estimated by “interpolating” from available coverage values in the same country-vaccine-dose time series, and/or by “borrowing” values from countries with similar covariate values. While borrowing allows one to produce estimates for a country-vaccine-dose time series with little or no data, care should be taken not to cause disadvantage or offence, without a clear and compelling explanation.

Solution steps

Reaching agreement on one complete solution might be difficult. But reaching agreement on how to carry out some of the steps towards a solution might be easier. WHO, UNICEF and IHME should work together to agree a common approach to answering the following tractable questions:

Survey:

- How to assign survey results to birth cohorts?
- How to evaluate and correct for recall bias?
- How to combine multiple survey values in one year?

Admin:

- Should admin coverage values be adjusted if there is no evidence of bias?
- What would constitute evidence of bias?
- Should covariates be used to estimate missing values?

- For example, should covariates be used to estimate the means of the prior distributions (admin bias and/or coverage)?
- To help answer this particular question, the results (expected values and uncertainties) with and without covariates could be compared. If there is little difference between the estimates in most cases, it would be difficult to justify the use of covariates. Whether or not the use of covariates improves the efficiency or bias of estimates is an empirical question that can only be answered through Monte Carlo simulation.

Once agreement has been reached on how to solve these more tractable problems, one can concentrate on the main issue: How to correct for admin bias?

Administrative bias treatment

The problem of admin bias should be solved directly, explicitly, within the data, within each country separately, by comparing admin and survey data, using a combination of rules, judgement, and/or statistics. The Imperial solution does not handle administrative bias internally, and the Southampton solution's administrative bias adjustment is overly simplistic. The IHME solution favours survey over admin even when there is no evidence of admin bias, and uses covariates to borrow coverage from other countries, and so will tend to underestimate missing coverage of high-performance countries. The Swiss-TPH solution does not tackle the problem of admin bias explicitly but uses admin coverage only as an explanatory variable of survey coverage, and uses covariates to borrow coverage from other countries.

A suitable solution to the admin bias problem may lie somewhere between WUENIC and IHME, both of which tackle the problem head on, using rules and statistics, respectively:

- WUENIC without the subjective judgements and ad hoc cut-offs (eg. >10%), replaced by statistical measures of consistency and reliability,
- IHME without borrowing admin bias using covariates, and with adjustment ONLY when there is statistical evidence of bias.

4.2 Simulate immunization coverage

We cannot know which method provides the most efficient and least biased estimates unless we know the actual coverage values. Monte Carlo simulation could be used to generate time series of admin and survey coverage values. At a minimum, the following time series would need to be generated for each country (or state within a country) and vaccine-dose:

- Shocks (type, date(s), impact on births, coverage, reported coverage)
- Annual births (considering underlying trend and effect of shocks)
- Infant mortality (considering underlying trend and effect of shocks)
- Doses administered (considering underlying trend and effect of shocks)
- Recorded doses administered (considering underlying trend and effect of shocks)
- Surveys (date, type, sample size, recall error)

The series could be generated by hand to reflect desired characteristics or it could be generated randomly by specifying the underlying probability distributions (births, birth growth rates, natural disasters, surveys, etc.). Series could easily be generated for many vaccines and many countries, and covariates and their covariance matrices could easily be added based on observed covariances.

With such simulated coverage time series, we could measure the bias and efficiency of each method under different circumstances (low, high, increasing, decreasing, chaotic coverage trends; low and high recall bias; denominator bias and numerator bias; frequent shocks and no shocks). The idiosyncrasies of each model could be revealed, explained, and treated.

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WUENIC 2.0

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

21 to 25 September 2020

Background

- WUENIC 1.0 started over 20 years ago and was the only source of annual national estimates of vaccination coverage
- Today, IHME also produces annual estimates of national vaccination coverage
- Used cases for WUENIC have changed over time
- WUENIC GATHER compliant – except never compared head-to-head and no quantitative uncertainty
- WHO and UNICEF have started a process to develop the next generation of immunization coverage estimates: WUENIC 2.0
 - Three modeler groups engaged (Swiss TPH, Imperial College, WorldPop at Southampton)
 - Stakeholder analysis done (by Swiss TPH)
 - Process under [IVIR-AC](#) guidance



WUENIC – Use cases

Initial



Assessing national immunization performance trends
to fulfill WHO and UNICEF mandates and monitor global initiatives (GVAP, SDGs)



Planning and providing a framework for setting goals
(E.g., IA2030)



Determining relationships
between service delivery and disease occurrence



Advocacy

Other uses and new demands



Performance-based financing (PBF) decisions SAGE explicitly advised against use of coverage estimates for PBF in 2011 <https://www.who.int/wer/2012/wer8701.pdf?ua=>



Forecasting and VPD risk assessment



Country vaccination coverage estimates national/subnational (e.g., India, Pakistan with WUENIC-like method)

Current and potential use of WUENIC in health related global initiatives

Sustainable Development Goals – *Leaving no one behind*



WHO (GPW13)

A world in which all people attain the highest possible standard of health and well-being



Immunization Agenda 2030

A world where everyone, everywhere, at every age, fully benefits from vaccines for good health and well-being



Gavi 5.0

Leaving no-one behind with immunization

- SDG M&E guiding principles: Country-owned, strengthening ability of countries to produce health statistics
- WHO-GPW13 uses country data in as much as possible

Exploring alternative methods to WUENIC - Timeline up to today



Previous IVIR-AC Recommendations

Proposed process to review estimation coverage approach

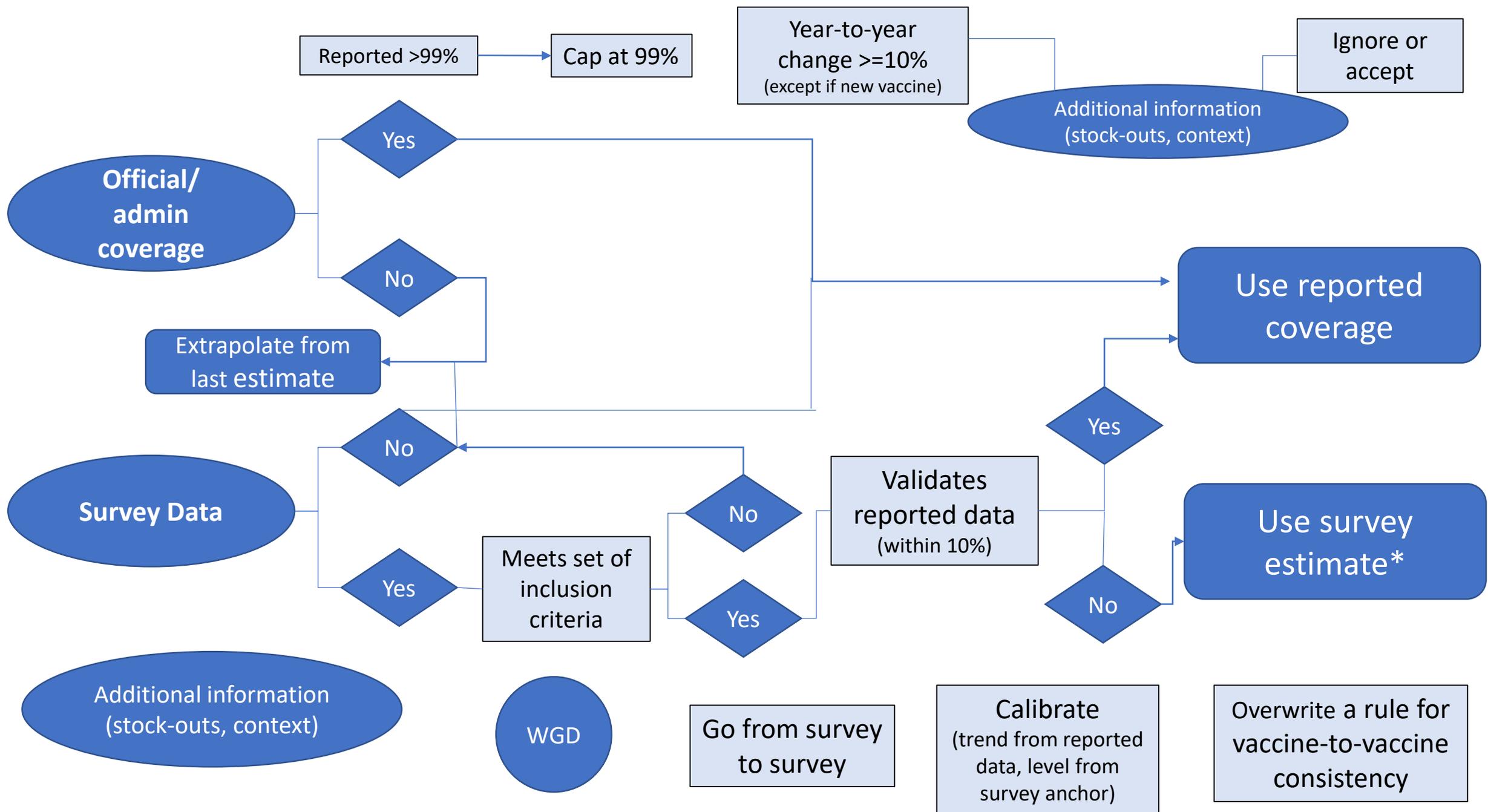
- IVIR-AC does not have any major concerns on the process proposed and agrees with the proposed plan to find and assess alternative approaches (*not replacing WUENIC*).
- Illustrate the current approach with a flow diagram of data inputs and decision rules → to improve transparency and to facilitate comparison with alternative approaches



High-level principles for evaluating alternative methodologies

- Models are only as good *as the data they are based on*
 - Parallel efforts are needed to improve country-level capacity for data collection and interpretation
- Use multiple data sources – acknowledging limitations of each
- Transparency with data and source code
- Formal quantification of uncertainty
- Appropriate validation – but absence of a “gold standard” is a limiting factor
- Clear communication to country level stakeholders – ensure country buy-in and ownership





*With recall bias adjustment for DTP3, PCV3

WGD – working group decision

Comparison of available models

Modeling Immunization Coverage

Introduction

- Three models were developed by external groups for modeling immunization coverage
 - A team from the Imperial College London proposed a methodology based on Gaussian processes.
 - WorldPop at Southampton University developed a Latent Gaussian Model using Integrated Nested Laplace Approximations (INLA).
 - The Swiss Tropical and Public Health Institute (Swiss-TPH) team proposed a two-stage approach. First all vaccines were modelled together using a beta regression. Then, the estimates from the first step were combined to survey-based estimates of specific vaccines to produce final estimates using a Bayesian approach.
- Based on initial feedback from the IVIR-AC sub-group, the model from Swiss-TPH was dropped. In the following slides, we will focus on the first two models.
- In addition, IHME uses modeling techniques to estimate annual national immunization coverage. IHME was not formally compared to the models above but appears in some of the slides.



Modeling Immunization Coverage

Models Description

	Imperial's Model	Southampton's Model
Input	DHS only Administrative Coverage	DHS, MICS, EPI and other surveys Administrative Coverage UNPD population estimates
Pre-processing	Computation of subnational (region) survey estimates for regional level modelling	Admin "bias correction" adjustment to produce complete series for modelling
Model (Bayesian framework for both)	Independent variables: None Dependent variables: subnational vaccination coverage National estimates are weighted averages of subnational estimates (using modelled proportions of vaccinated children)	Independent variables: None Dependent variables: adjusted administrative coverage Autoregressive of order 2 Independent WHO regional model fitting
Scope (of the current submissions)	~ 90 countries with DHS data From 1980 to 2020 National and subnational (regional)	~ 174 countries From 2000 to 2019 National estimates



Modeling Immunization Coverage

Pros vs Cons of the methods

	PROS	CONS
Imperial's Model	<ul style="list-style-type: none">• Use subnational data to get more information from the data• Estimates primarily driven by survey data	<ul style="list-style-type: none">• Processing subnational data (short-term challenge)• Less use of administrative coverage• No use of covariates
Southampton's Model	<ul style="list-style-type: none">• Administrative bias adjustment can help get more from reported data• Simpler computations	<ul style="list-style-type: none">• Some of the adjustment can be perceived as not fully justified• No use of covariates



Remarks

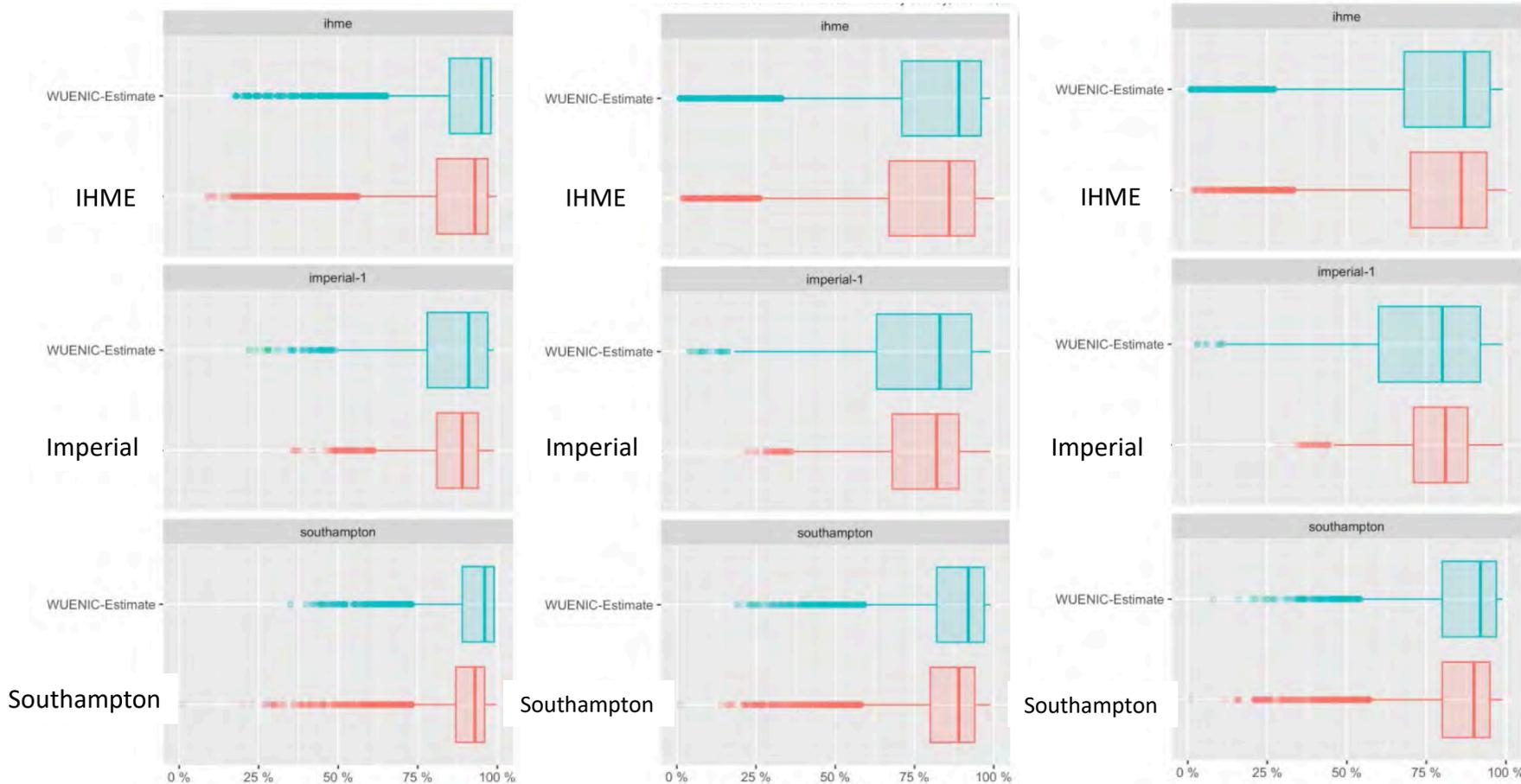
- Many of the cons listed above are due to the immaturity of the models
- Some of these cons can be improved in future iterations of the models

Modeling Immunization Coverage Comparison

DTP1 coverage

DTP3 coverage

MCV1 coverage



Modelled data and WUENIC comparisons available here (*currently only for internal use*)

<https://unicef.shinyapps.io/wuenic-model-explorer/>

Modeling Immunization Coverage

Comparison of the difference models' results with the current WUENIC results

- Note that the period is not the same, hence the number of comparison points is different across the models

	Period	Average of the differences	Percent greater than WUENIC	Percent within WUENIC within Interval	Average interval width
IHME	1980-2019	-1	50	54	8
Imperial-1	1981-2019	2	51	56	15
Southampton	2000-2019	-2	43	60	17

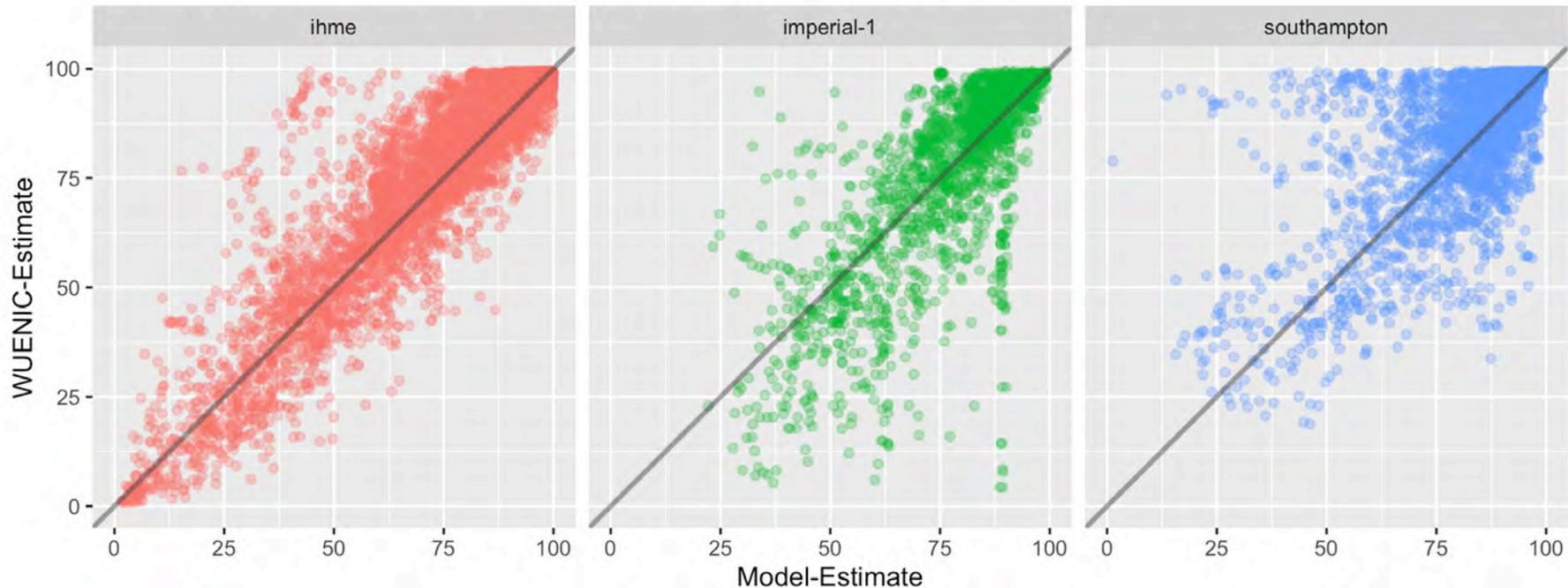


Country level comparisons can be found at: <https://unicef.shinyapps.io/wuenic-model-explorer/>
Modelled data and WUENIC comparisons available here (*currently only for internal use*)

Modeling Immunization Coverage

Comparison of WUENIC & modeled estimates for DTP3

Note: 45 degree line indicates no difference between WUENIC & model estimate



Country level comparisons can be found at: <https://unicef.shinyapps.io/wuenic-model-explorer/>
Modelled data and WUENIC comparisons available here (*currently only for internal use*)

Modeling Immunization Coverage

Simulation approach for comparison

- Simulation techniques were proposed as a possible approach for comparing the different models
- Ideally, in a simulation, a comprehensive universe is created and different models are fitted under realizations of that universe
- Given the lack of understanding/evidence on the underlying mechanism of the immunization coverage, creating comprehensive universes is not practical



Modeling Immunization Coverage

Simulation approach for comparison

Option 1

- Simulate a limited number of scenarios e.g. administrative data issues, stockouts, etc.
- **Limitations**
 - Modellers need a lot of information to fit their models (e.g. disaggregated estimates, recall information, UNPD data, etc. Hence a limited set of information may not be sufficient
 - Replicating some of these special cases to ensure enough data is produced may lead unexpected behaviours and/or lead to a universe that can be very different from the actual problem of interest

Option 2

- Use the existing survey and administrative data to generate plausible vaccination coverage data
- **Limitations**
 - There is a risk of producing plausible coverage values that are significantly influenced by the current WUENIC



Modeling Immunization Coverage

Simulation approach for comparison

An example of the challenges with simulated data



From: Monte Carlo Simulation of Immunization Coverage Rates, by Paul Colrain, July 2020.
Already shared with the IVIR-AC sub-working group.

Modeling Immunization Coverage

Simulation approach for comparison

Proposed simulation approach

- As a hybrid of the two options
- Use Option 2 (existing admin/survey data) to generate plausible vaccination coverage data
- Adjust a limited set of the simulated data to account for the different edge scenarios
 - Major shocks due to stockouts or other events
 - Data quality issues e.g. inconsistencies in reported data
 - Inconstant survey data
 - Etc
- Note that many of these issues will automatically exist in the plausible data from Option 2 but we can force additional situations for the purpose of testing the models.



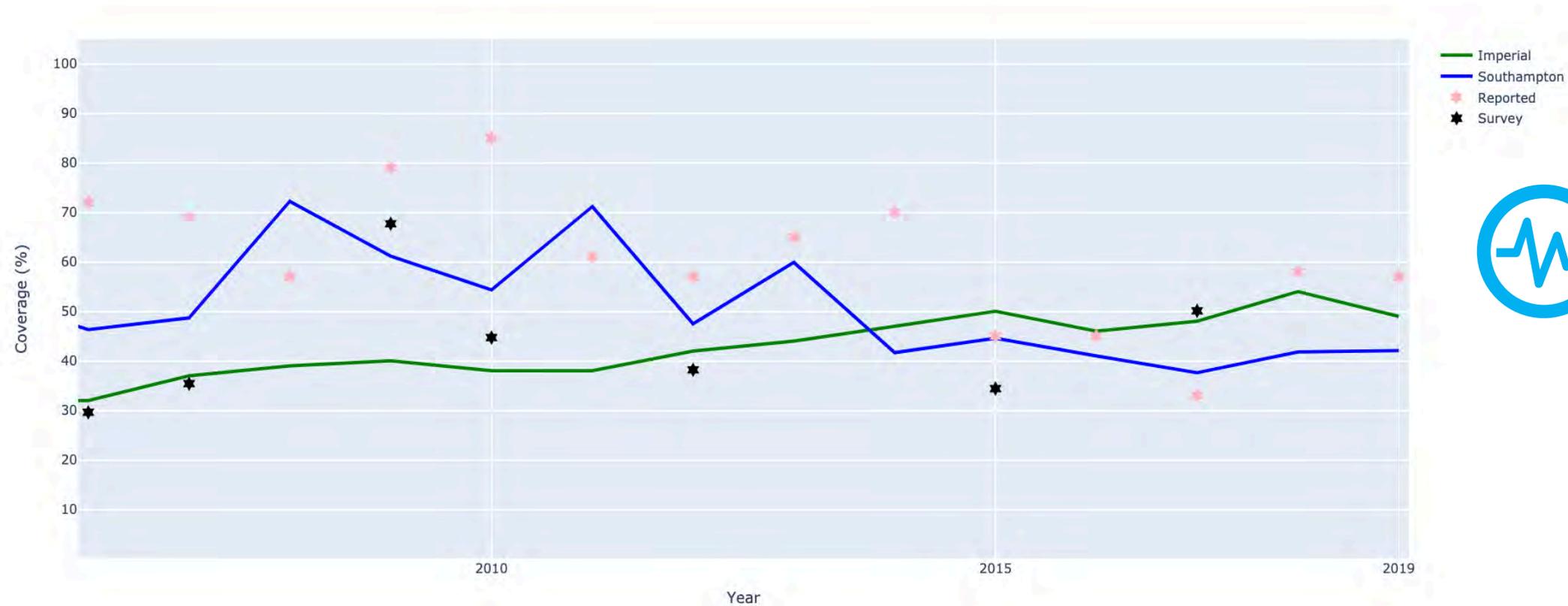
Modeling Immunization Coverage

Simulation approach for comparison



Modeling Immunization Coverage

Simulation approach for comparison



Modeling Immunization Coverage

Takeaway

- Both Imperial and Southampton models are not mature yet but have potential
- Further engagement with both modellers can help improve the models and possibly help address use-cases within or outside of WUENIC e.g. subnational estimates
- The “simulation” work should focus on testing selected features of the models e.g. borrowing information across countries, possible use of covariates



The big picture and summary

Main observations from the model-based methods for national coverage estimates

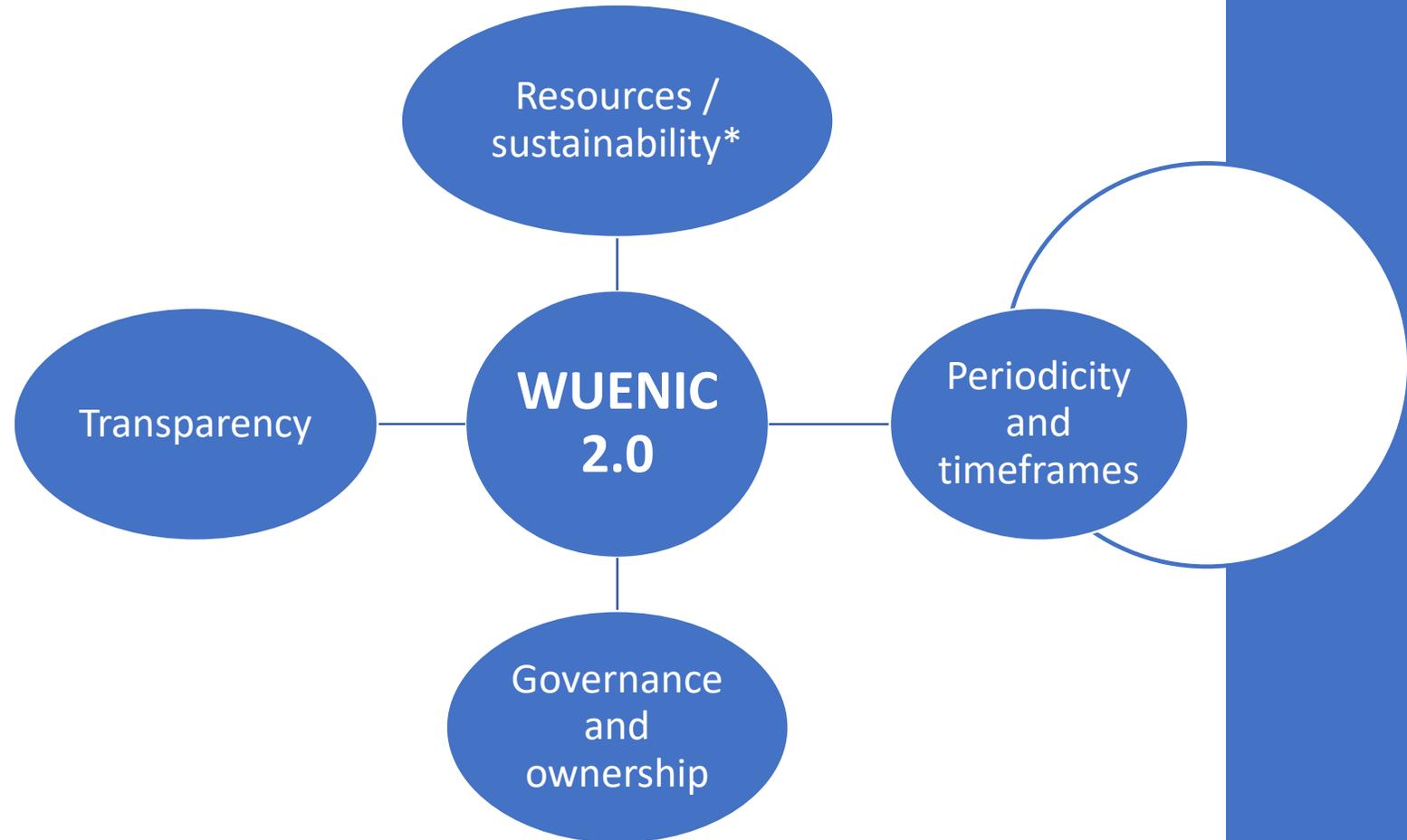
- Models did not produce estimates for every WHO/UNICEF Member State each year
- In some cases the estimates are very sensitive to small changes in data availability
- Smoother trends than WUENIC (*though IHME is trying to incorporate shocks to the system like conflict, stock-outs, etc.*)
- Uncertainty interval widths can range from <1 to 100
 - On average, IHME narrowest (~10) & Swiss-TPH widest (~45)
- WUENIC estimate falls within ~55-60% of models' uncertainty intervals, on average
- Global aggregation for IHME still produce estimates similar to WUENIC
 - Global DTP3 coverage (2019): WUENIC 85; IHME 82



Considerations for the way forward

Options being considered:

1. Improved rule-based WUENIC
- 2. Hybrid approach**
3. Model instead of rule-based approach



* Resources: Person/time for Production. Review. Consultations. Computational power.

WUENIC Guiding Principles and options

Guiding principles	Rationale	WUENIC 1.0	IHME (as a comparison)	Option(s)	Trade Offs
Objective	Monitor changes in routine immunization performance, not taking into account supplementary immunization activities or late vaccination	Estimate RI performance	Estimate RI performance as an input to burden of disease models	Estimation of immunity, forecasting	Different use cases
Years estimated	Since EPI was established in most countries to year with data available for most countries	1980 to previous year	From 1980 Up to previous year, but last year is forecasted	Estimating up to earlier years, for example 2020 estimating 2018	Data availability (particularly survey data)
		Estimate is done for every year	Estimate is done for every year	Stop at year with last “valid” data point (e.g., 5 years forward of a survey)	
Periodicity	Use of calendar years, as most common cycle for country EPI Planning	Annual	Annual	Every 2 years	Data availability vs. timeliness
Date of release	JRF data available for most countries, allowing country consultation, and in time to include in GVAP annual reporting to SAGE Agreed upon with Gavi (not documented)	Release by 15 July	Available before WHA	Later release	Data availability vs. timeliness
Revision of time series	Historical series are revised as new data (mostly surveys) becomes available to inform earlier years	Annually	Annually	Freezing earlier years	Not revising when known new data available Communication considerations

Guiding principles	Rationale	WUENIC 1.0	IHME (as a comparison)	Option(s)	Trade Offs
Countries included	To meet WHO mandate of monitoring the health situation of Member States To harmonize with UNICEF mandate of monitoring the situation of children around the world	All WHO & UNICEF Member States	Most countries (some small island states not done)	Most countries	Confidence in estimates, as countries with data limitations not done. If done only for countries with some data criteria it may be difficult to estimate regional/global
Estimate produced	To monitor goals or targets set by specific initiatives (GVAP, SDGs, polio eradication, Hep B control, YF)	BCG, HepB birth dose, DTP1, DTP3, HepB3, Hib3, Polio3, IPV1, PCV3, Rota last, MCV1, MCV2, Rubella, Yellow Fever	Similar vaccine/doses	Fewer vaccine doses	Simplify current process, as review is done vaccine by vaccine. No estimates for some vaccine/doses available
Dependencies between vaccine/doses	Coverage with one vaccine can be different from another even if recommended at same age (stock issues, avoidance of simultaneous injections)	Vaccine-specific*	DTP3 used to calibrate others	Base some vaccine/dose coverage on another	Simplify current process, as review is done vaccine by vaccine May bias estimates for some vaccines as performance may be different
Vaccine/doses included for a given country	As WUENIC is national estimate, vaccines in sub-populations not included	Those in national immunization schedule	It used to be done in some cases (e.g., Hib in China used in private sector)	Produce estimates for vaccines used sub-nationally	No standard pop estimation for subnational levels, except maybe WorldPop for some It would require a set of criteria (e.g., if introduced in >1 state/province)
	Current rule-based methodology requires at least one data point	Start year for which at least one data point has been reported	Not necessary to have a data point	Forecast	The estimate would have to be based on a different vaccine/dose
	Annual country performance, thus if vaccine introduce mid-year it is annualized Yellow Fever is estimated for entire country in those considered at risk in list kept by WHO (only affects few PAHO countries)	Annualize partial year/country (intro year; YF)	Unclear YF – not applicable	Start estimation for year with full vaccine use For YF, estimate for proportion of population targeted	It would reduce info for year of introduction (unless introduced January 1)

*With the exception of rubella-containing vaccine (RCV) that is based on measles, as all RCV currently used are combined with measles. Also, one vaccine estimate may inform another (e.g., vaccines recommended at same age, DTP1/DTP3)

Guiding principles	Rationale	WUENIC 1.0	IHME (as a comparison)	Option(s)	Trade Offs
Country specific/ "borrowing data" between countries	EPI performance is heavily influenced by EPI management. Thus, countries with similar socioeconomic or other characteristics may still perform widely differently Aligned with SDG and GPW13 principles	Country-specific	Covariates	Use of covariates	Assumptions about correlations between factors with EPI performance
Data smoothing	As per objective, the aim is to estimate annual performance, which can be affected by stock and "shocks" to the system (AEFI, sociopolitical crises)	Not done	Yes	Modelled	Smooth data may be easier to digest, but may lose information on EPI performance
Uncertainty	GoC is based on availability of data sources and their consistency, which is often done for rule-based approaches	Grade of Confidence (GoC) on estimate (1 to 3)	Credible intervals	It will depend on method used to estimate. If rule-based, explore more levels to GoC?	Desirable attribute Interpretability
Sub-national estimates**	As per WUENIC objective (national) Data quality of admin data Limited survey data availability	Not done	Has a different model for sub-national estimates in selected countries	Attempt for large countries	It would require to define set of countries and the sub-national level to estimate. The smaller the level, the more uncertainty
Country consultation	Mandated by WHO	Yes	No	Using externally produced estimates would not require it	Governance – WHO/UNICEF
Governance	Independent estimation process (and not an assessment of country data)	WHO/UNICEF	IHME, GBD	Using externally produced estimates	WHO/UNICEF not producing estimates

**WHO/UNICEF have supported a small number of countries to produce sub-national estimates using a similar approach to WUENIC 1.0 and to report their country-level aggregation as their official coverage. The ability to produce sub-national estimates has been limited by availability of coverage data different from admin.

Summary

- Current WUENIC rule-based approach was mostly GATHER compliant except:
 - Had not been compared with alternative approaches
 - Does not include quantitative estimates of uncertainty
- It has now been compared with modelling approaches
- Current rule-based approach has desirable properties (e.g., using country statistics in as much as possible, “understandability”) but there is room for improvement: revisit guiding principles, better document decisions, make it ultimately more transparent
- Models open new possibilities
 - Imperial model could be adapted to include additional inputs, and provides a framework to use subnational data
 - Southampton uses techniques that ultimately automate predicting an estimate, with the bonus of providing uncertainty
 - IHME is an established coverage estimation with a different goal and main use-case, but results are converging for most countries
- All estimation approaches are limited by the quality of underlying data and the fact that no “gold-standard” exists
- Way forward for “WUENIC 2.0” to be discussed in an ad hoc stakeholder consultation

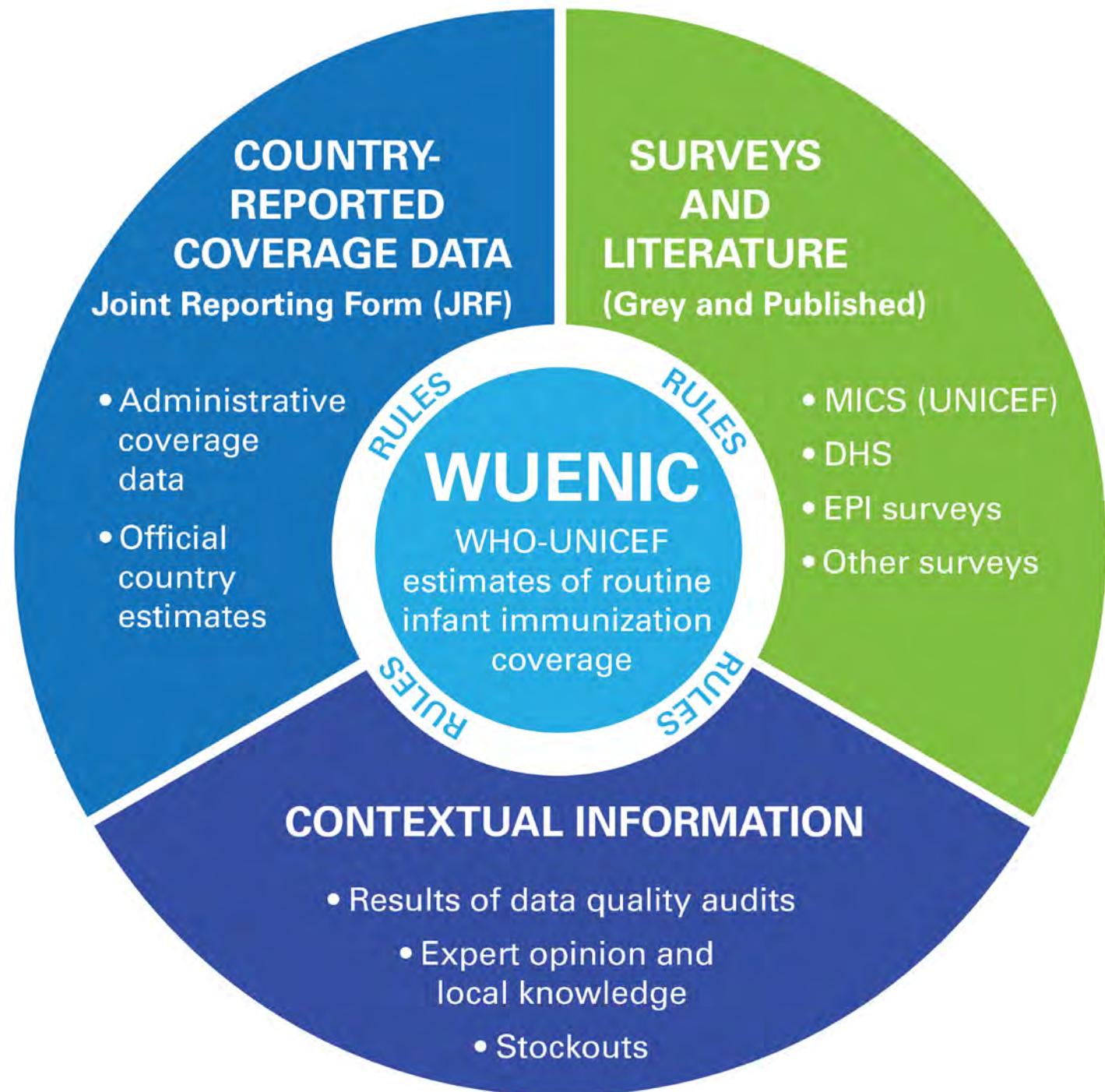
Questions to IVIR-AC

1. In light of use cases for WUENIC and observations on comparisons and simulations, what does IVIR-AC see as the main pros and cons of a modelling approach vis-à-vis the current rule-base method?
2. What model(s) to estimate national immunization coverage for Member States would IVIR-AC recommend to WHO and UNICEF for replacing and/or complementing WUENIC?



EXTRA SLIDES

Current WUENIC input data



WUENIC: strengths and limitations

STRENGTHS

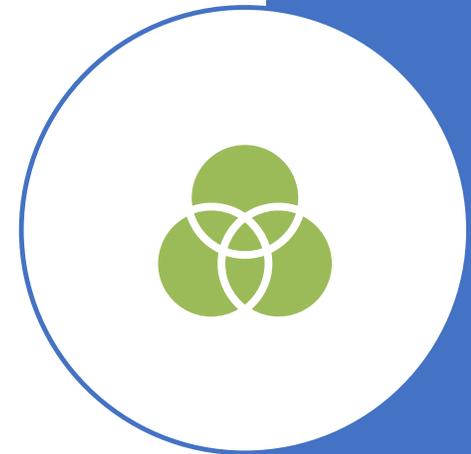
- Estimates are made using country specific data
- Programme contextual information is considered
- Grade of Confidence is used
- Historical series are revised as new data becomes available (updates from countries and surveys)

LIMITATIONS

- Estimates are affected by the quality of underlying data
- No quantitative estimation of uncertainty
- Most recent year estimates are informed by less data (surveys inform estimates for earlier year)

Main results from stakeholder consultation

- Two surveys: one to inform Swiss TPH models (84 respondents), one broader on uses of data and quality perceptions (512 respondents)
- “One-size does not fit all”
- Wide-range of views on what is important, especially by type of stakeholder
 - EPI managers seem to be a particularly different type of stakeholder
- Reliable data sources important for credibility
 - No data source universally trusted, but DHS, WUENIC and other surveys top three trusted sources
 - WUENIC credible (from 1 to 5): 4 (52%) and 3 (26%) in stakeholder survey 1
- Accuracy desired
 - Likely more than possible with available data
 - Stakeholders seem willing to compromise timeliness and representativeness in favor of accuracy
- Broad agreement that **better coverage data starts at the frontline**



WUENIC2.0 Model Summary Metrics

4/17/2020

Overview

The below tables present various summary metrics to provide a high-level view on how the proposed WUENIC model alternatives differ from the latest WUENIC estimates.

Summary metrics descriptions

- **mean_diff** : average percentage point difference of specified model estimates from WUENIC across entire, available time series
- **median_diff** : median percentage point difference of specified model estimates from WUENIC across entire, available time series
- **pct_gt_wuenic** : % of specified model estimates that are greater than WUENIC estimates across entire, available time series
- **pct_lt_wuenic** : % of specified model estimates that are less than WUENIC estimates across entire, available time series
- **ctry_n** : # of countries with alternative estimates to summarize
- **vacc_n** : # of vaccines with alternative estimates to summarize
- **year_n** : # of years with alternative estimates to summarize
- **total_n** : # with alternative estimates available to summarize

Tables

Table 1

Table 2

Table 3

Summary metrics across all available country+vaccine+year estimates, by model type

Model	yr_start	yr_end	mean_diff	median_diff	pct_gt_wuenic	pct_lt_wuenic	ctry_n	vacc_n	year_n
swiss-base	2000	2017	-5	-5	25	75	169	5	18
swiss-focal	2000	2017	-3	-2	34	66	119	5	18
imperial-1	1980	2018	4	0	54	46	99	5	39
imperial-2	1980	2018	3	-1	47	53	98	5	39
imperial-3	1980	2018	-2	-5	33	67	98	5	39
imperial-4	1980	2018	3	0	55	45	43	3	39
southampton	2000	2018	-1	-1	43	57	182	5	19

Boxplots

DTP1

DTP3

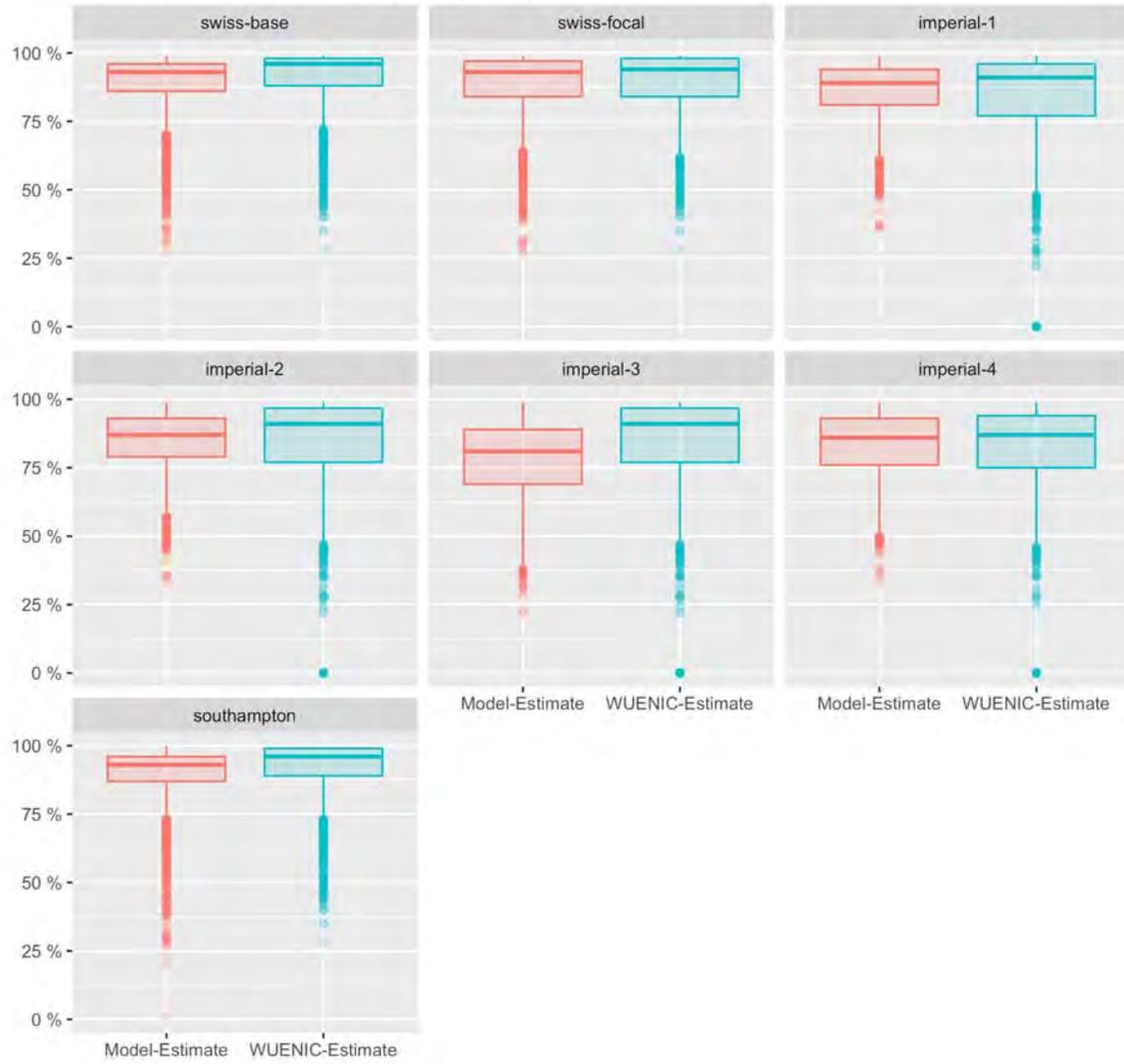
MCV1

MCV2

PCV3

DTP1 coverage estimate distributions

WUENIC estimates matched to each model by country, vaccine, and year



WUENIC2.0 Model Explorer – Shiny App to compare estimates from different methods

<https://unicef.shinyapps.io/wuenic-model-explorer/>

Estimating National-Level Vaccine Coverage: IHME and WUENIC Approaches

Background

On November 13-14 2019, the Institute for Health Metrics and Evaluation (IHME) and the WHO and UNICEF working group responsible for producing national estimates of vaccination coverage (the so-called, WUENIC) met in New York to compare the two methodological approaches for estimating national-level vaccine coverage, evaluate major differences in results, and discuss opportunities for collaboration and further comparison. Intended for users of these estimates, this document summarizes several of the key findings of this discussion and implications when comparing the IHME and WUENIC coverage estimates. As a higher-level description, IHME uses statistical method with available data across all countries to estimate country specific immunization coverage levels while WUENIC only uses data from the country of interest with a rule-based system to estimate immunization coverage.

Overview of estimation methods

Both IHME and WUENIC compare country-reported data to survey point estimates to assess the validity of country-reported estimates and apply adjustments where possible. IHME models the relationship between country-reported and survey data in a statistical framework by country and year for select antigens, and then applies an adjustment to official country-reported data. WUENIC uses a triangulation-based approach to assess the quality of the consistency of the reported data with external evaluations such as surveys and other relevant information such as stockouts of vaccine. Based on that assessment, WUENIC either accept reported data or survey estimates¹ or make some alternative decisions (e.g. calibrate based on some differences between reported and surveys, follow trends of reported, interpolate between surveys, extrapolate from surveys at the end of a time series, etc.). In summary, WUENIC is a rule-based system where WUENIC equals the reported country data unless there is evidence that challenges a country's reported data.

There are several differences in these approaches. For instance, the IHME model is able to apply a bias correction regardless of how closely the survey data matches the country-reported data. Under current rules, if survey data are within 10 percentage points of the country-reported data, WUENIC uses the reported data as the estimate. WUENIC is exploring the possibility of using different thresholds for levels of coverage, e.g. use a 5 percentage points for very high coverage level. The IHME approach can account for smaller amounts of bias, which may be important in countries with higher coverage. The WUENIC approach prioritizes official reported estimates from countries and recognizes that survey coverage estimates are imperfect with both sampling and non-sampling error.

In addition, the IHME model estimates administrative bias in all countries; if there are no surveys in a given country, the estimate of administrative bias borrows information from similar countries and years, with the assumption that bias is likely to be similar. WUENIC, on the other hand, does not borrow information from one country to apply to another; rather, all data review and estimate production is country specific. WUENIC does borrow information available for one antigen and apply that information to another antigen that is, for example, recommended for administration at a similar age. Additional analyses are planned to compare these two approaches and underlying assumptions.

¹ DTP3 survey estimates are adjusted for recall bias when the information is disaggregated by card and card and history. This adjustment may also affect other antigens when the DTP3 level is used to set other vaccine-doses levels.

Input data sources

IHME and WUENIC identified differences in input data sources as one of the drivers of differences in estimates. In some cases, WUENIC leverages data sources that are not publicly available – for instance, in India in the 1990s, WUENIC uses data reported by India to UNICEF, whereas IHME has used the publicly-available data that were reported to WHO. In other cases, IHME or WUENIC may include data sources that the other group is not aware of or has chosen to exclude from their models.

IHME and WUENIC are now working together to ensure that both groups are aware of all available data sources on vaccine coverage and to compare decisions regarding data exclusion. As part of this process, IHME plans to run a set of coverage models using the exact data set used by WUENIC, to distinguish between differences in estimates due to methodology and those due to data sources.

Recall bias adjustments and DTP dropout

For estimation of DTP3 and other multi-dose antigens, WUENIC uses a recall bias adjustment informed by available survey data (see Brown, Burton, and Gacic-Dobo, 2015). This adjustment is based on the assumption that recall of the first dose of a vaccine (i.e. DTP1) is likely to be better than recall of the third dose (i.e. DTP3) (see Dansereau, Brown, Stashko, and Danovaro-Holliday, 2020). This adjustment process assumes that dropout is similar among children with and without home-based records (HBR); a strong assumption recognized by WHO and UNICEF. IHME does not currently apply any recall bias adjustments for DTP3 coverage, given that the direction and magnitude of recall bias is difficult to predict, and that – if HBR retention is associated with better access to vaccine services – this adjustment could systematically overestimate coverage. In some settings, these two different assumptions can lead to large differences between IHME and WUENIC in coverage estimates, particularly where HBR retention is low, which often is in countries where administrative data are also problematic (see Cutts *et al*, 2016), and there are marked differences in reported coverage by HBR and by recall. The optimal approach to the issue of recall bias is still unclear. Further investigations will include IHME models run with and without application of the WUENIC recall bias adjustment to identify the locations and magnitudes most affected by the choice to adjust or not to adjust.

While countries have reported DTP3 coverage since the beginning of the JRF, country-reported data on DTP1 coverage was not routinely collected until 2010. In order to ensure internal consistency between DTP3 and DTP1 results and produce DTP1 estimates in early years despite this data gap, both IHME and WUENIC make assumptions regarding DTP1-DTP3 dropout. The IHME estimates use a continuation ordinal regression model (see Mosser *et al*, 2019). This approach uses data on DTP3 coverage and the proportion of children with fewer than three doses who have received at least one dose to model DTP1 coverage, while ensuring that DTP1 coverage is always greater than DTP3 coverage and cannot exceed 100%. WUENIC also caps DTP1 estimates at 99%, which sometimes results in a falsely reduced dropout rate.

Stockouts, shocks, and other delivery system disruptions

The WUENIC process, through the use of expert opinion and qualitative data sources, is often able to identify locations where vaccine delivery interruptions are likely to cause declines in coverage. Often, in the absence of additional information and independent assessments, the magnitude of decrease in coverage is inferred from the magnitude of decrease in administrative or official country-reported data with its associated data quality challenges.

IHME estimates include a statistical method to reflect stockouts in years where there is a decrease in administrative coverage and the country reports a stockout through the Joint Reporting Form (JRF). This model also makes the assumption that the true coverage decrease is proportional to the decrease observed in country-reported data. IHME estimates also includes a “mortality rate due to war and terror” covariate, which allows the estimates to reflect expected coverage decreases due to conflict.

Data on stockouts have only been collected through the JRF since 2003. These data are still imperfect, as there is no direct correlation between a reported stock-out and lack of vaccine at the service delivery points due to dose-buffers that may be available. However, long stock-outs might be more likely to result in shortages at the delivery level. Using materials shared by WUENIC, IHME has supplemented their database of supply disruptions, so that future IHME models will better reflect stockouts and supply disruptions in early years. In addition, this area was identified as an opportunity for further investigation by building on the modeling framework developed by IHME – for instance, to investigate whether changes in numerators alone better predict the impact of stockouts, or whether the magnitude/duration of stockout impact varies by baseline coverage level.

Age cohorts and vaccine schedules

Generally speaking, WUENIC uses data from a single annual cohort (e.g., 12-23 months) from each data source given that only data from published survey reports are used. When the cohort of 12-23 months is distributed over at least two years, WUENIC assigns the whole cohort to the year with the most children based on data collection period. This approach has its limitation since a significant portion of the 12-23 cohort can be assigned to a year different from their birth year. Where survey microdata are available, IHME uses data from multiple age cohorts from each data source following a re-analysis of the data. Current IHME methods assume negligible catch-up vaccination or differential recall bias or mortality due to immunization, and future plans for age-specific modeling may mitigate these assumptions. Based on discussions with WUENIC, IHME also plans to investigate card retention rates in older vs. younger cohorts (i.e., it has been recognized that the availability of documented evidence in home-based records tends to be lower among older compared to younger cohorts) and will use data sources provided by WUENIC to ensure that estimates reflect historical changes in vaccination schedules where possible.

Capturing and conveying uncertainty

As a statistical model, IHME coverage estimates are accompanied by estimated 95% uncertainty intervals, reflect the uncertainty captured through the modeling process. WUENIC estimates, generated using a rule-based methodology, are accompanied by qualitative Grade of Confidence (GoC) ratings (see Brown, Burton, Gacic-Dobo, and Karimov, 2013), which are also generated following rule-based criteria. As a first step to better capture and convey uncertainty in both methods, IHME and WUENIC plan to compare the GoC ratings to the modeled uncertainty estimates and identify places where assessments of uncertainty differ and may impact inference.

Timelines for production

Each year, WUENIC estimates are released on 15th of July and constitute an estimation of the full time series of vaccination through the preceding year. For instance, WUENIC estimates released in July 2021 will reflect national-level coverage rates from 1980 to 2020 and the last year of estimation will be 2020.

IHME estimates are produced annually as part of the Global Burden of Disease Study (GBD) and include estimates of coverage in the current GBD cycle year. For instance, the GBD 2020 estimates will be published in May 2021² and contain annual coverage estimates from 1980 to 2020. Because GBD publications occur prior to the annual JRF release each year, these estimates will include country-reported data and available survey data from 1980-2019. Until survey data and new JRF data from 2020 is available, these modeled estimates predict coverage in 2020 using past trends in coverage and covariate patterns. IHME recognizes that the current lack of alignment between GBD release schedules and JRF data availability leads to a data gap for each

² Annual GBD releases are currently planned to coincide with each year's World Health Assembly, in May. The release of GBD 2019 was planned for May 2020, but COVID-related disruptions to publication schedules have delayed the release.

year's published GBD estimates. After each year's JRF release, IHME produces interim, updated coverage estimates that incorporate the most recent available country-reported and survey data and are more directly comparable to the current WUENIC estimates. These revised estimates are disseminated directly to partners and available on request, but not currently published.

Given this difference, comparison of the estimates between IHME and WUENIC for recent years should be conducted with more care. Both approaches re-estimate the entire time series for each country in each year. Past estimates may therefore change as new information becomes available.

Dissemination of estimates

WUENIC estimates are released on 15 July. In recent years a joint WHO/UNICEF press release has accompanied the release of these estimates. In order to comply with WHO requirements to publish health indicators for its Member States, a draft version of WUENIC is produced in May and this version is shared with countries through WHO regions and UNICEF offices. This country consultation allows Member States to see the estimates produced and provide any additional information or any clarification; calls with countries can also happen during this period. This consultation is not intended to veto WUENIC and when countries disagree with the estimates, this is noted as text next to the graphs showing reported data alongside surveys and WUENIC over time. The estimates are finalized between late-June and early July. Each year, in Q4, a joint WER/MMWR article is published highlighting some aspect related to vaccination coverage, usually in collaboration with the US Centers for Disease Control and Prevention (CDC).

IHME coverage estimates are published annually along with all other covariates and results from GBD. These publications are planned for May of each year, in order to correspond with the World Health Assembly. In addition, these coverage estimates inform annual IHME publications that track progress towards health-related Sustainable Development Goals (SDGs; see Lozano *et al*, 2018) and coverage of universal health care (UHC; see Dieleman *et al*, 2018). While the IHME methods and results have been peer-reviewed and published as part of the GBD, SDG, UHC, and FHS efforts at IHME, there has not been a publication specifically focused on the IHME coverage results to date. A GBD 2019 coverage manuscript is in preparation. IHME does not have a direct equivalent to the WUENIC country consultation process. All GBD results and related publications, however, are circulated through IHME's global collaborator network for review and critique, and to identify additional data sources that could be used to estimate coverage. As of 2019, this network includes more than 3000 collaborators in 140 countries and consists of researchers, policy-makers and other content experts.

Use of estimates and associated caveats

Global / Regional Monitoring Frameworks

WUENIC estimates are broadly used in regional and global monitoring frameworks, including monitoring of national-level progress towards goals set in the Global Vaccine Action Plan (GVAP), Immunization Agenda 2030, the Gavi 5.0 strategy, and vaccine-relevant Sustainable Development Goal (SDG) targets. SDG monitoring guiding principles highlight country ownership and the strengthening of country capacity to produce health statistics, aligning with the WUENIC country consultation process. WUENIC estimates are also used by other organizations to track vaccination progress; for instance, the Millennium Challenge Corporation uses WUENIC estimates to assess program eligibility.

IHME estimates have also been used to track progress towards SDG targets (see Lozano *et al*, 2018) and coverage of universal health care (UHC; see Dieleman *et al*, 2018), and have been shared with collaborators at Gavi, BMGF, and other organizations for use in strategic planning.

In general, both WUENIC and GBD estimates show broadly similar patterns of global progress in vaccination coverage. When comparing global or regional estimates from WUENIC or GBD estimates, users should be aware that the population estimates used to aggregate to global and regional levels differs between groups.

WUENIC uses the UN Population Division estimates, while IHME uses population estimates produced for the GBD study. The historical estimates from both GBD and WUENIC are subject to revision based on the best available new data and may therefore change from cycle to cycle.

Several monitoring frameworks (e.g. GVAP, IA2030) have also called for monitoring of progress towards subnational targets. Through the Joint Reporting process, WHO and UNICEF collect subnational administrative data from countries, but currently do not produce official coverage estimates that are subnationally disaggregated. IHME uses geolocated survey data and geospatial modelling techniques to produce subnational coverage estimates for select antigens that are consistent with the GBD national-level coverage estimates (see Mosser *et al*, 2019).

Advocacy

WUENIC coverage estimates are broadly used for advocacy purposes by WHO, UNICEF, and other stakeholders. GBD coverage estimates are also used for advocacy purposes; for instance, GBD coverage estimates are used to show progress towards relevant SDGs and potential future coverage trajectories in the Bill and Melinda Gates Foundation's annual Goalkeepers reports, which are released in September of each year.

Impact on VPD occurrence

WUENIC coverage estimates are used to analyze the relationship between service delivery and disease occurrence, through triangulation with disease incidence data. In addition, WUENIC coverage estimates are commonly used as inputs to models estimating disease burden and risk, e.g. for measles risk assessment models. IHME coverage estimates are similarly used as modelling covariates to predict vaccine-preventable disease burden throughout the GBD study.

Use in other models

WUENIC coverage estimates are used as inputs into other models to help with strategic planning for vaccination delivery. For example, WUENIC coverage estimates are used in the model used by Gavi's Secretariat to forecast vaccine demand, especially for new vaccines. Coverage forecasts based on the GBD coverage estimates are produced for each GBD cycle as part of IHME's Future Health Scenarios work (FHS; see Foreman *et al*, 2018), and include baseline, best-case, and worse-case scenarios for future progress. In addition, GBD estimates have been used in analyses of the relationship between immunization funding and vaccine coverage (see for instance Ikilezi *et al*, 2020).

National-level coverage tracking and other uses

WUENIC coverage estimates are used by Gavi and, along with other metrics, to monitor country performance. It is unclear how much WUENIC estimates are used in different countries – from a Swiss TPH stakeholder survey, it appears that WUENIC use cases are mainly supra-national. IHME also shares GBD estimates with stakeholders including Gavi and others, who may use GBD estimates as an additional metric to monitor country vaccination levels. In some cases, WUENIC estimates have been used to help make financial decisions, despite WHO-SAGE advice to “use caution” in interpreting these coverage estimates for performance-based financing. As noted above, both WUENIC and IHME historical time series are subject to revision each year as new information becomes available, which may limit year-over-year comparisons. In addition, bias and noise in administrative data and the sampling and non-sampling error associated with survey data limit the ability of both the GBD and WUENIC methods to precisely capture year-to-year coverage changes with high certainty in many locations.

Table 1. Guiding principles matrix. Color for IHME denotes whether follow the same principle as WUENIC: green=yes, yellow=similar, blue=different

Guiding principles	Rationale	WUENIC 1.0	IHME (as a comparison)	Option(s)	Trade Offs
Objective	Monitor changes in routine immunization performance, not taking into account supplementary immunization activities or late vaccination	Estimate RI performance	Estimate RI performance as an input to burden of disease models	Estimation of immunity, forecasting	Different use cases
Years estimated	Since EPI was established in most countries to year with data available for most countries	1980 to previous year	From 1980 Up to previous year, but last year is forecasted	Estimating up to earlier years, for example 2020 estimating 2018	Data availability (particularly survey data)
		Estimate is done for every year	Estimate is done for every year	Stop at year with last “valid” data point (e.g., 5 years forward of a survey)	
Periodicity	Use of calendar years, as most common cycle for country EPI Planning	Annual	Annual	Every 2 years	Data availability vs. timeliness
Date of release	JRF data available for most countries, allowing country consultation, and in time to include in GVAP annual reporting to SAGE Agreed upon with Gavi (not documented)	Release by 15 July	Available before WHA	Later release	Data availability vs. timeliness
Revision of time series	Historical series are revised as new data (mostly surveys) becomes available to inform earlier years	Annually	Annually	Freezing earlier years	Not revising when known new data available Communication considerations
Countries included	To meet WHO mandate of monitoring the health situation of Member States To harmonize with UNICEF mandate of monitoring the situation of children around the world	All WHO & UNICEF Member States	Most countries (some small island states not done)	Most countries	Confidence in estimates, as countries with data limitations not done. If done only for countries with some data criteria it may be difficult to estimate regional/global

Guiding principles	Rationale	WUENIC 1.0	IHME (as a comparison)	Option(s)	Trade Offs
Estimate produced	To monitor goals or targets set by specific initiatives (GVAP, SDGs, polio eradication, Hep B control, YF)	BCG, HepB birth dose, DTP1, DTP3, HepB3, Hib3, Polio3, IPV1, PCV3, Rota last, MCV1, MCV2, Rubella, Yellow Fever	Similar vaccine/doses	Fewer vaccine doses	Simplify current process, as review is done vaccine by vaccine. No estimates for some vaccine/doses available
Dependencies between vaccine/doses	Coverage with one vaccine can be different from another even if recommended at same age (stock issues, avoidance of simultaneous injections)	Vaccine-specific*	DTP3 used to calibrate others	Base some vaccine/dose coverage on another	Simplify current process, as review is done vaccine by vaccine May bias estimates for some vaccines as performance may be different
Vaccine/doses included for a given country	As WUENIC is national estimate, vaccines in sub-populations not included	Those in national immunization schedule	It used to be done in some cases (e.g., Hib in China used in private sector)	Produce estimates for vaccines used sub-nationally	No standard pop estimation for subnational levels, except maybe WorldPop for some It would require a set of criteria (e.g., if introduced in >1 state/province)
	Current rule-based methodology requires at least one data point	Start year for which at least one data point has been reported	Not necessary to have a data point	Forecast	The estimate would have to be based on a different vaccine/dose
	Annual country performance, thus if vaccine introduce mid-year it is annualized Yellow Fever is estimated for entire country in those considered at risk in list kept by WHO (only affects few PAHO countries)	Annualize partial year/country (intro year; YF)	Unclear YF – not applicable	Start estimation for year with full vaccine use For YF, estimate for proportion of population targeted	It would reduce info for year of introduction (unless introduced January 1)

Guiding principles	Rationale	WUENIC 1.0	IHME (as a comparison)	Option(s)	Trade Offs
Country specific/"borrowing data" between countries	EPI performance is heavily influenced by EPI management. Thus, countries with similar socioeconomic or other characteristics may still perform widely differently Aligned with SDG and GPW13 principles	Country-specific	Covariates	Use of covariates	Assumptions about correlations between factors with EPI performance
Data smoothing	As per objective, the aim is to estimate annual performance, which can be affected by stock and "shocks" to the system (AEFI, sociopolitical crises)	Not done	Yes	Modelled	Smooth data may be easier to digest, but may lose information on EPI performance
Uncertainty	GoC is based on availability of data sources and their consistency, which is often done for rule-based approaches	Grade of Confidence (GoC) on estimate (1 to 3)	Credible intervals	It will depend on method used to estimate. If rule-based, explore more levels to GoC?	Desirable attribute Interpretability
Sub-national estimates**	As per WUENIC objective (national) Data quality of admin data Limited survey data availability	Not done	Has a different model for sub-national estimates in selected countries	Attempt for large countries	It would require to define set of countries and the sub-national level to estimate. The smaller the level, the more uncertainty
Country consultation	Mandated by WHO	Yes	No	Using externally produced estimates would not require it	Governance – WHO/UNICEF
Governance	Independent estimation process (and not an assessment of country data)	WHO/UNICEF	IHME, GBD	Using externally produced estimates	WHO/UNICEF not producing estimates

*With the exception of rubella-containing vaccine (RCV) that is based on measles, as all RCV currently used are combined with measles. Also, one vaccine estimate may inform another (e.g., vaccines recommended at same age, DTP1/DTP3)

**WHO/UNICEF have supported a small number of countries to produce sub-national estimates using a similar approach to WUENIC 1.0 and to report their country-level aggregation as their official coverage. The ability to produce sub-national estimates has been limited by availability of coverage data different from admin.

Session 4:

MR-MAPs (Measles-Rubella Microarray Patches)

Estimating demand for MR-MAPs: project update



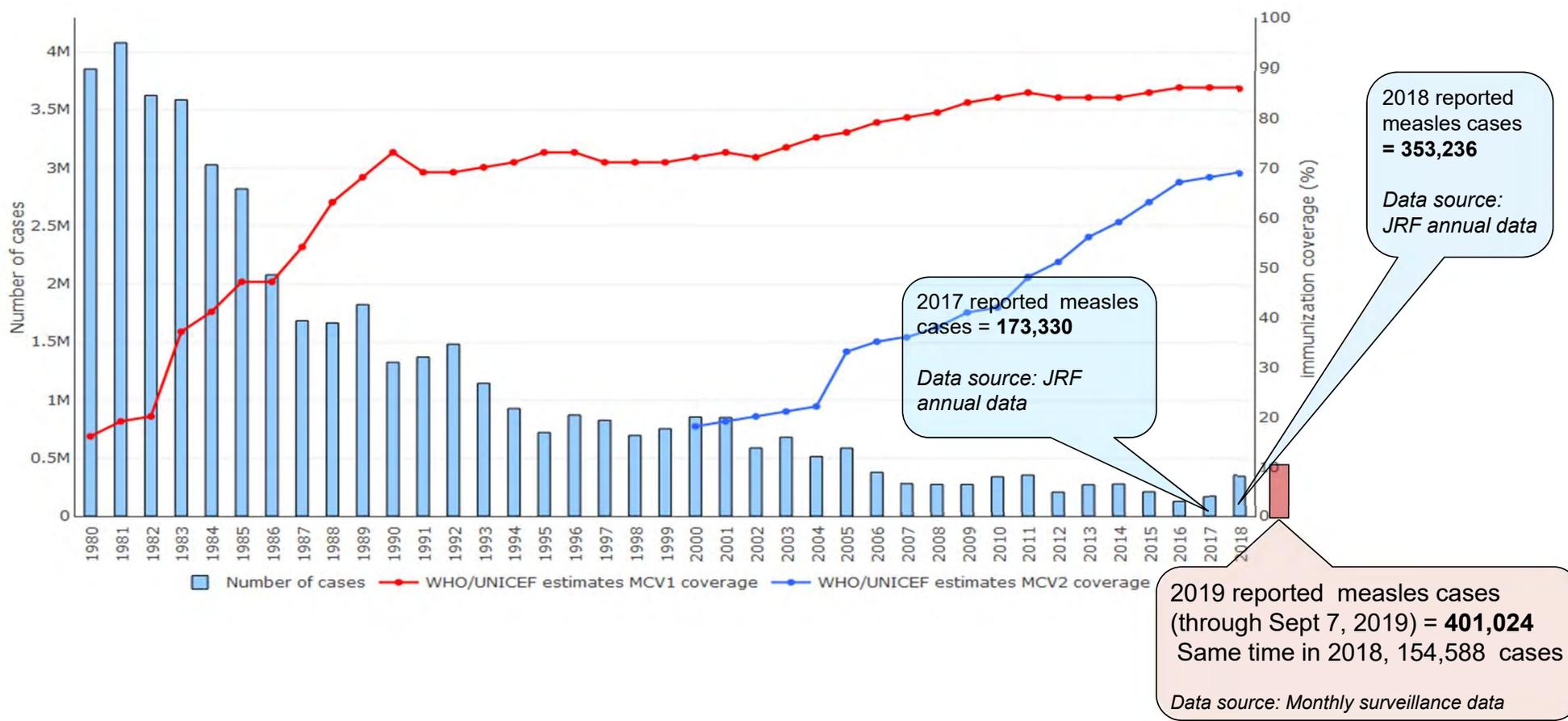
Mateusz Hasso-Agopsowicz

Birgitte Giersing

Overview of the session

1430-1440 10'	Accelerating the clinical development of MR-MAPs (Measles-Rubella Microarray Patches): an introduction to workstreams.	<ul style="list-style-type: none"> • High-level summary of activities related to MR-MAP product development • Rationale for MR-MAP demand sizing 	For information	B Giersing / M Hasso-Agopsowicz
1440-1510 30'	Understanding where and how will MR-MAPs be used: Identification of MR-MAP use cases and approach to size the MR-MAP demand	<ul style="list-style-type: none"> • Identification and validation of use case scenarios to deliver MR-MAPs: overview of methodology and results • Methodology to estimate the size of the MR-MAP use cases: anticipated variables • Key questions regarding the methodological approach and limitations of sizing of use cases 	For information	C Mantel (MMGH Consulting) M Ko (MMGH Consulting)
1510-1540 30'	Q&A and Discussion	<ul style="list-style-type: none"> • Does IVIR-AC agree that the approach to identify and verify the MR-MAPs use cases is appropriate, systematic and scientific? • Does IVIR-AC have suggestions to improve the methodologies to calculate the size of each of the use cases? 	For recommendation	J-D Lelièvre and D C Lyimo

Global reported Measles cases and MCV1 and MCV2 coverage, 1980-2018



Challenges of current Measles Containing Vaccine delivery and administration



- Safety of reconstitution and administration
- Stringent cold chain requirements
- Complex handling, time for administration and availability of trained health care workers
- Vaccine hesitancy & wastage
- Medical waste disposal



Potential public health benefits of vaccine-MAPs

- Increased **ease-of-use**; avoids reconstitution and requires less preparation
- Fewer components, **simplifying** supply chain logistics.
- **Increased acceptability** by caregivers and vaccinees.
- **Sharps-free**, which improves safety.
- Potential to save **health care worker time** by eliminating the need for reconstitution.
- Potential for **enhanced heat stability** and **freeze resistance**
- **Broad applicability** to all/most parenteral vaccines and might facilitate novel vaccine combination.
- MAP delivery may **enhance immunogenicity** so that fewer doses and/or less antigen per dose may be required



Recommendation by SAGE, October 2016

Outcomes from WHO MCV-MAP meeting



.....SAGE recommended that the most expeditious clinical development and regulatory pathway to licensure of measles containing vaccines (MCV) micro-array patch (MAP) be determined, and that barriers to the development, licensure, and use of MAPs for measles and rubella vaccine delivery be identified and addressed urgently.



Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

2 DECEMBER 2016, 91th YEAR / 2 DÉCEMBRE 2016, 91^e ANNÉE
No. 48, 2016, 91, 561-584
<http://www.who.int/wer>

MR-MAP Key Challenges

Understand the product

What are the key product attributes of MR-MAPs to make an impact in LMICs?

Use case

How will MR-MAPs be used when introduced to country immunisation programmes?

Market

What will be the demand for each of the use cases (sizing)? How will that determine the importance of product attributes?

Development pathway and licensure

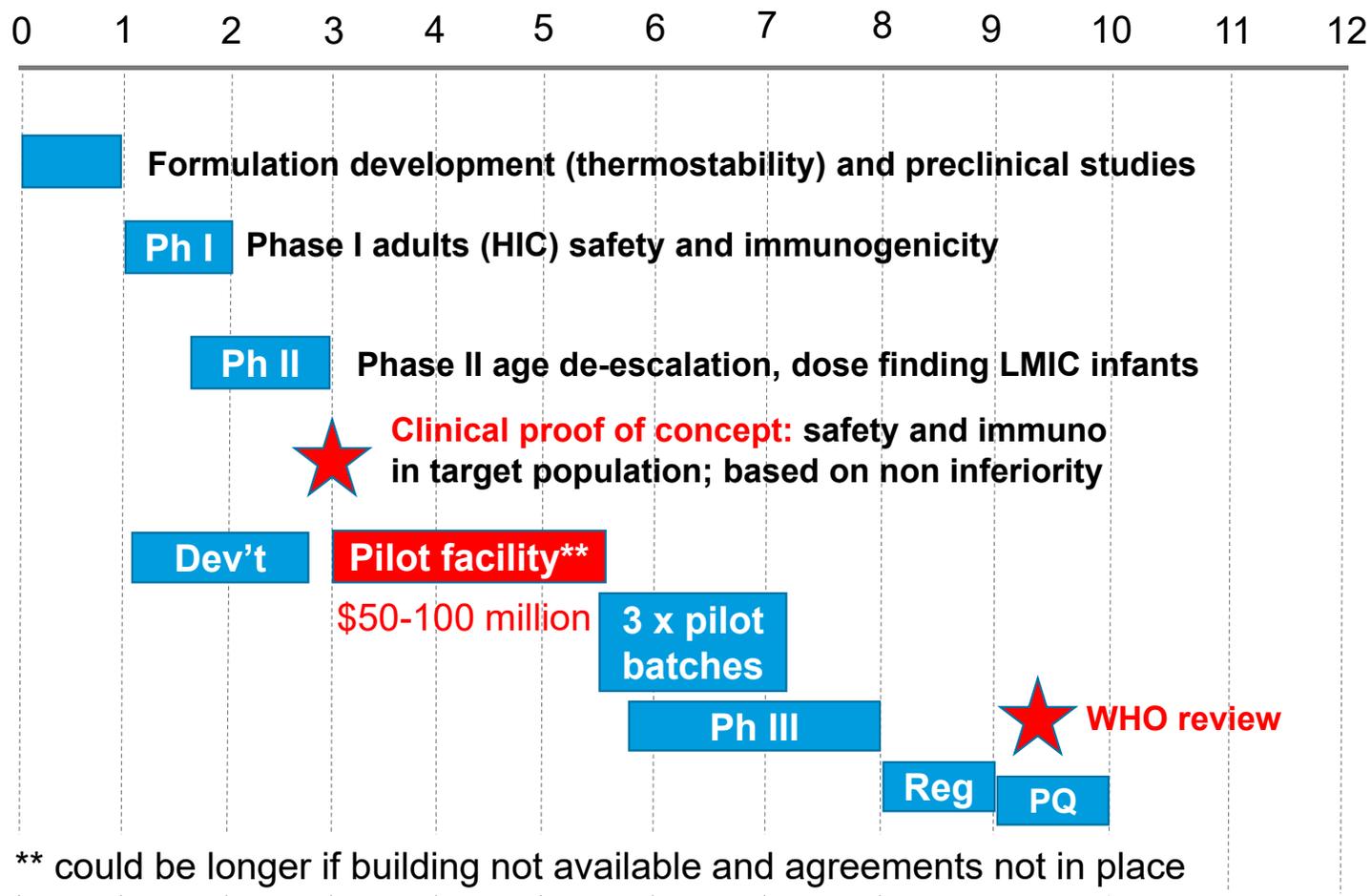
What are the additional activities that we need to undertake to prioritise MR-MAP development?

Measles & Rubella MAP WG



Name	Affiliation
Katrina Kretsinger	WHO
Natasha Crowcroft	WHO
Lidia Kayembe	CDC
Mark Papania	CDC
Martin Meltzer	CDC
James M Robinson	Consultant
Pieter Neels	Consultant
Michael Free	Consultant
Robin Biellik	Consultant
Courtney Jarrahan	PATH
Collrane Frivold	PATH
Darin Zehrung	PATH
Marion Gruber	FDA
Nicolas Peyraud	MSF
William Moss	JHU
Kristen Earle	BMGF
Carsten Mantel	MMGH Consulting
David Durham	University of Newcastle (AUS)
Jean-Pierre Amorij	UNICEF

Investment in MAP pilot facility has been a major bottleneck for MCV-MAP



Still no MR-MAP candidates in clinical studies...

MR vaccine manufacturers not convinced of value proposition and return on investment

Recommendation by SAGE, October 2016

Outcomes from WHO MCV-MAP meeting



.....SAGE recommended that the **most expeditious clinical development and regulatory pathway to licensure of measles containing vaccines (MCV) micro-array patch (MAP) be determined, and that barriers to the development, licensure, and use of MAPs for measles and rubella vaccine delivery be identified and addressed urgently.**



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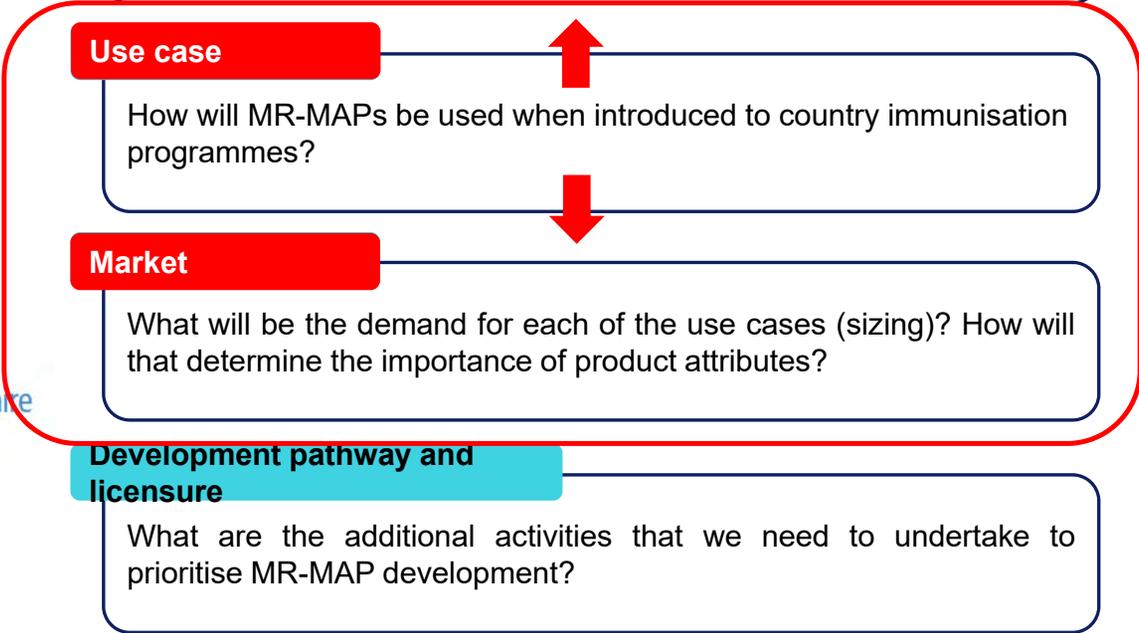
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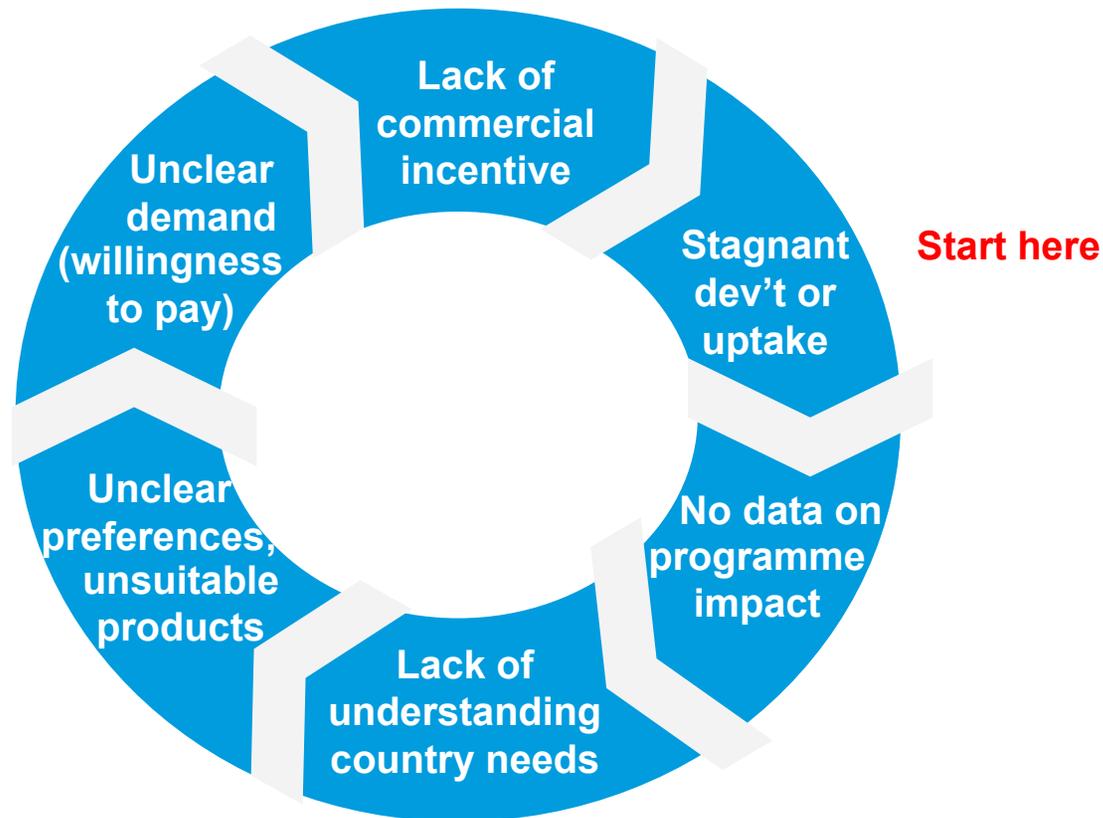
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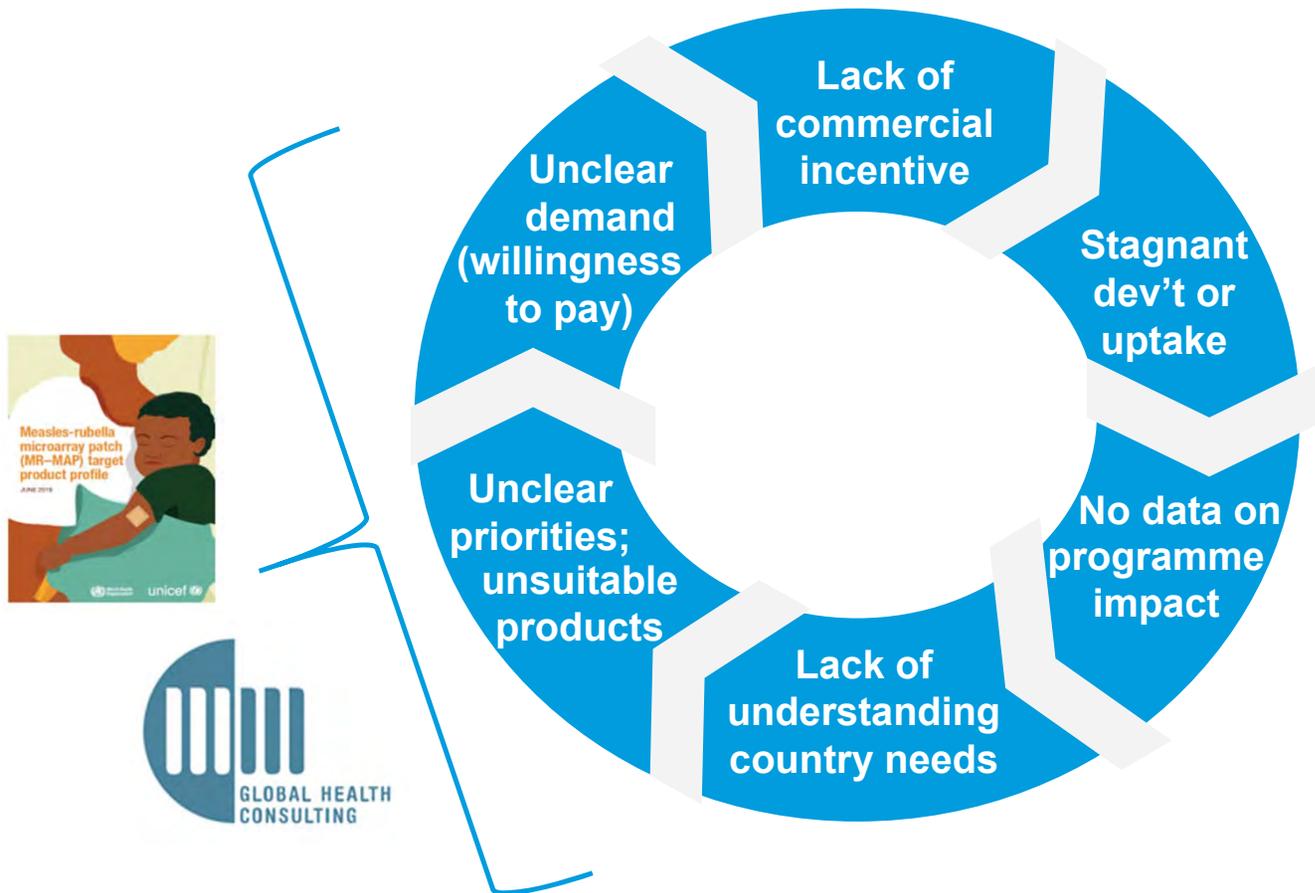
What are the additional activities that we need to undertake to prioritise MR-MAP development?



The investment conundrum for MCV-MAPs...



The investment conundrum for MCV-MAPs...



In summary...



- MAPs address several priority vaccine delivery challenges, for multiple vaccines
 - Significant potential to improve equitable vaccine coverage
- We need to understand how MAPs will be used in the context of licensed vaccines (use case); relative cost of goods, cost to fully immunize a child, vaccine effectiveness and demand by end-users will be critical
 - Identifying the use case and potential demand is a fundamental component the value assessment to advance MR-MAP through clinical development.
 - In addition, we need a methodology to articulate and establish value of MAP products within immunization programmes.



Questions for IVIR-AC



- Does IVIR-AC agree that the approach to identify and verify the MR-MAPs use cases is appropriate, systematic and scientific?
- Does IVIR-AC have suggestions to improve the methodologies to calculate the size of each of the use cases?

Closing slide



World Health
Organization

WHO

20, Avenue Appia
1211 Geneva

Switzerland



Understanding where and how MR MAPs will be used

Identification and sizing of MR MAP
use cases

September 2020

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TABLE OF CONTENTS

01

**Developing
the MR MAPs
use cases**

02

**Validating the
proposed use
cases**

03

**Approach to
size the use
cases**

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Timelines and key milestones



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01

**Developing
use cases**

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What is a Use Case?

A specific situation in which a product or a service could potentially be used to accomplish a defined goal

Use cases are used for multiple reasons



Product Design

What are the most appropriate product features to address the subjects emerging and unmet needs?



Program Design

How should the program be designed to maximize its reach and efficiency?

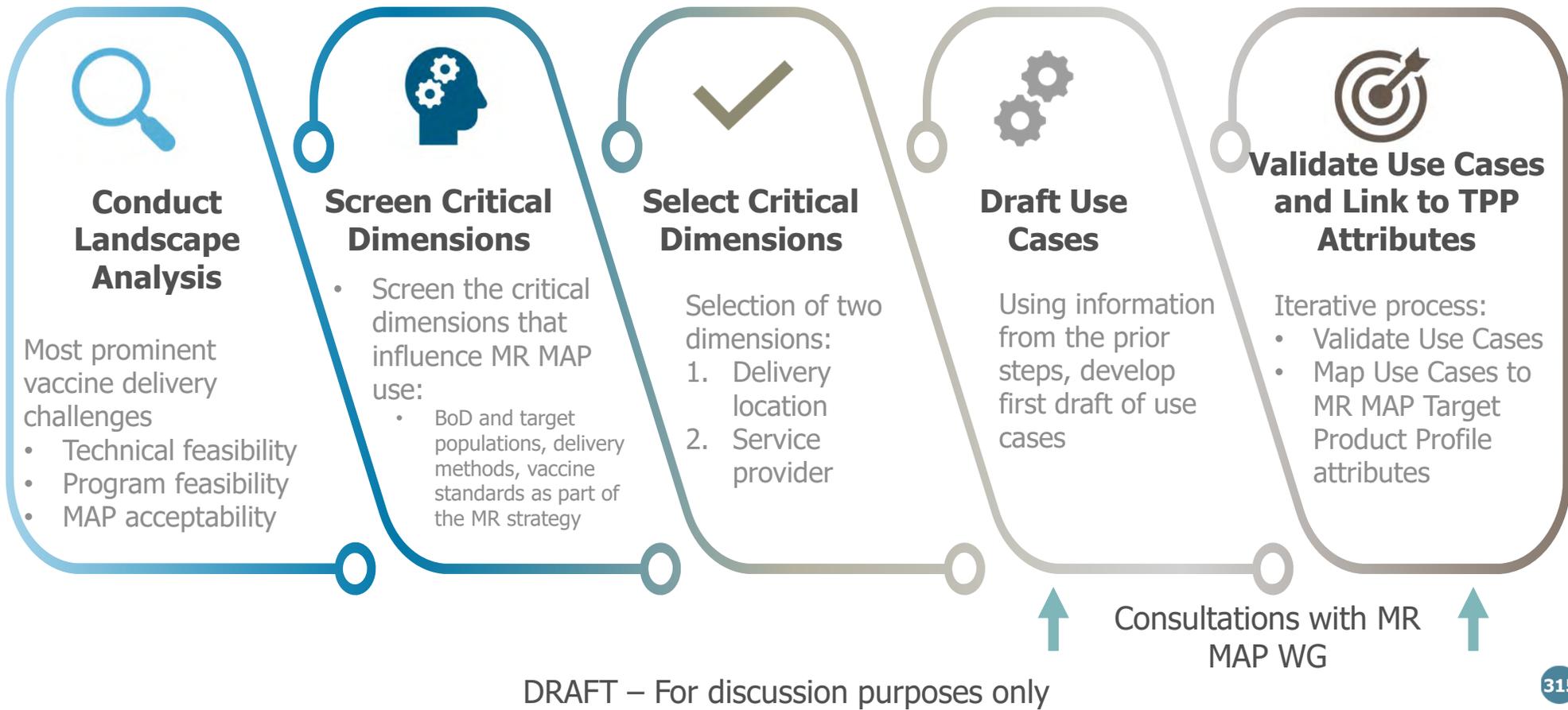


Product and program critical success factors

What product or program features contribute to the success or failure of the intervention?

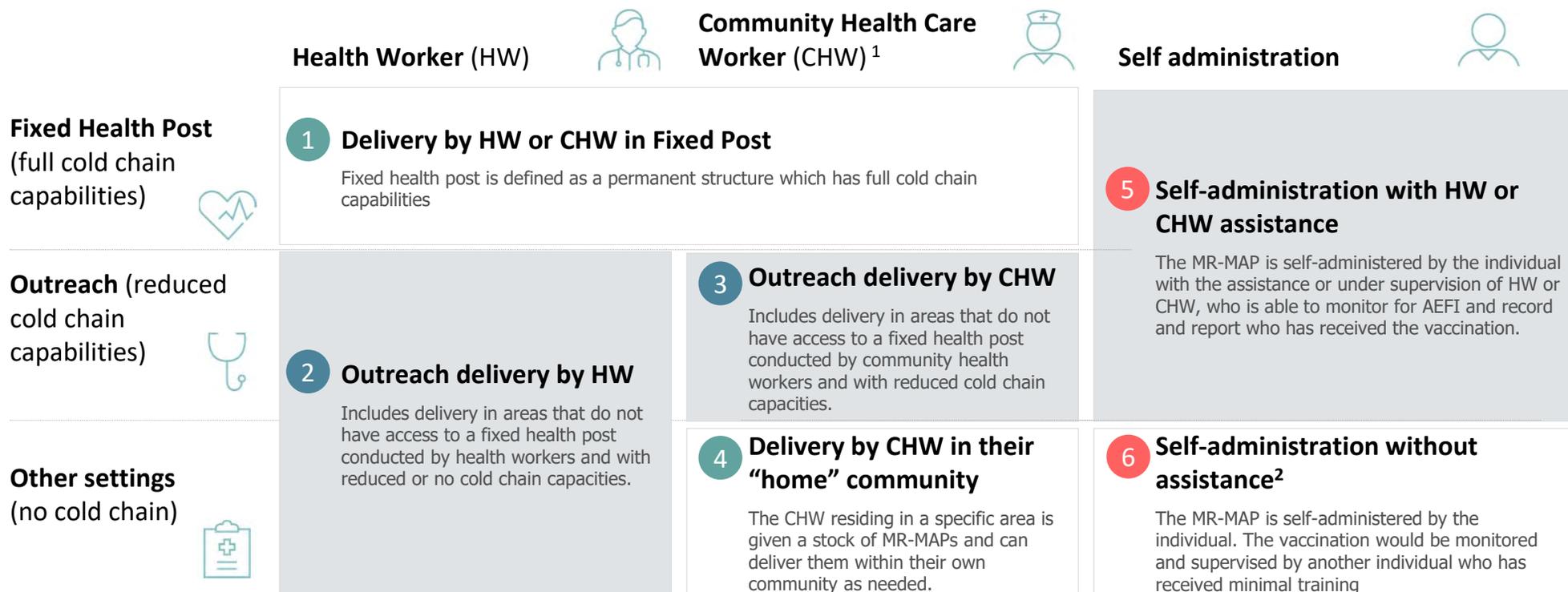
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How were the MR MAP Use Cases developed?



Final use cases identified for MR MAPs

Use cases can be used across various vaccination programmes such as routine immunization, periodic intensification of routine immunization, outbreak response immunization, supplementary immunization activities, or antenatal care immunization



1. Community health worker provide health education, referral and follow-up, case management and basic preventive health care and home visiting services to specific communities. They provide support and assistance to individuals and families in navigating the health and social services system. Occupations included in this category normally require formal or informal training and supervision recognized by the health and social services authorities

2. This may include community member assistance, (e.g., teachers, elders, etc.) who have not been training in MAPs but can monitor and document the administration

02

**Validating use
cases**

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Objectives of the stakeholders consultations

Survey

Broad consultation to obtain general perceptions of the Use Cases as well as input and feedback to refine their definitions or identify new Use Cases

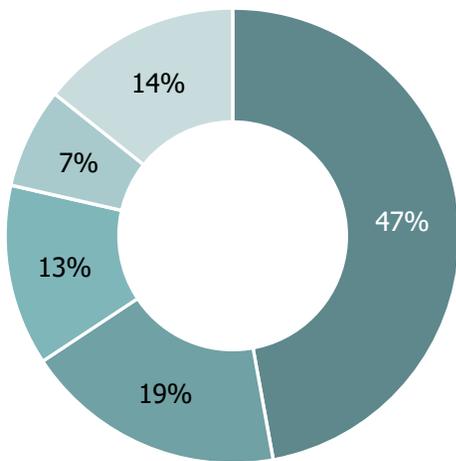
Interviews

Deep dives into the country perspectives for how the MR MAPs could be used and where they would be most beneficial

Survey Demographics – Organization Type, Role and Region

Total number of respondents: 70

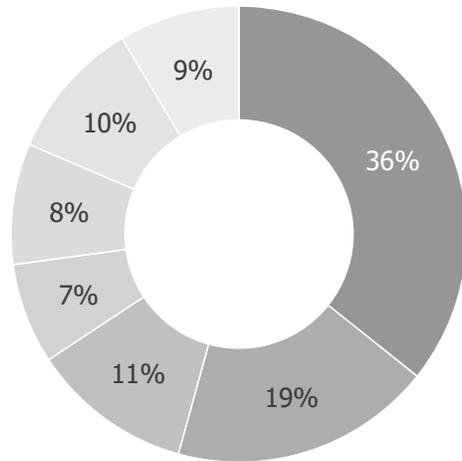
Type of organisation



- Agency of the United Nations
- Industry / Product Development / Design
- Implementation but not gov't or UN
- Ministry of Health
- Other

Others include: Donors (2), Independent (2), and CDC (4), and Academia (2)

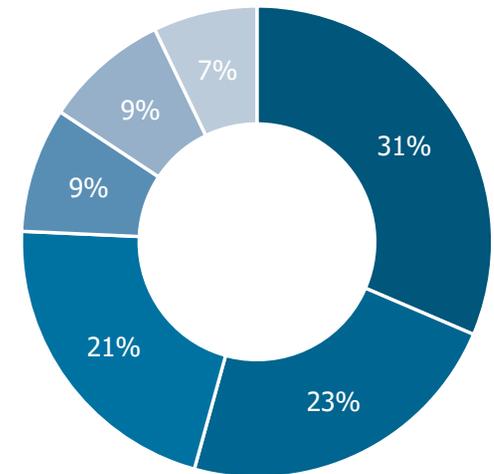
Current role



- Immunisation
- Epidemiologist
- Researcher
- EPI manager
- Surveillance
- Develop / Manuf
- Other

Others include: Health system specialist (2), vax logistics (1), health economist (1), public health specialist (1), trading (1)

Region



- AMRO
- SEARO
- AFRO
- EMRO
- EURO
- WPRO

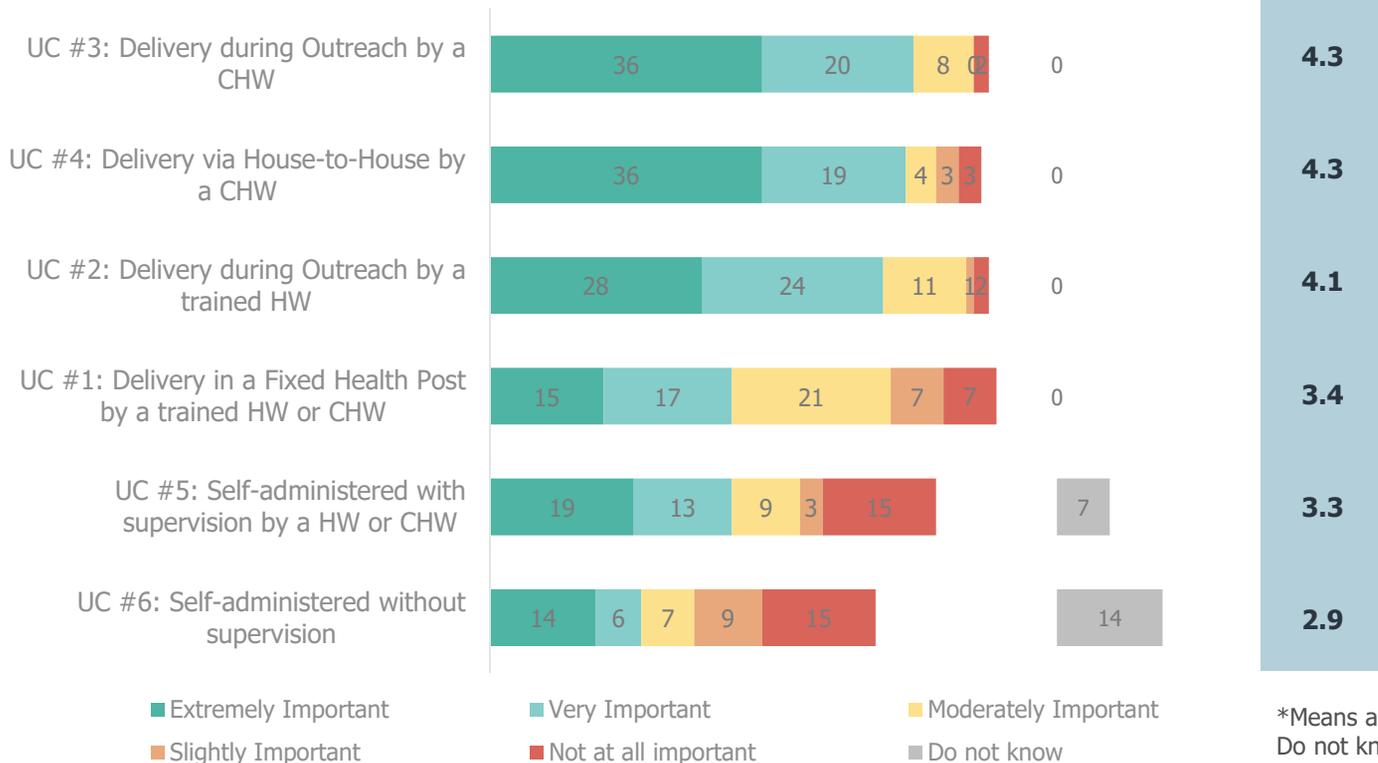
*Analysis conducted based on the country where respondents indicated they were based in

only

Survey: Importance of the defined use cases

Total number of respondents: 67

Q11: Importance of MAPs to achieve MR goals (N)



High level of importance assigned to Use Case #2-4, more discordant opinions for Use Case #1, 5, and 6

Additional scenarios identified:

- Related to use of MAPs in humanitarian and emergency situations or school settings
- Other potential situations: missed opportunities in clinical settings including emergency rooms, mass gatherings, by less well-trained personnel
- **These additional scenarios were classified under the existing use cases and definitions adjusted to reflect the feedback**

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Key findings from the survey



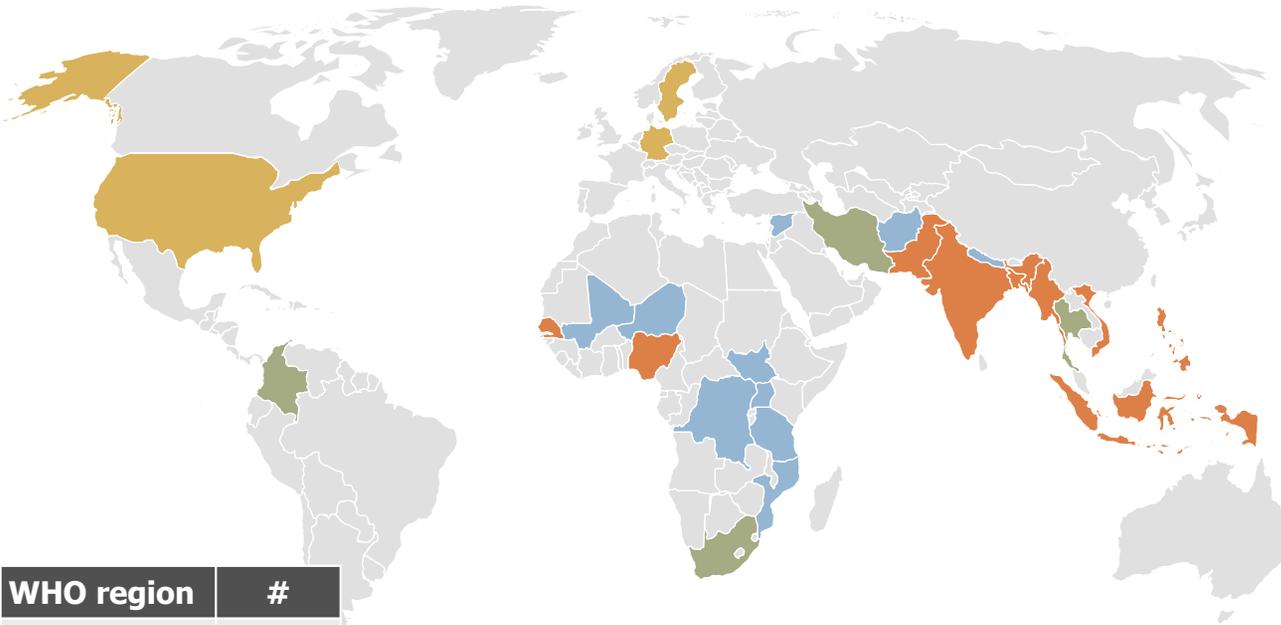
- General agreement on MAP use cases using outreach and house-to-house delivery (UC2 to UC4)
- Discordant opinions on use cases with self-administration (UC5, UC6) and fixed health posts delivery (UC1) as well as which countries (by income group) may use MAPs



- More feedback from government representatives or individuals working in countries obtained from interviews
- This included exploration regarding self-administration and fixed health post use

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Interview demographics



WHO region	#
AFRO	12
AMRO	3
EMRO	5
EURO	2
SEARO	5
WPRO	3

WB income group [†]	#
High income	3
Upper middle income	4
Lower middle income	10
Low income	11

- Low income
- Lower middle income
- Upper middle income
- High income

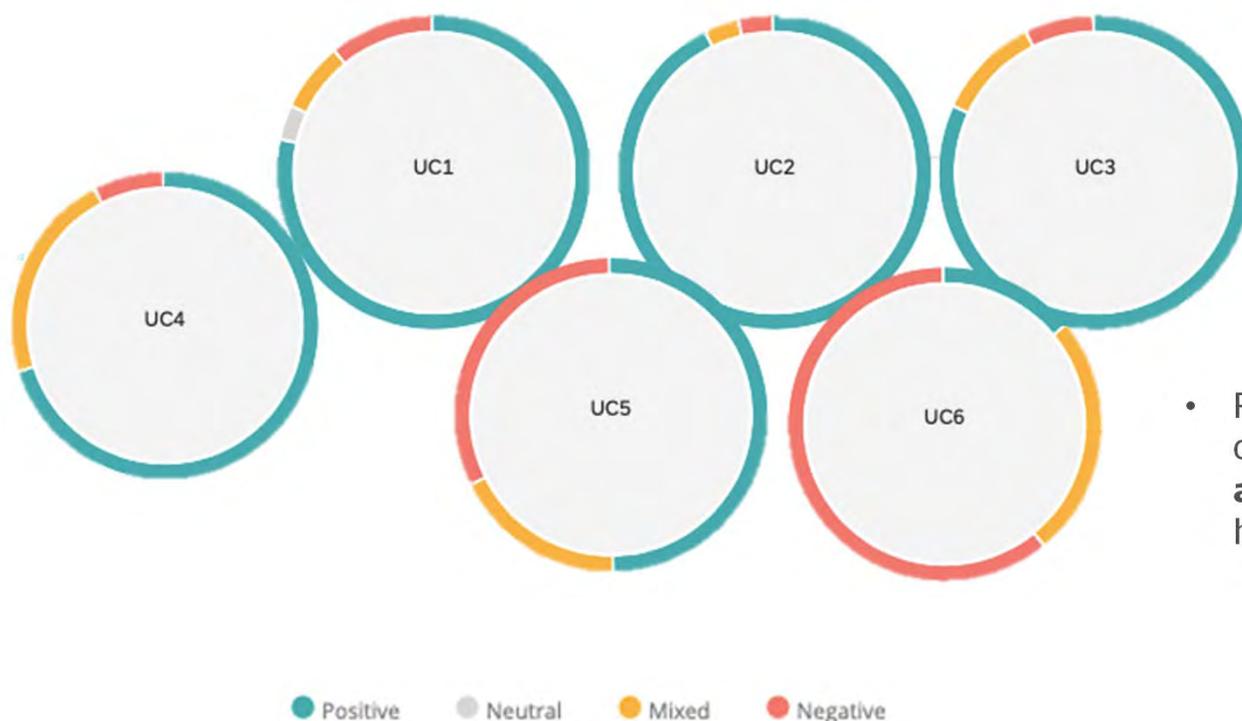
*Two individuals were interviewed for both Tanzania and Nigeria
Two individuals represented regional offices

- 30 individuals were interviewed across the World Bank Income Group Classifications
 - 2 WHO regional reps
 - 26 countries*
- Interviewees comprised of 16 EPI managers and 14 WHO immunization focal points at the country or regional level

poses only

Interviews: Appropriateness of different use cases in countries

Interpretations of appropriateness were driven by specific-country situations and goals



- Most respondents believe **UC1-4 were appropriate**
 - While UC3 and UC4 were cited as the most interesting, there were more mixed responses. Driven by concerns to properly train all CHWs and legal constraints on who can deliver vaccines
 - UC1 can be always be applied (except it is unlikely for countries using MMR), some did not want to upset their existing programme and systems
- Respondents were cautious about UC5 and UC6, citing **recording and reporting vaccination and monitoring of AEFI as the key barriers**, however
 - Some felt **UC5 was the most appropriate**
 - Others indicated that UC5 and UC6 could be used **in the future** after initial introduction in health facilities

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Key needs identified during the interviews



- ✓ **Safety & efficacy**
Must be demonstrated and needs to be comparable to the needle & syringe administration (e.g. delayed anaphylaxis?).
- ✓ **Studies and pilots**
Many indicated they would pilot MAPs prior to larger scale use. Some highlighted the need for local studies of MAPs.
- ✓ **Training**
Need for intensive training with instructions for appropriate MAP use (e.g., location of administration site, length of application time).
- ✓ **Thermostability**
Key assumption highlighted by many as a necessary characteristic. Should also include VVM.
- ✓ **Costing analysis**
An in-depth analysis considering total systems costs should be conducted – not just cost/dose.
- ✓ **Coverage improvements**
Coverage improvements, (likely to be minimal), will need to be measured and communicated.
- ✓ **Information and Communications**
Excellent communications are needed at two levels:
 - NITAGs and NIPs to make policy and programmatic decisions
 - Communities to increase acceptance and counteract rumors, DR this includes HWs and CHWs

Key emerging themes from interviews

UC3 and UC4 had the highest level of interest

- **Country specific context** and goals affect how MR MAPs will be used, but most felt UC1-4 were possible with UC3 & UC4 being the most interesting
- Respondents felt that MAPs will largely help to **reach remote, border, or security compromised** areas as well as **pockets of susceptible and vulnerable populations** (migrants, slums areas)

MMR/MMRV countries also expressed interest in using MAPs

- **HICs** and others with MMR / MMRV in routine schedules are interested in using MR MAPs in specific settings
- Some were open to using MR MAPs for **traveler vaccination, hesitant populations** demanding low-valent vaccines, **asylum seekers** or other marginalized groups

More acceptance of UC5 and UC6

- **UC5 and UC6 are more nuanced** and respondents saw opportunities, especially for UC5 in times of COVID-19 (DRC, Mozambique, Indonesia)
- Barriers of **legal constraints, monitoring & reporting** must be addressed if UC5 and UC6 will be used

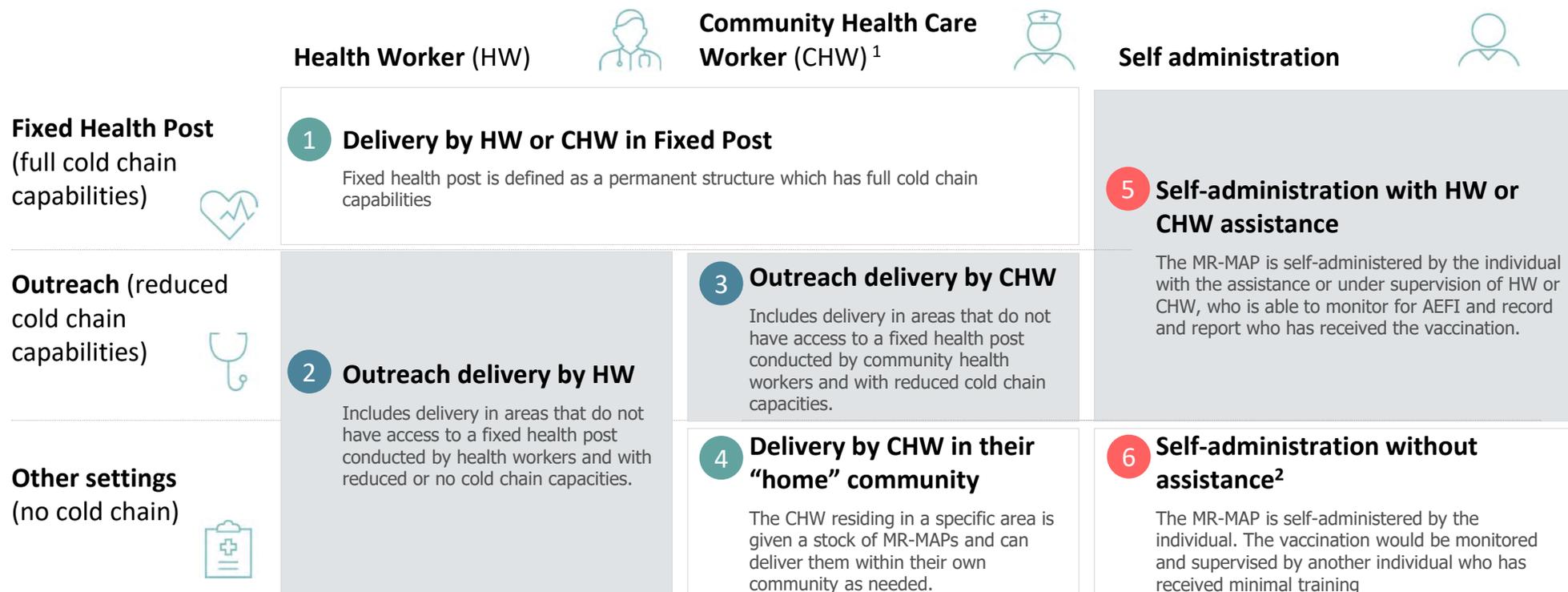
All respondents felt MR MAPs will be a positive innovation

- There is a lot of interest and anticipation for MR MAPs. All interviewees viewed MR MAPs as a positive innovation that could **help them achieve their MR related goals** and many asked for further information

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Final use cases identified for MR MAPs

Use cases can be used across various vaccination programmes such as routine immunization, periodic intensification of routine immunization, outbreak response immunization, supplementary immunization activities, or antenatal care immunization



1. Community health worker provide health education, referral and follow-up, case management and basic preventive health care and home visiting services to specific communities. They provide support and assistance to individuals and families in navigating the health and social services system. Occupations included in this category normally require formal or informal training and supervision recognized by the health and social services authorities

2. This may include community member assistance, (e.g., teachers, elders, etc.) who have no formal training in MAPs but can monitor and document the administration

Source: www.who.int/hrh/statistics/workforce_statistics

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04

**Approach to
size use cases**

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MR-MAP sizing exercise

Why?

Aims to capture the **potential use** (number of doses) of MR-MAPs **per use case** for strategic and directional discussions with stakeholders, including manufacturers / developers and potential users / purchasers

How?

Given the innovative characteristics of MR-MAPs, the lack of relevant historical data, and absence of specific market research, the approach and assumptions will be driven mostly by expert opinion, particularly focused at the **country level**

Assumptions

- No supply constraints
- Will be the first attempt to estimate size and likely to undergo refinements and adjustments

Note: this will not be a demand estimate

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Sizing of the use cases

Short-term goal

Estimate the potential use (ref: 2030), including the approach, assumptions and identification of data sources

*Will be developed via 3 virtual calls in Sept / Oct 2020 with MR MAP WG, MI4A Advisory Group experts, and country representatives

Medium-term goal

Refine the estimates of potential use (ref: 2030-40) and if relevant, develop a demand forecast

*This will likely require further country-focused market research and need to consider time dimensions

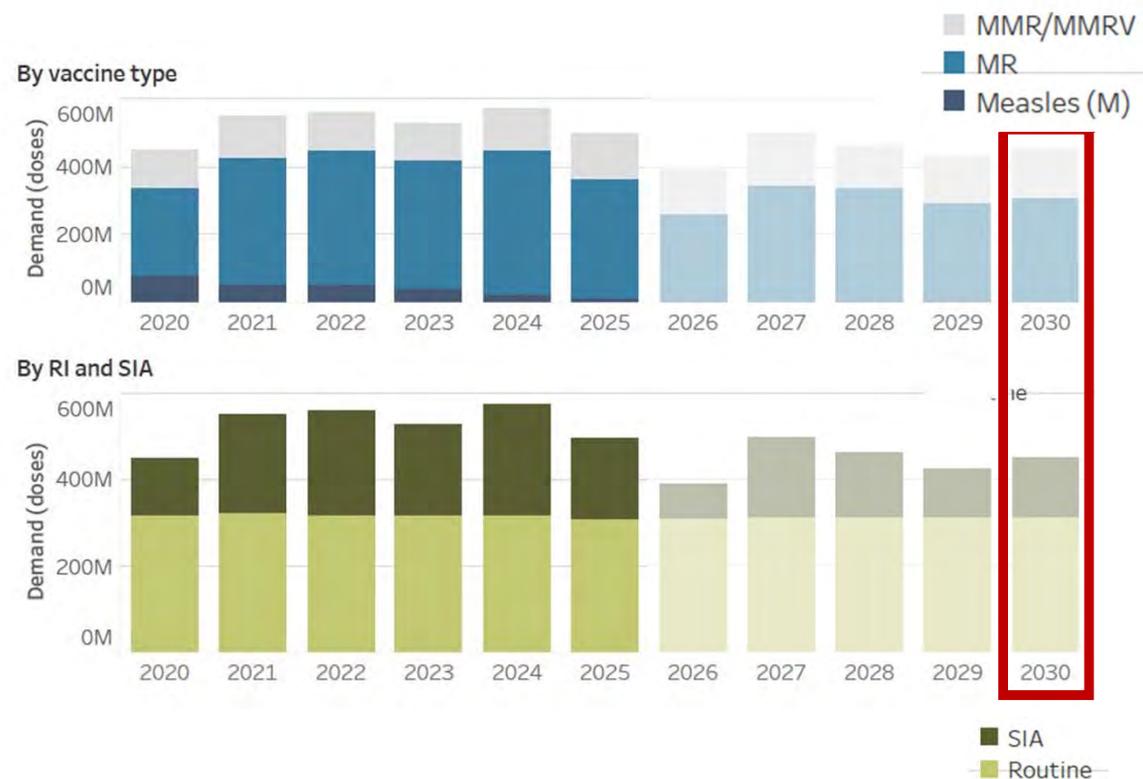
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MI4A provides the foundation for the sizing exercise

- MI4A market studies have 5 key components of global demand, global supply, demand-supply balance, pricing, and key areas for action
- The MI4A MCV demand includes:
 - Routine, SIA, and outbreak activities
 - Forecasts demand from 2020-2030
 - All 194 WHO Member States

Sizing exercise will use MI4A assumptions for demand in 2030, including country vaccine product choice and projected coverage

MI4A MCV global demand



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MI4A key data sources

- **General:**

- JRF schedule data

- ECDC vaccine scheduler

- UNPD population estimates

- WUENIC coverage estimates

- Other WHO immunization data (i.e. purchase data, Repository)

- **Vaccine specific:**

- Regional offices

- Subject-matter experts

- Other available forecasting efforts (e.g., Gavi SDS, UNICEF measles forecasting, academic modeling)

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Assumptions will be developed either by individual country or by country groups

For discussion:
Are the country groupings appropriately capturing the different contexts that will drive the sizing of use cases?

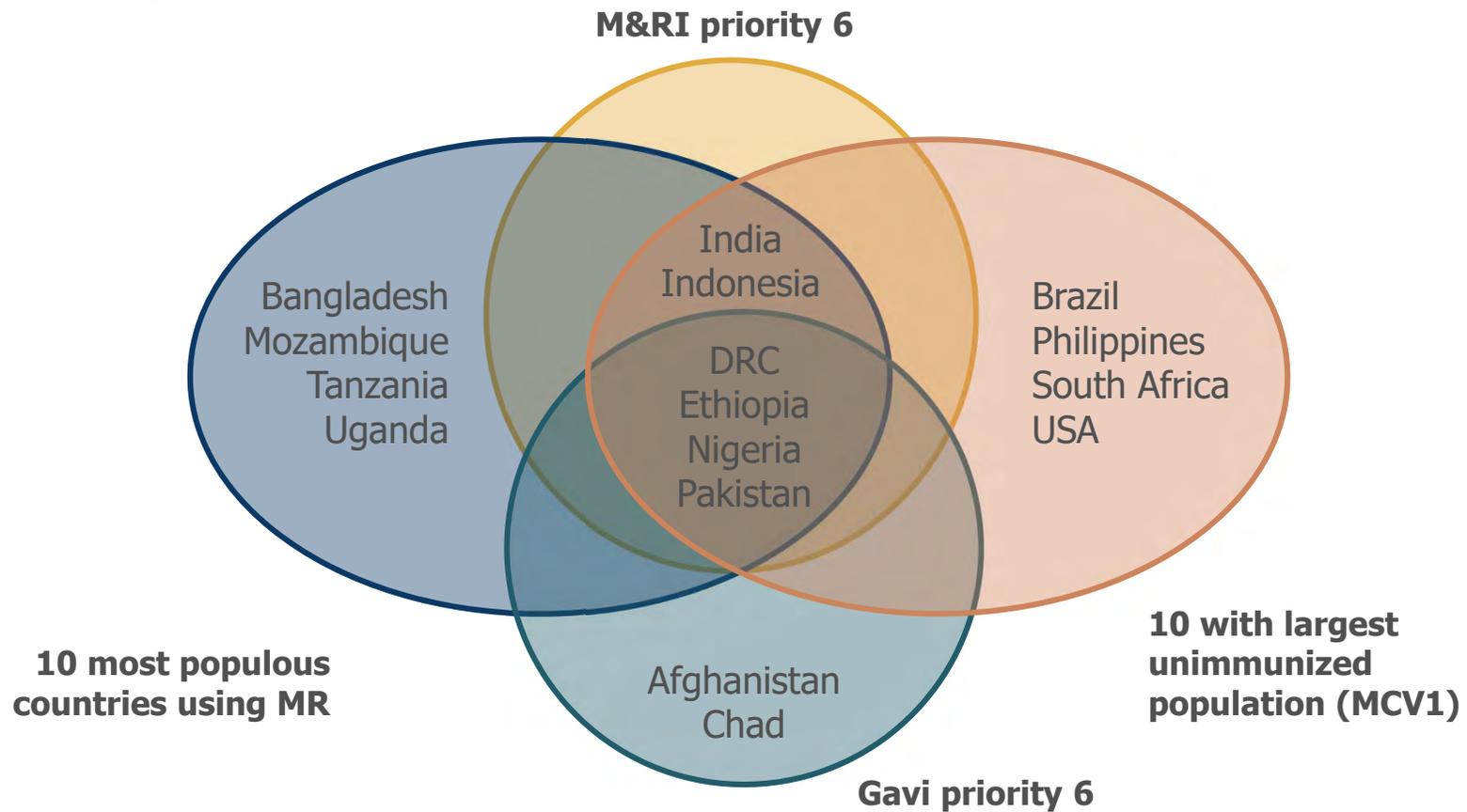
Individual

- The 10 most populous countries using MR
- The 10 with highest un-immunised population (MCV1)
- 6 priority countries identified by M&RI
- 6 priority countries identified by Gavi

Groups

- 1: Countries that exclusively use MMR / MMRV
- 2: Countries that use MMR / MMRV in routine but MR / M in SIAs
- 3: AFRO & EMRO
- 4: SEARO & WPRO

16 countries will have individual assumptions



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Overview of MR MAPs use case sizing approach

*For illustrative purposes only

MI4A MCV forecasted demand for routine and SIA

% increase in MCV demand due to MAP use

% MR Needle & Syringe use

% MR MAP use
*Anticipates switches to MR MAP

UC1

UC2

UC3

UC4

UC5

UC6

Size for each use case

% delivered in fixed post and outreach

% delivered by HW or CHW

% self-administration

Key variables to estimate size of use cases

For discussion:

- Is this preliminary approach feasible to estimate use case sizes?
- What are your recommendations to improve the approach over the medium/long-term?
- What are appropriate data sources to improve the approach and assumption?

Illustrative example: the key assumptions for the UCs will look like this for Routine and SIA demand

	% increase due to MR MAP use	Fixed post - HW	Outreach-HW	Fixed post CHW	Outreach - CHW	Outreach in home community-CHW	Self-Admin w/ supervision	Self admin w/o supervision	% allocated to MR MAP use
Routine	10%	40%	10%	20%	10%	5%	10%	5%	20%
SIA	20%	60%	10%	10%	10%	10%	0%	0%	50%

These variables relate to the defined MR-MAP use cases and should add to 100%

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Formulas for UC1 & UC2

Formula for UC1 (Use in Fixed post by HW or CHW)

$$\text{MI4A routine demand} \times \left(1 + \text{\% in increase in demand due to MR MAP} \right) \times \left(\text{\% by HW (Fixed Post)} + \text{\% by CHW (Fixed Post)} \right) \times \text{\% MR MAP use}$$

Formula for UC2 (Use in Outreach by HW)

$$\text{MI4A SIA demand} \times \left(1 + \text{\% in increase in demand due to MR MAP} \right) \times \text{\% by HW (Outreach)} \times \text{\% MR MAP use}$$

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Potential data sources that could be used

Health worker / Community health worker

Available data sources:

- WHO Global Health Workforce Statistics (part of Global Health Observatory)
- World Bank Database

Limitations:

Data on community health workers is reported sporadically or non-existent.

- Only 40 of 194 countries have reported data as of 2010.

Fixed post delivery or outreach delivery

Available data sources:

- Country-specific comprehensive multi-year plans (cMYP)
- Estimates of proportion of doses provided in outreach settings among all routine dose; magnitude of missed opportunities
- SIA / outbreak doses versus routine doses (JRF)

Limitations:

- Data does not exist for all countries
- Data may not be reflective of the future (10+ years)

Security compromised / remote areas

Available data sources:

- World Bank Database (rural population)
- UNHCR Database (refugee and internally displaced persons indicators)

Limitations:

- Uncertainty in predicting how these values, particularly security compromised populations, will change in the next 10+ years

Areas of uncertainty

01

Data for usage of different delivery strategies (e.g., delivery in fixed health post versus outreach; delivery by HW versus CHW or self-administration) is limited or may not have been updated; majority of data will be reliant on country expert opinion

02

Uncertainty on MR-MAP's impact on MR coverage growth and percentage of MR-MAP use

03

The defined use cases could have potential overlap. This is not problematic when looking at individual use cases but can impact demand estimates.

04

Sizing is only referencing data on 2030, additional work will need to be conducted to understand the future evolving trends and if needed to develop a demand forecast

For discussion:

- How does IVIRAC recommend we manage the limitations of the data sources while considering expert opinions?

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Advisory Group: anticipated topics and outputs to develop use case size estimates

16 Sep: Where are we and what has been done?

- **Topics:** Results from the interviews and surveys, country perspectives on MR-MAPs, an overview of the approach to develop the use cases and generic assumptions to size the use cases
- **Outputs:** Understand country perspectives for using MR-MAPs, obtain agreement on approach to size use cases, including the key variables and identification of relevant data sources

5 Oct: Where can we go with MR-MAPs?

- **Proposed Topics:** Discuss the approach to group countries and discuss the key assumptions for each country group or individual country
- **Anticipated outputs:** Agreement on the country groupings and approach and assumptions to estimate the size of MR-MAP Use Cases

TBD: Bringing it all together

- **Proposed Topics:** The validation of estimated size of the MR-MAP Use Cases and alignment with and discussion of implications on the target product profile (TPP), discussion on potential scenarios to develop range of estimates
- **Anticipated outputs:** Agreement on the results and the estimated sizes for each use case in 2030, including a range of estimates via scenarios and identification of key implications on the TPP

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Discussion questions

Country groupings

- Are the country groupings appropriately capturing the different contexts that will drive the sizing of use cases?

Approach to estimate UC sizes

- Is this preliminary approach feasible to estimate use case sizes?
- What are your recommendations to improve the approach over the medium/long-term?
- What are appropriate data sources to improve the approach and assumption?

Limitations of data sources

- How does IVIRAC recommend we manage the limitations of the data sources while considering expert opinions?

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THANK YOU!

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Diving deeper into UC5 and UC6

UC5

- 14 respondents indicated UC5 as appropriate
 - Hard-to-reach areas, security compromised areas, humanitarian situations, outbreaks, or in specific and / or older age groups
- Countries indicating UC5 as most appropriate included Indonesia, DRC, and Mozambique
- One country cited MAPs as a powerful tool against hesitancy as it can empower the parents and involve them in the vaccination
- Impact of COVID-19: Parent could apply the vaccine under HW supervision and monitoring

UC6

- 4 respondents indicated UC6 as appropriate
 - The inability to monitor for AEFIs and to track vaccination considered key barriers to implementation
- 1 country indicated UC6 is being used already for Polio and that with appropriate communications, communities could “take great pride in ensuring their children receive the interventions”
- However, respondents did also see possibility of use in situations as described for UC5

for discussion purposes only

MI4A to inform global and local access strategies



MARKET INFORMATION FOR
ACCESS TO **VACCINES**

Enhance the **understanding of global vaccine demand, supply and pricing dynamics** and identify affordability and shortage risks

Convene global health partners to define strategies and activities by WHO to address identified risks

Strengthen **national and regional** market understanding for improved access to vaccines supply

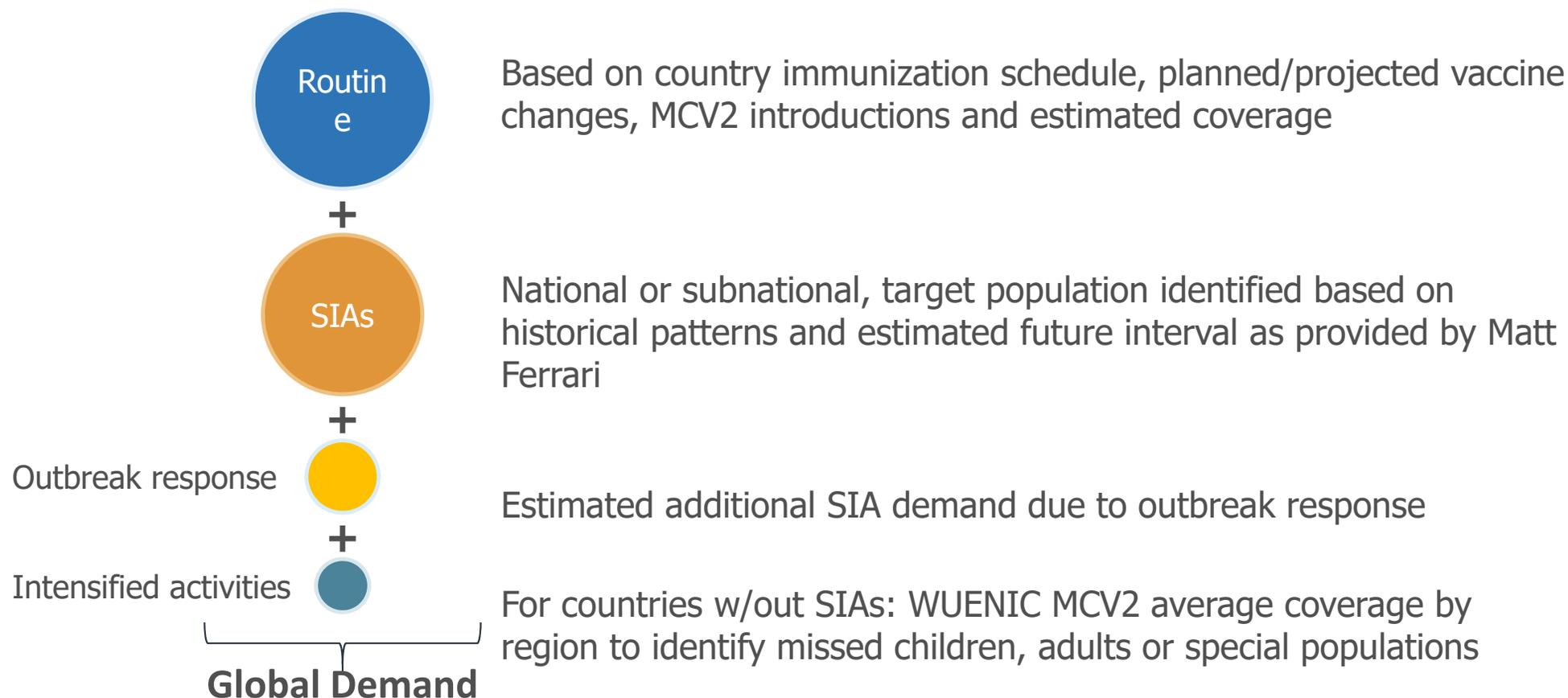
- MI4A builds on the success of the V3P project and is a key initiative of the SAGE-endorsed WHO MIC Strategy
- Links to WHA resolutions 68.6 and 69.25 to increase availability of (vaccine) price information and support Member States in addressing the global challenges of medicines and vaccine shortages

Definition of Demand - reference to the programmatic doses required by a country each year

- **Estimated programmatic doses required:** for **future years**, the **average estimated number of doses a country would need to procure to meet its immunization program needs**, whether these are routine – national or subnational – campaigns/SIAs, or for special risk groups only. This requirement includes wastage (depending on the presentation) and buffer
- **Estimated *fulfilled* programmatic doses required:** for current or prior years, when reported procurement data are not available, the estimates refer to the number of doses a country would have procured to meet its needs. When possible, this estimate will also incorporate specific events that may have greatly altered the requirements such as overstocking, catastrophic event causing discards, etc.

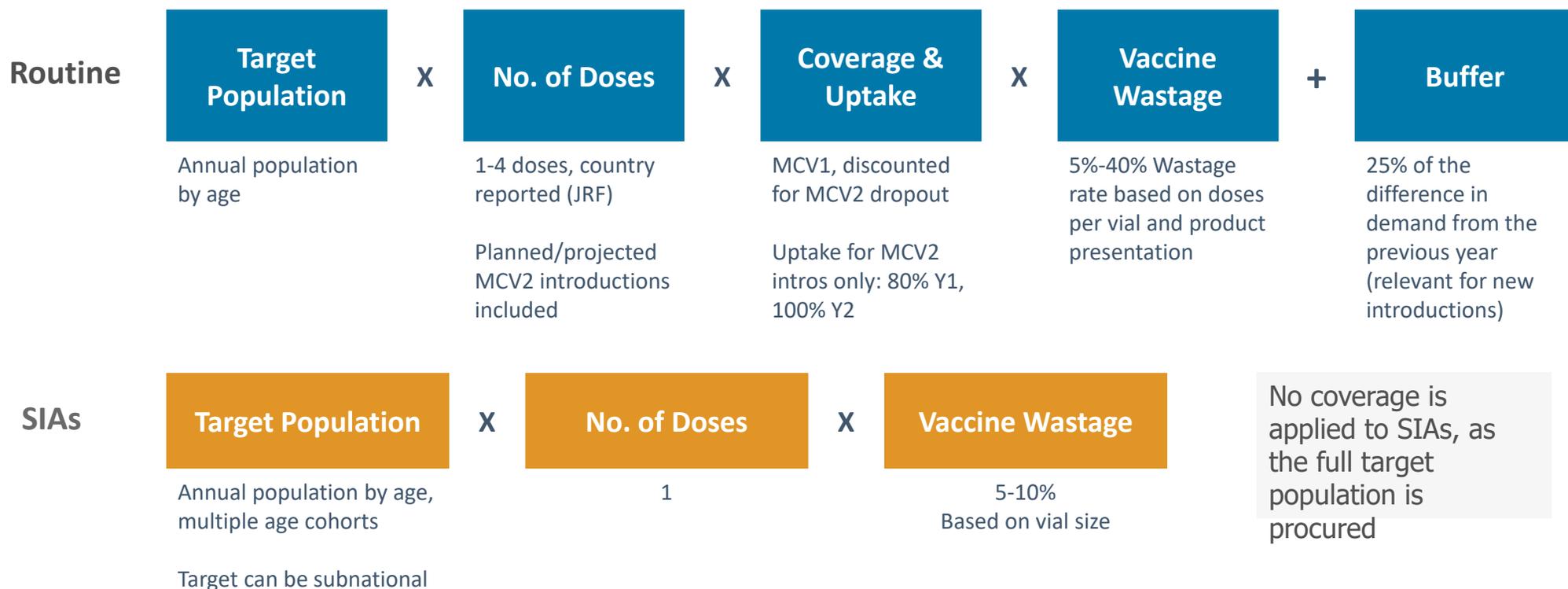
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Demand Forecasting Base Case Methods: Overview



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Demand Forecasting Base Case Methods: RI & SIAs



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Formulas for UC3 to UC4

Formula for UC3 (Outreach by CHW)

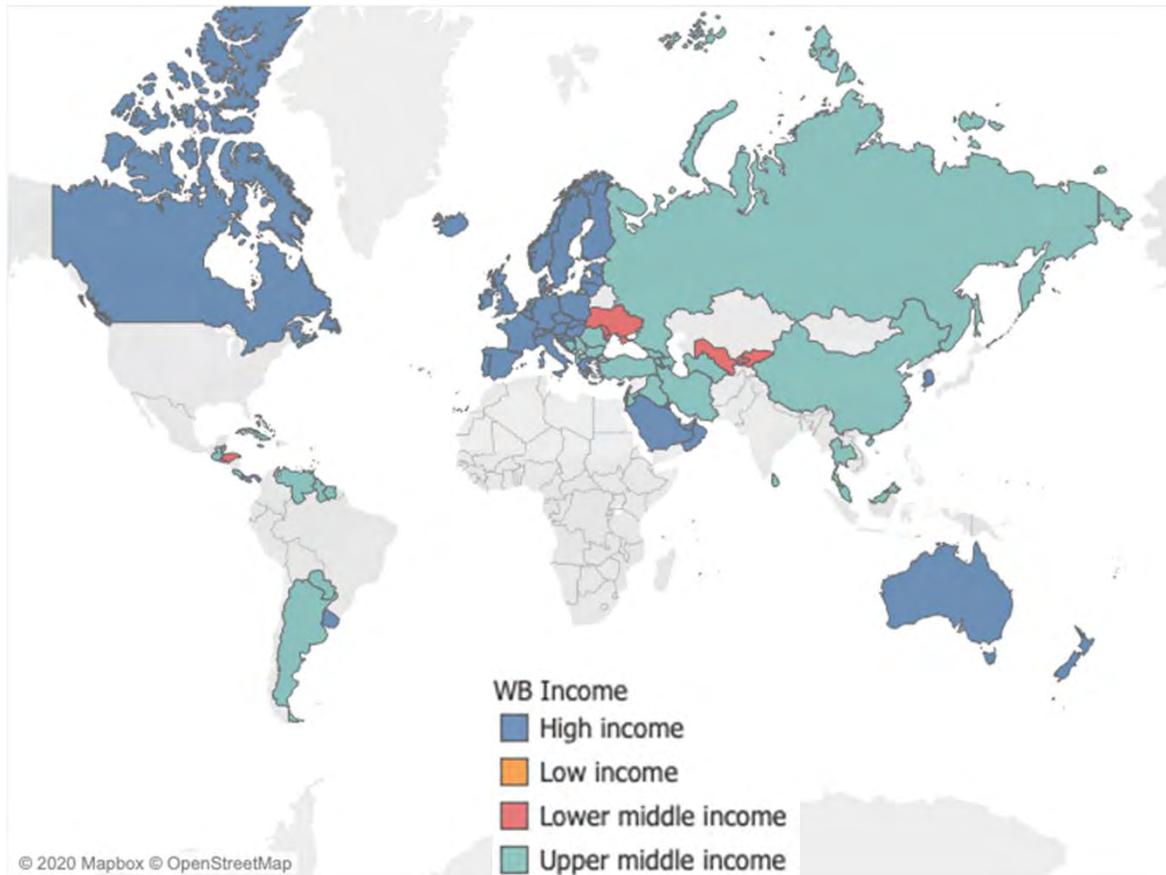
$$\text{MI4A SIA demand} \times \left(1 + \begin{array}{c} \% \text{ in increase} \\ \text{in demand due} \\ \text{to MR MAP} \end{array} \right) \times \begin{array}{c} \% \text{ by} \\ \text{CHW} \\ \text{(Outreach)} \end{array} \times \% \text{ MR} \\ \text{MAP use}$$

Formula for UC2 (Use in Outreach by HW)

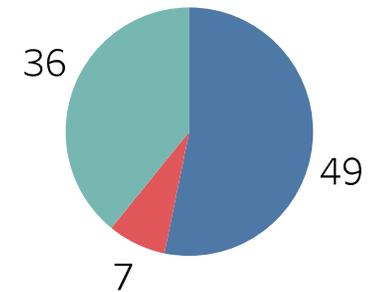
$$\text{MI4A SIA demand} \times \left(1 + \begin{array}{c} \% \text{ in increase} \\ \text{in demand due} \\ \text{to MR MAP} \end{array} \right) \times \begin{array}{c} \% \text{ by CHW} \\ \text{(Outreach in home community)} \end{array} \times \% \text{ MR} \\ \text{MAP use}$$

DRAFT – For discussion purposes only

Group 1: Countries using MMR / MMR exclusively



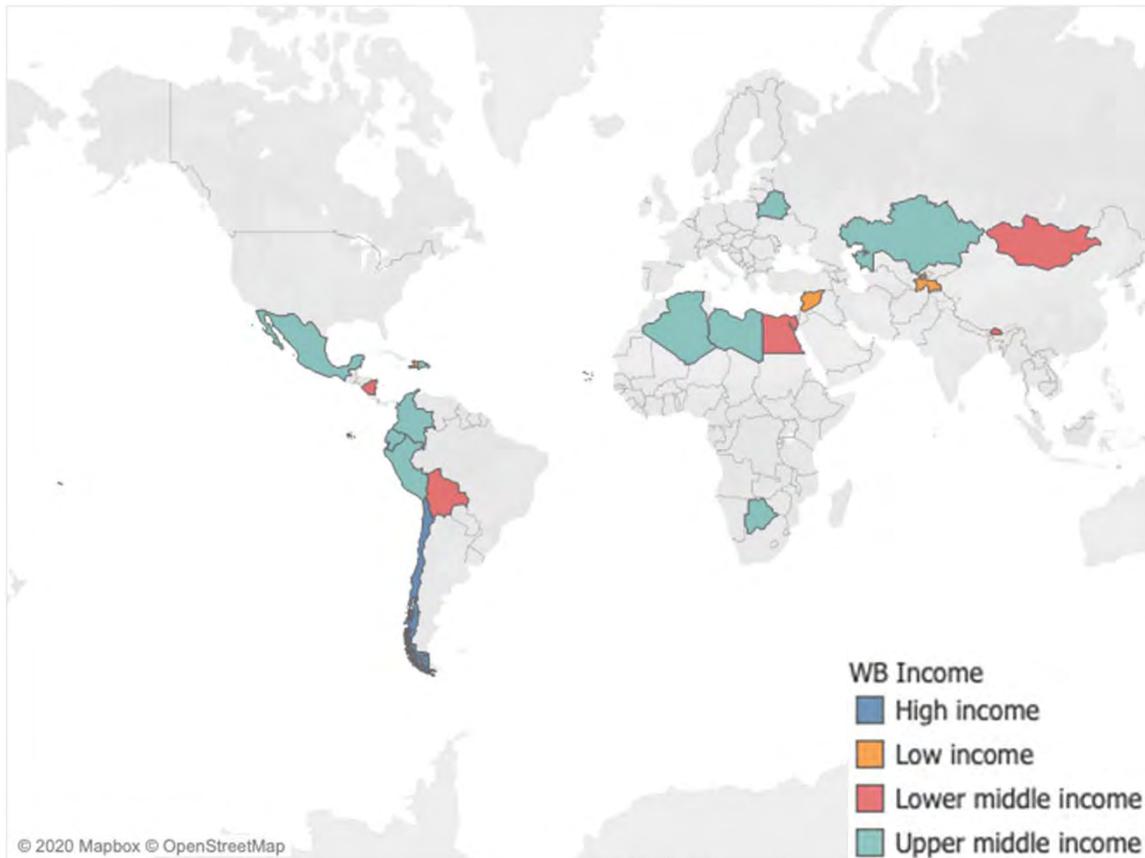
• To



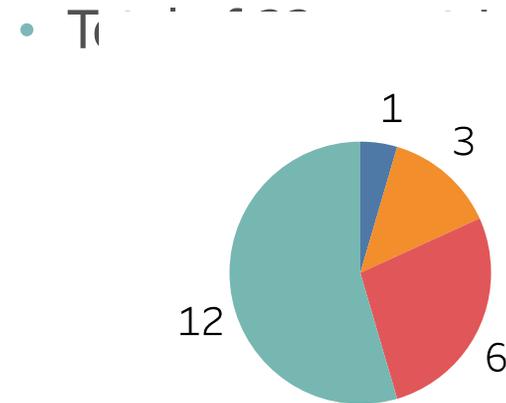
- Anticipate their MR MAPs use to be limited to specific populations or in outbreak situations only
- UC 2-6 are most applicable

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Group 2: Countries using MMR / MMRV in routine schedules but M / MR in SIAs

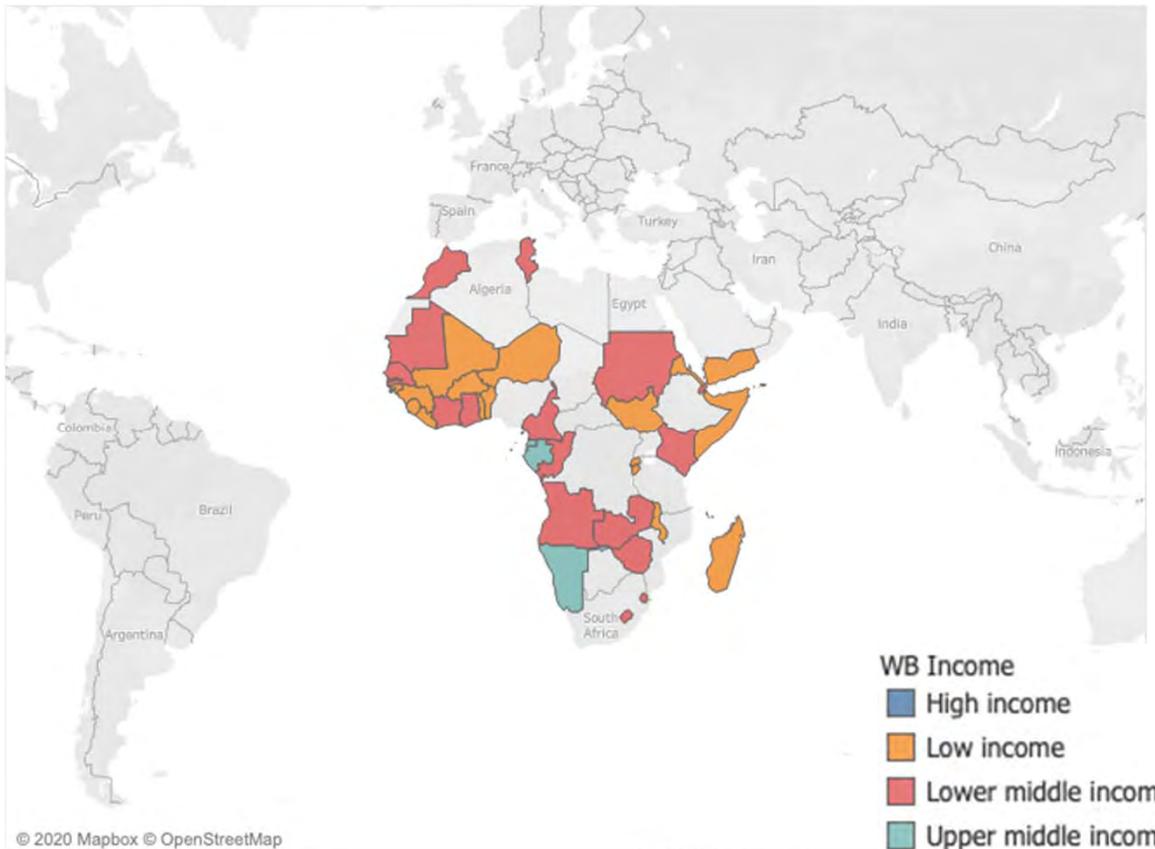


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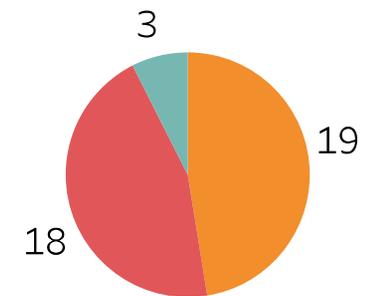
- Anticipate that MMR/MMRV use to largely focused on SIAs, catch-ups or outbreak
- UC2-5 are most applicable

Group 3: Countries in AFRO and EMRO regions



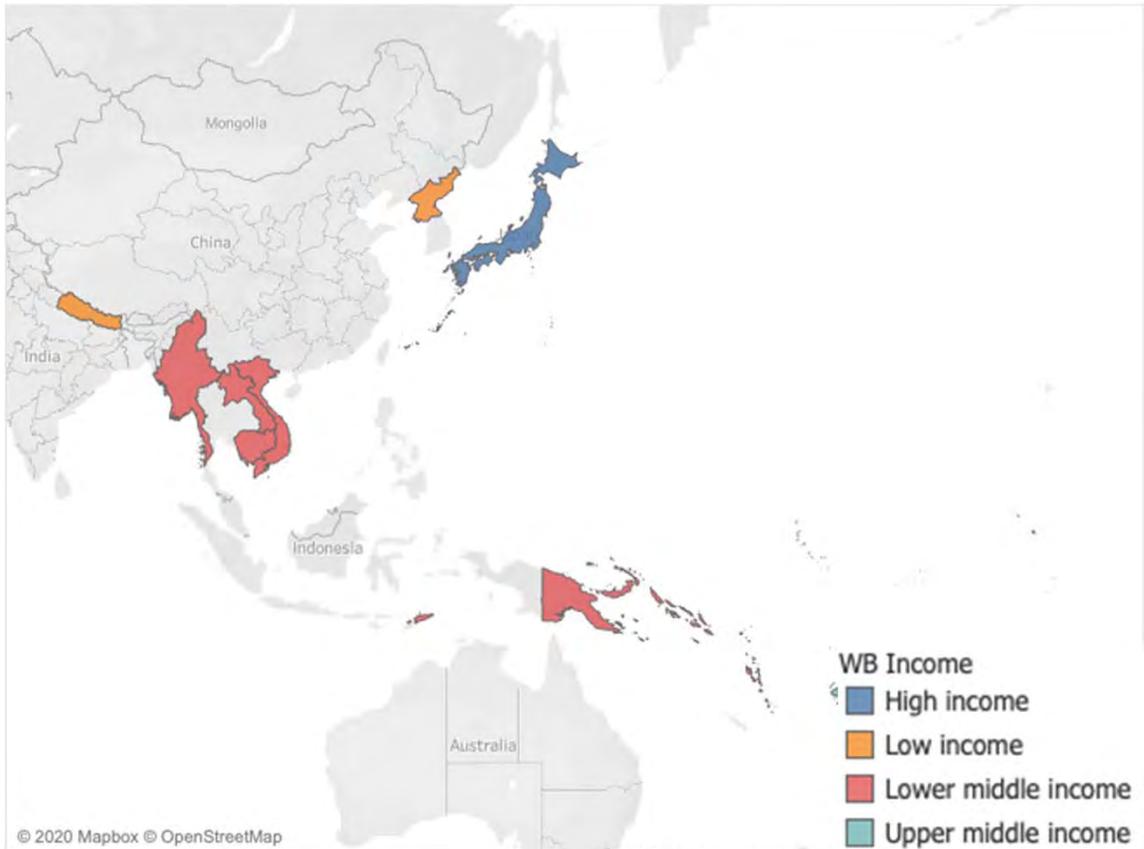
DRAFT – For discussion purposes only

- Total 22 countries



- Anticipate their MR MAPs use in all settings except for self-administration without trained supervision
- UC1-5 are most applicable

Group 4: Countries in SEARO and WPRO regions

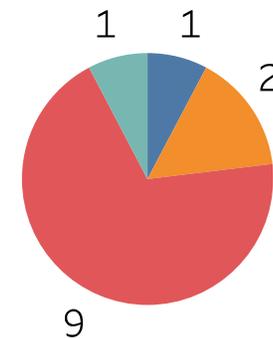


DRAFT – For discussion purposes only

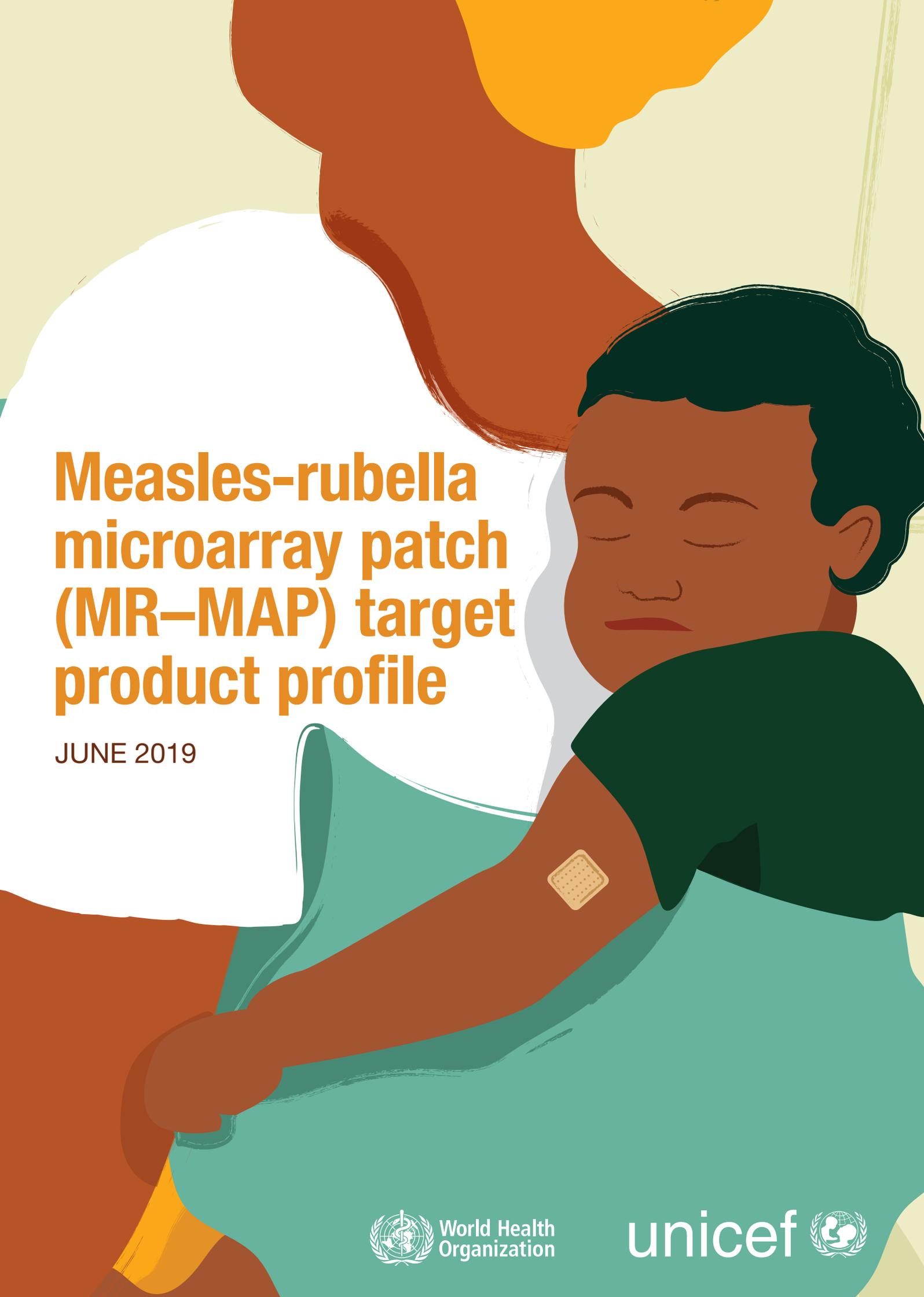
For discussion:

- Do you agree with the proposed country groupings?

• To



- Anticipate their MR MAPs use in all settings except for self-administration without trained supervision
- UC1-5 are most applicable

An illustration of a caregiver holding a child. The caregiver is shown from the chest up, wearing a white lab coat and has a small bandage on their right arm. The child is lying in the caregiver's arms, wearing a teal shirt. The background is a mix of warm colors like orange, yellow, and brown.

Measles-rubella microarray patch (MR-MAP) target product profile

JUNE 2019

Measles-rubella microarray patch (MR–MAP) target product profile

JUNE 2019

Measles-rubella microarray patch (MR-MAP) target product profile

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Preface

This target product profile (TPP) describes the minimal and optimal product characteristics for a measles and rubella (MR) microarray patch (MAP) vaccine, with a particular focus on delivery considerations for low- and middle-income countries (LMICs). It is intended to inform MAP developers, vaccine developers, procurement agencies and funders on MR-MAP research and public health priorities, and to facilitate the most expeditious development of MR-MAP candidates that would address the greatest and most urgent public health need in LMICs.

The document is based on an initial MR-MAP TPP developed by PATH and the World Health Organization (WHO) in 2016. It has been updated following input from a WHO working group of independent subject matter experts from diverse areas of expertise, including epidemiology, immunology, manufacturing and clinical development, regulatory affairs, health economics and policy. Specific aspects of the TPP were refined through consultations with various immunization stakeholders including the Immunization Practices Advisory Committee (IPAC) and the TechNet-21 community.

A draft was disseminated widely for public consultation in December 2018 among relevant stakeholders including MAP developers and vaccine manufacturers. The comments received were reviewed by the WHO MR-MAP working group and, where appropriate, incorporated into the TPP. This updated version is endorsed by the United Nations Children's Fund (UNICEF) and co-published with WHO.

While this document contains assumptions concerning regulatory considerations to help frame the rationale for the proposed characteristics, this TPP should not be considered as a regulatory document. The TPP will be updated as product development of MAP technology evolves, or as other changes in the identified need or research and development landscape emerge.

The document is divided into three major sections:

1. General considerations comparing the attributes of an MR vaccine delivered by MAP with those of the current, lyophilized MR vaccine;
2. Generic product characteristics for an MR vaccine on solid coated or dissolvable MAPs; and
3. Generic product characteristics for MAPs for delivery of MR vaccines.

Sections 2 and 3 describe the minimally acceptable and optimal targets for MR-MAP product attributes. However, these attributes are not currently listed in order of priority or importance; should an MR-MAP profile be sufficiently superior to the minimal characteristics under one or more categories, this may outweigh deficiencies in meeting a specific minimal characteristic in the suitability of product procurement.

The primary target audience for this TPP is any entity intending to develop a vaccine for national immunization programme use, including in low resource settings, and eventually to seek WHO prequalification and UNICEF procurement following licensure of its product. However, it is important to note that while this TPP defines aspirational goals for MR-MAP vaccine attributes, it does not supersede the evidence-based assessment by WHO's Strategic Advisory Group of Experts on Immunization (SAGE) for policy recommendation on use; other existing WHO guidance on vaccine development or prequalification; or assessments conducted by national regulatory authorities (NRAs), the European Medicines Agency (EMA), or the United States Food & Drug Administration (FDA).

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Johns Hopkins University, Baltimore MD, USA; Mark Papania, CDC, Atlanta GA, USA (PDVAC member); Nicolas Peyraud, Médecins sans Frontières, Geneva, Switzerland; Pieter Neels, Consultant, Antwerp, Belgium; David Robinson, Bill & Melinda Gates Foundation, Seattle WA, USA; James M. Robinson, Consultant, St Augustine FL, USA; Marian Wentworth, Management Sciences for Health, Arlington VA, USA (PDVAC member); Darin Zehrung, PATH, Seattle WA, USA.

We would also like to extend our thanks to Marion Gruber, United States Food and Drug Administration (US FDA), members of IPAC for their review and input, as well as the many individuals and institutions who provided comments on the draft at the public consultation stage.

Abbreviations

CCID₅₀	50% cell culture infectious dose	ORI	outbreak response immunization
COGS	cost of goods sold	PDVAC	Product Development for Vaccines Advisory Committee
CTC	controlled temperature chain	PQ	prequalified
EMA	European Medicines Agency	PSPQ	Programmatic Suitability for Prequalification
gPPP	generic Preferred Product Profile	PTTI	peak temperature threshold indicator
HCW	health care worker	RI	routine immunization
HF	human factors	SAGE	Strategic Advisory Group of Experts on Immunization
ID	intradermal	SC	subcutaneous
IPAC	Immunization Practices Advisory Committee	SIAs	supplementary immunization activities
IQR	inter-quartile range	TCID₅₀	50% tissue culture infective dose
LMIC	low- and middle-income countries	TPP	target product profile
MAP	microarray patch	UNICEF	United Nations Children's Fund
MCV1	measles-containing vaccine first dose	VPPAG	Vaccine Presentation and Packaging Advisory Group
MCV2	measles-containing vaccine second dose	VVM	vaccine vial monitor
MMR	measles–mumps–rubella	VVM–TI	vaccine vial monitor with an integrated threshold indicator
MMRV	measles–mumps–rubella–varicella	WHO	World Health Organization
MR	measles–rubella		
NRA	national regulatory authority		
NS	needle and syringe		

1. Introduction

The potentially favourable product attributes of microarray patches (MAPs, also known as microneedle patches) render them of considerable interest for delivery of measles–rubella (MR) vaccines, particularly within low- and middle-income countries (LMICs). MAPs possess perceived operational advantages that could ultimately increase equitable coverage and facilitate vaccine administration in inaccessible areas, especially if they contain thermostable vaccine. The MR–MAP would constitute a new vaccine product, based on a potentially disruptive technology (i.e. an innovation that creates demand, eventually disrupting an existing market). For this reason, the product attributes of MR–MAPs need to be competitive with those of existing licensed MR vaccines that require a stringent end-to-end cold chain, reconstitution followed by storage in the dark at 2–8°C and administration with an auto-disable (AD) needle and syringe (NS)¹ by a trained health care worker (HCW).

In order to rationalize the product development, procurement and introduction costs that will be required for implementation, MR–MAPs should have all or some of the following properties,

in addition to comparable safety and equivalent immunogenicity with a currently prequalified (PQ) MR vaccine: less costly to deliver (thermostable, small footprint, administered with minimal instruction); easier and safer to administer (remove the need for and risks associated with reconstitution); easier to dispose of (free of sharps); and be considered acceptable by recipients and vaccinators (pain- and/or needle-free).

The following is a target product profile for a MAP presentation based on dry vaccine formulations of a live-attenuated MR vaccine. It articulates preferences for both solid coated and dissolvable microneedle formats but is not relevant for hollow microneedle arrays intended to deliver liquid or reconstituted vaccines. Delivery of combination MR vaccines has been identified as a priority public health use case for MAPs, to help achieve the measles and rubella elimination targets set by the Global Vaccine Action Plan.² The MR combination was selected for the likelihood that it will be used widely by the time that MR–MAP products are expected to be available for programmatic use in LMICs in the late 2020s.

¹ World Health Organization, United Nations Children’s Fund, United Nations Population Fund. Safety of injections: WHO-UNICEF-UNFPA joint statement on the use of auto-disable syringes in immunization services. Geneva: World Health Organization; 2003.

² Global vaccine action plan 2011–2020. Geneva: World Health Organization; 2013.

2. General considerations for an MR vaccine delivered by MAPs

Indication



Current, lyophilized MR vaccine

Prophylactic vaccination against both measles and rubella virus infection of susceptible infants, children, adolescents and adults.



Guidance for MR-MAP

Same as for the currently lyophilized MR vaccine.

Notes: Measles–mumps–rubella (MMR) or measles–mumps–rubella–varicella (MMRV) vaccines are typically delivered as measles-containing vaccines for high-income countries, but these vaccine combinations are unlikely to be widely used in low-income countries.

Use-case scenarios



Current, lyophilized MR vaccine

For use in routine immunization (RI) service delivery, supplementary immunization activities (SIAs), outbreak response immunization (ORI) and vaccine stockpiling of MR vaccine.



Guidance for MR-MAP

Same as for the currently lyophilized MR vaccine. In addition, with its potential ease of use and improved thermostability profile, MR-MAP could be used in “house-to-house” campaigns and temporary or fixed post sites, potentially enlisting an expanded cadre of vaccinators.

Notes: The WHO position paper states that *all children with 2 appropriately timed doses of measles vaccine should be the standard for all national immunization programmes. Countries aiming at measles elimination should achieve ≥95% coverage with both doses equitably to all children in every district (regardless of measles-containing vaccine first dose (MCV1) coverage rates).*³

To reach this goal, countries should take all measures to increase delivery of two doses of MCV through routine services. In addition, SIAs in a variety of targeted age groups are utilized in most LMICs, in addition to vaccination offered through RI.

MR-MAPs are ideally suited for delivery through RI, SIAs and ORI due to ease of use. MR-MAPs have a strong comparative advantage in the context of weak health systems such as fragile and rural/remote settings, and nomadic and urban poor populations. In situations without health support, such as refugee camps and post-disaster communities, in which trained HCW may not be available, the potential for vaccine administration by community health volunteers becomes essential.

In certain settings, nationwide immunization campaigns may not be programmatically efficient, cost-effective or feasible (e.g. due to variations in subnational RI coverage, civil unrest, political instability, or financial constraints) and targeted subnational SIAs may be implemented to reduce the accumulation of susceptible individuals. The number of doses administered in national or subnational SIA settings is dependent on the coverage of MCV1 and measles-containing vaccines second dose (MCV2) achieved through routine immunization; thus, projections are possible for different RI performance scenarios.

³ Measles vaccines: WHO position paper. Wkly Epidemiol Rec. 2017;92(17):205–27.

Dose regimen and schedule



Current, lyophilized MR vaccine

First dose (MCV1): aged 9 months and above.

Second dose (MCV2): ideally delivered at 15–18 months, or in accordance with WHO recommended schedules.

The minimal interval between MCV1 and MCV2 is 4 weeks.³

Children as young as 6 months may receive a dose of MCV in special circumstances³ (called MCV0 and not counted toward the two recommended doses).

All commercially available live attenuated measles vaccines, either as monovalent vaccine or in combination with rubella, mumps, or varicella vaccines, or some combination of these, can be used interchangeably to protect against measles.³



Guidance for MR–MAP

Same as for the currently lyophilized MR vaccine.

MR–MAP may be used interchangeably with currently available measles and rubella vaccine.

Notes: MR–MAP requires safety data from 9 months of age, and data to demonstrate a short-interval repeat dosing (i.e. 4 weeks between doses) is acceptable providing the immunogenicity is comparable with conventional vaccines.

For more information on inclusion of additional age groups, please refer to the “Target Population” in section 3.

As for the current vaccine, MR–MAP vaccines should be able to be co-administered at different anatomical sites and with other vaccines including Japanese encephalitis, yellow fever, DTP-containing vaccines, meningococcal vaccine, hepatitis B, inactivated poliovirus, Haemophilus influenzae type b conjugate vaccine, and pneumococcal vaccines.³

Formulation



Current, lyophilized MR vaccine

Formulation contains MR vaccine as the active ingredient. Current formulation requires an end-to-end cold chain and reconstitution at the point of use.

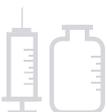


Guidance for MR–MAP

Additional or alternative excipients/additives might be needed depending on MAP format (solid coated or dissolvable), particularly to improve thermostability and light sensitivity.

Notes: It will be imperative that MR–MAPs are compliant with relevant quality and manufacturing attributes to ensure safety, quality and efficacy as well as programmatic suitability. These will be defined during development of the product and assessed by regulatory experts to ensure license of the products.⁴ All the necessary excipients/additives/stabilizers would be evaluated as part of the final formulation, to be approved for parenteral administration and within the acceptable limits.

Presentation



Current, lyophilized MR vaccine

Current presentation consists of multi-dose vial of lyophilized MR vaccine that must be stored at 2–8°C. It is reconstituted with diluent prior to injection and stored in the dark at 2–8°C for up to 6 hours before discarding.



Guidance for MR–MAP

A single dose presentation, composed of an integrated MR-vaccine delivery device in which MR vaccine is presented as a solid coated or dissolvable microarray format.

Notes: Because of the possible dose-sparing advantages of MAPs for intradermal (ID) delivery, there is the potential for a reduced dose of virus compared to current MR doses.⁵ This will be based on confirmed non-inferiority studies of immune response with supporting evidence of virus replication after MR–MAP delivery. It should be noted, however, that to date, there are no data from studies in humans or non-human primates to suggest that ID or MAP delivery of measles or rubella vaccine results in dose-sparing.^{6–8}

⁴ Requirements for measles, mumps and rubella vaccines and combined vaccines (live). In: WHO Expert Committee on Biological Standardization: forty-third report. Geneva: World Health Organization; 1994: Annex 3 (WHO Technical Report Series, No. 840).

⁵ Moon S et al. Dose sparing and enhanced immunogenicity of inactivated rotavirus vaccine administered by skin vaccination using a microneedle patch. *Vaccine*.2013;doi:10.1016/j.vaccine.2012.11.027.

⁶ Cutts FT, Clements CJ, Bennett JV. Alternative routes of measles immunization: a review. *Biologicals*. 1997;doi:10.1006/biol.1997.0103.

⁷ Edens C, Collins ML, Goodson J L, Rota PA, Prausnitz MR. A microneedle patch containing measles vaccine is immunogenic in non-human primates. *Vaccine* 2015;doi:10.1016/j.vaccine.2015.02.074.

⁸ Joyce JC et al. A microneedle patch for measles and rubella vaccination is immunogenic and protective in infant rhesus macaques. *J Infect Dis*.

3. Generic product characteristics for an MR vaccine on solid coated or in dissolvable MAPs

Two targets (minimally acceptable and optimal) have been assigned for each of the following MR-MAP attributes, according to the current understanding and development status of this technology.

- Minimally acceptable target: This case represents the “should meet” requirements necessary for suitability of the MAP technology within current MR delivery settings in LMICs. If these criteria are not met, the MR-MAP technology is likely to be considered unsuitable for programmatic delivery of MR vaccine.
- Optimal target: This case represents the “should aim for” recommendations. The criteria represent a potential scenario that would be a significant improvement over the current presentation of lyophilized multi-dose vials that require administration by a trained HCW, resulting in a quantifiable reduction in total systems cost and increased reach of the MR-MAP vaccine.

Target population



Minimally acceptable target

Routine immunization: infants aged from 9 months for the first dose, and at least 1 month later for the second dose.

Campaigns (i.e. SIAs and ORIs): children aged 9 months and above, adolescents and adults at risk.



Optimal target

Same as minimal, with the addition of infants aged 6–9 months, if supported by effectiveness data post-licensure.

Notes: WHO recommends that in countries with ongoing transmission in which the risk of measles mortality among infants remains high, MCV1 is administered at 9 months of age, with the routine dose of MCV2 at age 15–18 months.

WHO recommendations, unless otherwise stated, are global, and based on epidemiological analysis that may target wide age groups, such as adolescents and susceptible adults, that are beyond the current age range targeted by funding agencies. Thus, the target population is not restricted to infant/child age groups but includes all susceptible individuals above 9 months of age.

For MCV0 recommendation, see “dose regimen and schedule” in section two. Immunogenicity and safety data in 6 month-old infants immunized with MR-MAPs should be collected as part of post-licensure studies to support a licence indication in this population; however, preclinical data suggest that maternal antibodies in infant rhesus macaques cannot be overcome by MR-MAP administration.⁹

Target countries



Minimally acceptable target

All countries currently providing MR vaccines.



Optimal target

Availability and use of MR-MAP in all countries, including those where MMR and MMRV are recommended.

Notes: According to the Global Measles and Rubella Strategic Plan: 2012–2020,¹⁰ all six WHO regions have committed to measles elimination, four of which have also set rubella control or elimination targets.

Countries using MR or MMR in their national schedule should use the combined vaccine rather than measles-only formulations in all children, including those aged 6 months to <1 year.¹¹

Ideally, the MAP manufacturing platform would support production of MCV for the global market (i.e. including MMR and MMRV vaccines).

⁹ Joyce JC et al. A microneedle patch for measles and rubella vaccination is immunogenic and protective in infant rhesus macaques. *J Infect Dis.* 2018;doi:10.1093/infdis/jiy139.

¹⁰ Global measles and rubella strategic plan 2012–2020. Geneva: World Health Organization; 2012.

¹¹ Measles vaccines: WHO position paper. *Wkly Epidemiol Rec.* 2017;92(17):205–27.

Safety



Minimally acceptable target

Adverse events should be no more serious than those of the current NS delivery using the subcutaneous (SC) route.



Optimal target

Adverse events should be less frequent and less serious than those for current NS MR vaccination using the SC route.

Notes: The safety of MR–MAPs would need to be established in prelicensure safety studies in the target population for whom this product is indicated. With the current MR vaccine, adverse reactions following measles vaccination are generally mild and transient. Within 24 hours of vaccination, vaccine recipients may experience sensation and tenderness at the site of injection, which usually resolve in 2–3 days. Approximately 7–12 days after vaccination, systemic reactions occur in about 5–15% of recipients including fever of $>39^{\circ}\text{C}$ for 1–2 days. A transient rash may occur in about 2% of recipients. Adverse events, with the exception of anaphylactic reactions, are less likely to occur after MCV2 vaccination.

The application of a dissolvable MAP coated with an inactivated influenza vaccine resulted in a mild and transient reactogenicity, mostly reported as tenderness (66% recipients), erythema (40% recipients), and pruritus (82% recipients), lasting on average between 2–3 days. Of participants scored, 80% indicated they experienced no pain.¹² No serious adverse events have been recorded with MAP vaccine delivery to date, but few vaccine delivery studies have been undertaken (refer also to the reactogenicity paragraph in section 4).

Risks related to reconstitution with wrong, or incorrect use of diluents will be eliminated, and risks related to other types of operational errors should be reduced.

Immunogenicity



Minimally acceptable target

Seroconversion rates should be non-inferior to a currently prequalified SC MR vaccination when given at 9 or 10 months of age (reported seroconversion 92.2%, inter-quartile range (IQR) 84–96).¹³



Optimal target

Same as minimal target.

Notes: Antibodies to H and F measles proteins contribute to virus neutralization and are the best correlates of protection against measles virus infection. The presence of neutralizing antibodies demonstrated by appropriate standardized serologic assays and validated by WHO is considered the most reliable correlate of protection (protective level, >120 IU/mL).¹⁴ Other assays such as commercial enzyme immunoassay (EIA) kits have been used previously to measure immunogenicity.¹⁵ The choice of assay will need to be agreed with the relevant NRA.

Non-inferiority should be demonstrated in comparison to the immune response with NS administered vaccine. The 5% margin has been used previously in a non-inferiority trial of an aerosolized measles vaccine.¹⁶ However, the appropriate non-inferiority margin needs to be selected in consultation with regulatory agencies, and the established seroconversion rate of the licensed SC vaccine considered,¹³ as well as statistical analysis and clinical judgement in accordance with established protocols.^{17,18}

Frequently cited figures show that 89.6% (IQR 82–95) of children seroconvert when vaccinated at 8–9 months of age; 92.2% (IQR 59–100) seroconvert when vaccinated at 9–10 months of age; and 99% (IQR 95.7–100) of children seroconvert when vaccinated at 11–12 months of age.¹³

In a review of field studies, rubella vaccination induced a seroconversion rate of $>95\%$ after a single dose in susceptible individuals aged 12 months and older.¹⁹

¹² Rouphael NG, Paine M, Mosley R, Henry S, McAllister D V., Kalluri H, et al. The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch (TIV-MNP 2015): a randomised, partly blinded, placebo-controlled, phase 1 trial. *Lancet* 2017. doi:10.1016/S0140-6736(17)30575-5.

¹³ The immunological basis for immunization: measles. Geneva: World Health Organization; 2009.

¹⁴ Chen RT et al. Measles antibody: reevaluation of protective titers. *J. Infect. Dis.* 1990;doi:10.1093/infdis/162.5.1036.

¹⁵ Wiedmann RT et al. M-M-R@II manufactured using recombinant human albumin (rHA) and M-M-R@II manufactured using human serum albumin (HSA) exhibit similar safety and immunogenicity profiles when administered as a 2-dose regimen to h. *Vaccine*. 2015;doi:10.1016/j.vaccine.2015.03.017.

¹⁶ Low N et al. A randomized, controlled trial of an aerosolized vaccine against measles. *N Engl J Med.* 2015;372:1519–29.

¹⁷ Guideline on the choice of the non-inferiority margin. Brussels: European Medicines Agency; 2005.

¹⁸ Center for Drug Evaluation and Research. Non-inferiority clinical trials to establish effectiveness: FDA guidance. Washington (DC): United States Food and Drug Administration; 2016.

¹⁹ Rubella vaccines: WHO position paper. Geneva: World Health Organization; 2011

Stability



Minimally acceptable target

Vaccine potency stability profiles should be superior to current MR vaccine stability, i.e. vaccine vial monitor 14 (VVM14) when stored at 2–8°C (24 months), and must be amenable to controlled temperature chain (CTC), i.e. a single excursion for at least 3 days at 40°C.²⁰



Optimal target

Stability profiles should have enhanced thermostability, i.e. use under CTC conditions for at least 2 months.^{21,22}

Shelf life to be longer than 24 months at 2–8°C, particularly if to be considered for stockpiling.

MR-MAP should offer improved storage conditions over current MR vaccine requirements.

Doses should be formulated to prevent risk of damage from freezing.

Notes: Stability condition definitions:

Condition	Temperature	Stability timeline minimum
Full cold chain (“shelf life”)	2–8°C	24 months
CTC	At least 40°C	≥ 3 days, 2 months preferred

CTC applies to vaccines capable of tolerating at least 40°C for a minimum of 3 days prior to use, designated for use in campaign or special strategy settings, labelled with specific use conditions, and licensed for this use by the relevant regulatory authorities. Testing and validation of MR-MAP stability characteristics should be implemented according to WHO guidance on extended controlled temperature conditions (ECTC).²² Based on assessment of common supply chain structures, up to 2 months thermostability would remove reliance on cold chain equipment and logistics at health posts and stocking of vaccines at unequipped facilities. This would also offer the potential for house-to-house delivery.^{21,23} This target was proposed by immunization programme experts including IPAC members. However, the cold chain would still be required for the majority of other EPI vaccines at the current time.

Vaccine vial monitors (VVM)



Minimally acceptable target

Individual MR-MAPs should be labelled with an appropriate VVM.



Optimal target

Individual MR-MAPs should be labelled with an appropriate VVM and accompanied by a peak temperature threshold indicator (PTTI), or a VVM with an integrated threshold indicator (VVM-TI).

Notes: The creation of a new VVM type may be needed to fit the thermostability characteristics of the product if thermostability exceeds 30 days at 40°C.²⁴ VVM or VVM-TI should be placed on the primary packaging of the individual MR-MAP.

PTTI could accompany the vaccine or be placed on either primary or secondary packaging depending on the delivery strategy and microplanning.

²⁰ Controlled temperature chain: frequently asked questions. Geneva: World Health Organization; 2016 (www.who.int/immunization/programmes_systems/supply_chain/resources/CTC_FAQ_English_November_2016.pdf?ua=1, accessed 5 March 2019).

²¹ Karp CL et al. Evaluating the value proposition for improving vaccine thermostability to increase vaccine impact in low and middle-income countries. *Vaccine*. 2015;doi:10.1016/j.vaccine.2015.05.071.

²² Guidelines on the stability evaluation of vaccines for use under extended controlled temperature conditions. Geneva: World Health Organization; 2016.

²³ Kahn A-L, Kristensen D, Rao R. Extending supply chains and improving immunization coverage and equity through controlled temperature chain use of vaccines. *Vaccine*. 2017;doi:10.1016/j.vaccine.2016.10.091.

²⁴ What is VVM and how does it work? Geneva: World Health Organization; 2011.

Dosage



Minimally acceptable target

Target dosage should be defined by the quantity (i.e. virus potency on product release) of vaccine required to give a non-inferior immune response to the currently available injectable vaccine delivered in 0.5 mL by the SC route (≥ 1000 of 50% cell culture infectious dose (CCID₅₀) of each virus per dose) throughout projected shelf life of product.²⁵



Optimal target

MR-MAP should require a reduced quantity (potency on product release) of active biologic ingredient compared with amount of active biologic ingredient contained in 0.5 mL of injectable MR vaccine without reduction in induced immunogenicity throughout projected shelf life of MR-MAP product.

Notes: Endpoint dilution assays such as the 50% tissue culture infective dose (TCID₅₀) or CCID₅₀ are used to measure the infectious virus titre. These assays measure the amount of virus required to kill 50% of inoculated tissue culture cells, and are recommended in the manufacturing process and production control for measles and rubella by WHO.²⁶

WHO recommends a minimal potency for measles vaccine of 1000 viral infective units (3.0 log₁₀ TCID₅₀). Vaccines with potencies between 3.0 and 4.6 log₁₀ are considered to be standard titre vaccines, and vaccines with potencies above 4.7 log₁₀ are defined as high-titre vaccines.²⁶

Measures of potency using methods other than TCID₅₀ are in development and may be considered as a future basis for licensure, subject to approval by relevant NRAs.

²⁵ Measles vaccines: WHO position paper. Wkly Epidemiol Rec. 2017;92(17):205–27.

²⁶ Requirements for measles, mumps and rubella vaccines and combined vaccines (live). In: WHO Expert Committee on Biological Standardization: forty-third report. Geneva: World Health Organization; 1994: Annex 3 (WHO Technical Report Series, No. 840).

4. Generic product characteristics for MAPs for delivery of MR vaccines

Product registration path



Minimally acceptable target

Following licensure by a WHO listed authority, MR-MAPs should be eligible for prequalification by WHO; and should comply with its programmatic suitability for prequalification (PSPQ) guidelines.



Optimal target

Same as minimal target.

Notes: MR-MAPs would be considered a novel vaccine product and need to be evaluated for regulatory approval.

WHO PQ would be needed for UNICEF procurement of MR-MAPs. The PQ process would include discussion with a relevant WHO listed authority and the Standing Committee on PSPQ, as the MAP vaccine product would fall into the category of 'unique' characteristics.²⁷

Article 58 of Medicines for use outside the European Union,²⁸ including vaccines, aims to facilitate patient access to essential medicines in LMICs, including new or improved therapies for unmet medical needs, which are intended to prevent or treat diseases of major public health interest. The procedure combines EMA's scientific review capabilities with the local epidemiology and disease expertise of WHO and national regulators in the target countries, to provide a unique development and assessment pathway.

Experience with some analogous technologies (such as transdermal patches with small or large molecule non-vaccine medicines) may be useful for drafting initial regulatory guidelines.

Dose presentation



Minimally acceptable target

Product should be provided in an integrated (vaccine and patch combination) single dose, single-use (disposable) MAP format.



Optimal target

Same as minimal target. The size of MR-MAP should be driven by the minimal surface required to achieve the optimal antigen dose.

Notes: MR-MAPs do not require diluent nor the step of vaccine reconstitution. Relevant MAP formats are either dissolvable or vaccine coated onto a solid or porous substrate.

²⁷ Joyce JC et al. A microneedle patch for measles and rubella vaccination is immunogenic and protective in infant rhesus macaques. *J Infect Dis.* 2018;doi:10.1093/infdis/jy139.

²⁸ Medicines for use outside the European Union. Brussels: European Medicines Agency; 2015 (www.ema.europa.eu/en/human-regulatory/marketing-authorisation/medicines-use-outside-european-union).

Primary and secondary packaging



Minimally acceptable target

Primary packaging (in direct contact with vaccine) should seclude patch projections to prevent intervention resulting in damage and/or contamination of projections during shipping and storage.

For patches that require storage at 2–8°C: product should be contained within suitable secondary packaging compatible with the immunization supply chain, with a cold-chain storage volume per dose no greater than a single dose vial of injectable MR vaccine (21.09 cm³).



Optimal target

Primary package requirements same as the minimal target.

For patches that require storage at 2–8°C: product should be contained within suitable secondary packaging that is compatible with the immunization supply chain and require less cold-chain storage volume per dose than a 10-dose vial of injectable MR vaccine (2.11 cm³).

Notes: Suitable secondary packaging for MR-MAPs will protect them against damage, moisture transfer, and sunlight exposure if deemed necessary. If the patches require an applicator (single use or re-usable), it should be integrated or shipped together with the patches, and ideally not in the cold chain.

Secondary packaging configuration should minimize volume, weight and the need to repackage for in-country distribution, as defined by the Vaccine Presentation and Packaging Advisory Group's (VPPAG) generic Preferred Product Profile (gPPP) for vaccines.²⁹

Current packing vial volumes per dose:³⁰

Storage volume of single dose vaccine (diluent)	Comparison MR product
2.11 cm ³ (3.14 cm ³)	10-dose glass vial
4.22 cm ³ (5.48 cm ³)	5-dose glass vial
21.09 cm ³ (12.53 cm ³)	1-dose glass vial

Note: Diluent is not stored in the cold chain but is to be kept cool. Currently, UNICEF only supplies 5- and 10-dose vials, as countries have not expressed a preference for smaller presentation volumes. For patches that do not require cold storage, comparator volume for total packaging (CTC and out of cold chain) is vaccine vial with diluent (33.62 cm³) + syringe (~60 cm³).

Secondary packaging that allows the vaccinator to visualize the number of remaining doses should be considered.

Tertiary packaging



Minimally acceptable target

Product should be contained within suitable tertiary packaging that is compatible with the existing immunization supply chain.



Optimal target

Same as minimal target.

Notes: Tertiary packaging should comply with the VPPAG's gPPP recommendations. Compatible packaging is defined as that which minimizes weight and volume and limits the need for repackaging for in-country supply chain distribution.²⁹

Labelling



Minimally acceptable target

Primary container labelling should meet recommendations outlined by the VPPAG's gPPP for vaccines, and WHO's PSPQ guidelines as outlined by the Committee on Biological Standardization (ECBS).



Optimal target

Same as minimal target.

Notes: The VPPAG's gPPP for vaccines outlines recommendations for minimal labelling content, conventions and font. If CTC is indicated, additional labelling is required (see section 3, Vaccine Vial Monitors). MAPs can be labelled on their primary package (e.g. foil pouch) as well as on the secondary packaging (e.g. carton).

²⁹ Generic preferred product profile for vaccines. Geneva: World Health Organization; 2015.

³⁰ WHO prequalified vaccines [Extranet]. Geneva: World Health Organization.

Route of administration



Minimally acceptable target

Product should be suitable for delivery to dermis or epidermis in an anatomic site that is acceptable to immunization programmes.



Optimal target

Same as minimal target.

Administration should not result in visible external serum leakage onto a disposable component.

Notes: The term ID has been used for the delivery route and target tissue for MR-MAPs. Some patches might deliver primarily ID, but others might deliver to both the epidermis and dermis. There are insufficient data to specify the optimal depth or target tissue within the skin.

Human factors (HF)



Minimally acceptable target

A summative usability evaluation must demonstrate that safety-related use errors related to the device, applicator (if needed), labelling, and training have been identified and mitigated.



Optimal target

Same as minimal target.

Notes: For intended users and the scenarios of use for MR-MAP (section 2, Use-Case Scenarios), HF of the device must be assessed in the relevant target population (children and adults) and geography. The usability engineering process in IEC 62366-1:2015 Medical devices – Part 1: Application of usability engineering to medical devices should be followed in order to verify and validate the final MR-MAP design and applicator (if required for use). This includes establishing a usability engineering file. HF principles outlined in ANSI/AAMI HE75 Human factors engineering – Design of medical devices should be adhered to. Key components of HF for an MR-MAP are described in other sections of this TPP, including labelling, packaging, user training requirements, application site, delivery time, wear time, applicator, indication of successful vaccination, and disposal.

Application



Minimally acceptable target

MAP delivery requires a single-use applicator (while maintaining compliance with packaging requirements).

Applicator (if required) should fixate to the skin and provide an impact for penetration. Minimal force to be required for the application reproducibly ensuring complete delivery.

Any patient-contact surfaces of an applicator should be disposable to prevent cross-contamination among vaccinees.



Optimal target

MAP should be able to be delivered onto the skin consistently and successfully without the need for a separate applicator.

Notes: If an applicator is required, packaging the applicator(s) and MAPs together, or integrating them, would be preferable from a usability and logistics perspective, provided this has no unacceptable negative impact on cost or cold chain storage volume.

User training requirements



Minimally acceptable target

Minimal device training is required; HCW or trained lay health worker with printed instructions should be able to administer MAP correctly after minimal training.



Optimal target

No device training required; HCW, trained lay health worker or caregiver should be able to administer MR-MAP correctly using printed pictorial instructions.

Notes: Some studies have shown that people with minimal training can apply MAPs.^{31,32} Ideally, MR-MAPs are to be used by minimally trained HCWs in routine vaccination settings or by lay health workers with printed instructions in campaign settings after training. The MR-MAP should be simple, intuitive, and easy enough to use in clinic-based or outreach vaccination settings since it is expected that MAPs will be used in both rural and urban settings (particularly in fragile contexts in low-resource settings).

Printed instructions must be made available in at least one of the recognized languages of the destination country, pre-tested for comprehension, and revised as needed.

Delivery time: time required to apply the MAP



Minimally acceptable target

For SIAs, total time for delivery of one MR-MAP should be comparable to that of one SC MR injection with NS, including time for reconstitution from a vial.

For routine settings, delivery time should be acceptable to the immunization system in question (informed by usability evidence).



Optimal target

For SIAs, total time for delivery of 10 MR-MAPs should be comparable to that of 10 SC MR injections, including time for reconstitution from a 10-dose vial.

Notes: “Total delivery time” consists of preparation and administration. Because MR-MAPs are to be used in both routine activities and SIAs, decreasing the time required to deliver each dose would have a significant impact on overall programme logistics and capacity.

Preparation and application of MAP should be comparable to the estimated time required for reconstitution and delivery of a lyophilized vaccine from a 10-dose vial in routine settings (approximately 70 seconds for reconstitution and delivery of the first dose and 20 seconds for each subsequent dose; after the assessment of the vaccinee and vaccine-related paperwork).³³

Wear time: minimal time that the MAP must be worn for the entire dose of the vaccine to be successfully delivered



Minimally acceptable target

Up to 5 minutes, under observation, before removal of MAP by HCW, trained lay health worker or caregiver.



Optimal target

Less than 1 minute, under observation, before removal of MAP by HCW, trained lay health worker or caregiver.

Notes: Specifying and monitoring acceptable “wear time” of the patch is likely to be critical to ensure effective immunization as some MAP technologies might require extended (and monitored) wear time after patch application for reliable antigen delivery: from seconds to several minutes. Wear time is determined by clinical studies to evaluate the immune response induced by the MR-MAP in the appropriate target groups; desirable and acceptable wear times have been solicited from experts in the immunization field, including members of IPAC. Operational research will be needed to determine the acceptable time in the context of MR-MAP RI and SIAs.

RI is often performed alongside other vaccinations and health interventions and so an extended wear time for the MR-MAP might not extend the total time per vaccinee. A wear time of up to 5 minutes is deemed acceptable, given the recommendation to observe vaccinees post vaccination (including those administered by NS).

Appropriate systems for verification of the 5-minute period will need to be established. As a general principle, reduction of MAP wear time should be prioritized by developers to further reduce the risk of removal by infants and toddlers. There should be minimal safety concerns associated with leaving the patch on for longer periods.

³¹ Donnelly RF et al. Hydrogel-forming microneedle arrays can be effectively inserted in skin by self-application: a pilot study centred on pharmacist intervention and a patient information leaflet. *Pharm Res.* 2014;doi:10.1007/s11095-014-1301-y.

³² Norman JJ et al. Microneedle patches: usability and acceptability for self-vaccination against influenza. *Vaccine.* 2014;doi:10.1016/j.vaccine.2014.01.076.

³³ Pentavalent Vaccine in the Uniject™ Injection System: A Time and Motion Study. Seattle WA: PATH; 2014.

Delivery: indication of a successful vaccination



Minimally acceptable target

The design should include at least one functional, auditory or visual cue during or after application of a single dose as an indicator of successful MAP application.



Optimal target

The design should include more than one functional, auditory or visual cue during or after application of a single dose as an indicator of successful MAP application.

Notes: The specific indicator for a successful vaccine delivery depends on the tolerance of the system for over- or under-application pressure and the subsequent effect on immunogenicity and adverse events. Some delivery systems might include a visual (such as patch colour change, dye transfer or intrinsic change in skin colour) or auditory or pressure cue (such as a click) for correct application. Note that the cue indicates the correct skin application (penetration) of the MAP but not necessarily confirmation of vaccine delivery, which depends on skin penetration and correct wear time.

Effectiveness of visual cues may be dependent on skin tone/ texture and end-user acceptability concerns with this method may need to be assessed.

Cue must only be able to be activated once per MAP; failure to activate the cue will indicate the MAP has already been used or the application process was faulty.

MR-MAPs that are integrated with an applicator for successful delivery are prevented from being repeatedly applied by an MR-MAP spring mechanism, i.e. once activated, they are disabled.

Delivery: application site



Minimally acceptable target

Site of application should not impede efficacy of vaccination.



Optimal target

Same as minimal target.

Notes: Whether the MR-MAP would be dislodged during application by the vaccinee (or person administering) is unknown and resistance to this should be designed into the device. Ideally, the patch and applicator should be of minimal visual interest, particularly for paediatric vaccines. Locations on infants and toddlers that are less likely to be disturbed and/or removed (such as the scapular region), and the upper arm in older children are likely to be more favourable, assuming they are not detrimental to immunogenicity. Some MAPs in development are being tested on other anatomical sites such as the wrist, forearm, shoulder and thigh.

Minimal patch size is a consideration for application to infants.

Reactogenicity



Minimally acceptable target

Local reactogenicity is expected to be more serious or frequent than that associated with SC MR vaccination, albeit with less perception of pain.



Optimal target

Same as minimal target

Notes: Visible erythema is expected to occur post vaccination with MR-MAP and may take weeks to fully resolve. The frequency and severity of such reactions should be assessed in prelicensure clinical safety trials and prior to introduction to assess vaccine acceptability, taking into consideration other benefits of the MR-MAP vaccine and the NS comparator.

Cost per immunized child



Minimally acceptable target

Incremental increase (to be decided) to cost of goods sold (COGS) should be acceptable if MAPs offer sufficient additional programmatic benefits, including reducing vaccine hesitancy, which could enable greater vaccine reach.



Optimal target

Total cost to immunize a child (COGS plus delivery) should be lower than standard SC injection delivery methods.

Notes: Any incremental increase in COGS should reasonably be able to be offset by costs associated with delivery, such as cold chain, administration and disposal, assuming acceptability to end user, resulting in the ability to reach a greater proportion of the target population, i.e. as measured by the total systems effectiveness approach.

Disposal



Minimally acceptable target

Product should allow for safe disposal as biohazard or sharps waste, at a health care facility, with similar sharps waste volume compared with NS delivery and reconstitution.



Optimal target

Product should not be considered sharps waste and thus be acceptable as biohazardous waste. It should also have lower clinical waste volumes compared with NS delivery and reconstitution.

Notes: After application, the MR-MAP will need to be disposed of, either at the immunization setting itself or, in the event of extended wear, in a community setting.

Both dissolvable and solid coated patches can carry residues of live attenuated virus and should be considered as biohazardous waste and need to be disposed of within the clinical waste system. If the MR-MAP is not capable of penetrating or lacerating the skin without an applicator, it could be considered as non-sharps waste, but consultation with appropriate regulatory and programmatic agencies will be needed to confirm this based on field data.

The degree of risk to the vaccinator and community is likely to be much less than for traditional NS application (and previous reconstitution), if the MAP and its packaging have been suitably designed or if studies demonstrate that accidental exposure is not possible. In a survey of IPAC and TechNet-21 members, both dissolvable and solid patches were considered biohazardous waste.

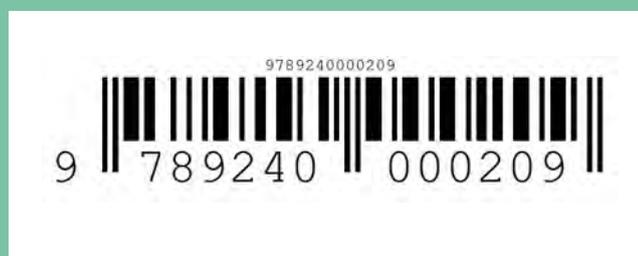
In line with the VPPAG's gPPP, materials used in delivery devices, primary containers, and secondary and tertiary packaging should be chosen to minimize the environmental impact of waste disposal for resource-limited systems. MAPs and disposable applicators need to be made of a material that can be safely treated and be compatible with available waste treatment methodologies in health centres (incineration and/or disinfection) without causing harm directly or indirectly to the environment and health.

For further information please contact:

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Report

MR MAPs Use Cases
Survey and Interview Results

August 2020

DRAFT

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Executive Summary

Objectives

MMGH, at the request of WHO IVB, is defining and estimating the potential size of Use Case (UC) scenarios for Measles-Rubella (MR) microarray patches (MAP) delivery. As part of this first phase of work, MMGH developed draft UC scenarios and their relevant definitions and validated the draft UCs through surveys and interviews. The final output for Phase 1 is to arrive at a set of validated and clearly defined UC scenarios.

MMGH derived UCs based upon an iterative process which identified delivery location and service provision (e.g., skill level for vaccine administration) as the key dimensions. The figure below provides the draft six UCs that were used for surveys and interviews.

Figure 1: Draft six UCs for MR MAPs

	FULLY TRAINED HEALTH WORKER (HW)	PARTIALLY TRAINED COMMUNITY HEALTH WORKER (CHW)	SELF ADMINISTRATION
FIXED HEALTH POST (full cold chain capabilities)	1. Delivery by HW in fixed posts RI, catch-up (ANC visit) <i>All geographies**</i>		5. Self-administration with HW assistance RI/PIRI, catch-up (SIA), ORI <i>All geographies**</i>
OUTREACH* (limited cold chain capabilities)	2. Outreach delivery by HW RI/PIRI, catch-up (SIA, school), ORI <i>MICs/LICs</i>	3. Outreach delivery by CHW RI/PIRI, catch-up (SIA, school), ORI <i>MICs/LICs</i>	
ANYWHERE (no cold chain)		4. CHW delivery in "home" community Catch-up (SIA), ORI <i>MICs/LICs</i>	6. Self-administration with no HW assistance RI/PIRI, catch-up (SIA), ORI <i>All geographies**</i>

* Includes school-delivery, mobile outreach, house-to-house, etc.
 RI = Routine Immunization PIRI = Periodic Intensification of Routine Immunization
 ORI = Outbreak response immunization SIA = Supplementary Immunization Activities
 ANC = Antenatal Care

** All geographies using MR vaccine

Survey

The surveys aimed to obtain perceptions on the six proposed UCs (Figure 1) as well as feedback to refine the definitions and / or identify any additional UCs. 111 individuals were sent personalized links through the Qualtrics™ software and an anonymous link was posted on the TechNet website. 70 individuals responded to the survey, including partial responses.

The respondents rated UC3 (Outreach by community health worker (CHW)), UC4 (CHW delivery in their home community), and UC2 (Outreach by health worker (HW)) with the highest level of importance (based on calculated means), followed by UC1 (delivery in fixed post), UC5 (self-administration with HW assistance), and UC6 (self-administration without HW assistance). ~25% to 30% of the respondents rated UC5 and UC6 were not important at all. The stratified analysis also indicated that those with an industry perspective rated UC5, UC6, and UC1 as more important than those at the global and regional / national levels. A high percentage of the respondents (69% to 88%) felt that UC1, UC2, UC3, UC4 would be used in non-Gavi lower middle-income (LMIC) and Gavi LMICs and low-income countries (LIC), with ~45% and 25% signalling UC5 and UC6, respectively, would not be used for LMICs and LICs. The percentages for high-income (HIC) and upper middle-income countries (UMIC) using MR MAPs were significantly lower with only ~57% of respondents indicating that UC1 would be appropriate, and ~30-35% as appropriate for UC2, UC3, UC4, UC5, and UC6.

Finally, the respondents indicated they expected positive effects of MR MAPs and that these would be beneficial to assist countries in achieving their MR goals, including the reduction of programmatic errors, increasing equitable MR vaccine coverage, increasing the research in insecure and fragile areas, and reducing MR vaccine wastage.

The survey results identified four areas of discord amongst the respondents – related to UC1, UC5, and UC6 and whether HICs / UMICs would utilise the MR MAPs. These issues were further explored during the interviews.

Interviews

The interviews aimed to obtain country level perspectives by conducting deep dives into how MR MAPs could be used, where these would be the most beneficial, and to explore the identified trends from the surveys. MMGH contacted 49 individual EPI managers or WHO country immunisation focal points. MMGH interviewed 30 individuals across all WHO regions and World Bank Income Group classifications.

The interviewees identified logistics and transportation, vaccine acceptability, scarcity of human resources, including lack of trained personnel, and vaccine administration as key challenges hindering their MR programmes. The interviewees also indicated that UC1, UC2, UC3, and UC4 could be used by countries but with caveats considering specific contextual factors. Further, while respondents were initially cautious towards UC5 and UC6, upon further discussion, both UCs seemed to be viable with the respondents identifying two key barriers– the inability to record and report vaccination and the inability to monitor for AEFIs. UC6 remained the most divisive, similar to the surveys, with some country respondents indicating that it would be possible if appropriate advocacy and communications were conducted while others did not see any circumstances where they could accept UC6. Further, respondents from HICs and UMICs indicated that they would also have specific use of MR MAPs, particularly in specific populations such as vaccine hesitant persons, asylum seekers, travellers, older age groups, or isolated communities.

When asked how MR MAPs could impact their MR programmes, all respondents replied in a positive manner – focusing on that MR MAPs would increase programme efficiency, increase MR coverage and reduce inequities, decrease vaccine logistics and transportation, and increase vaccine acceptance. The interviews also revealed that the type of vaccination programme (e.g. routine, PIRI, SIA, outbreak response) did not have significant bearing on the UC scenarios for MR MAPs.

Conclusions and next steps

The results of the surveys and interviews indicated that all six UC scenarios are generally viable and can eventually be utilised across all types of immunisation programmes (e.g., routine immunisation, periodic intensified routine immunisation, supplementary immunisation activities, outbreak response , etc). The UCs have been revised and expanded to clarify the potential situations in which countries could use MR MAPs (Figure 2).

Figure 2: Final MR MAPs Use Cases

	HEALTH WORKER (HW)	COMMUNITY HEALTH CARE WORKER (CHW)*	SELF ADMINISTRATION
FIXED HEALTH POST (full cold chain capabilities)	1. Delivery by HW or CHW in Fixed Post		5. Self-administration with HW or CHW assistance
OUTREACH (reduced cold chain capabilities)	2. Outreach delivery by HW	3. Outreach delivery by CHW	
OTHER SETTINGS (no cold chain)			4. Delivery by CHW in their "home" community

The MR MAP WG agreed to continue exploring UC5 and UC6 (self-administration) and include HICs and UMICs as part of the sizing exercise. The MR MAP WG was more divided on whether to continue assuming that MR MAPs would be thermostable.

As the next phase, the MMGH project team will work with WHO IVB to facilitate and coordinate a set of three virtual meetings to discuss the methodology and assumptions to size the six use cases for 2030. This work will be guided by key experts who are part of the MR MAPs WG as well as WHO's Market Information for Access Initiative (MI4A).

DRAFT

I. Introduction

Microarray patches (MAPs) consist of hundreds or thousands of tiny projections that deliver dry vaccine just below the skin surface, with some MAPs applied like a bandage and others requiring an applicator for delivery. MAP presentations and their characteristics have potential advantages over the current vaccine presentation of needle and syringes. For Measles-Rubella MAPs, they are anticipated to be single dose, remove the need for reconstitution, and have enhanced heat stability and freeze resistance. These characteristics can help to address key technical MR delivery challenges, such as reducing vaccine wastage, reducing potential programmatic errors and ultimately increasing safety, removing sharps waste, reducing cold chain requirements, and increasing acceptance. As such, MR MAPs are perceived to significantly ease delivery of MR vaccines and may significantly enhance equitable coverage of MR. However, MR MAPs are currently in pre-clinical development and not anticipated to become available for another 10 years.

MMGH, at the request of WHO IVB, is defining and estimating the potential size of Use Case (UC) scenarios for MR MAPs delivery in countries. A UC is defined as “a specific situation in which a product or a service could potentially be used to accomplish a defined goal”.

To define the MR MAPs UCs, MMGH conducted the following steps:

- Conducted a landscape analysis of MR MAP technical and programme feasibility and its acceptability
- Screened critical dimensions that were identified from the landscape analysis. These dimensions included:
 - Burden of disease and target population
 - Delivery methods
 - Vaccine standard as part of the MR strategy
- Based on the information gathered in the first two steps, selected two dimensions of delivery location and service provider.
 - **Delivery location** defined as the level of infrastructure available at the time of delivery
 - **Service provided** defined as the level of skills available for vaccine administration.
- As part of this, additional dimensions of **geographies** and **vaccination programmes** (e.g., routine, catch-up or outbreak response) were also identified as relevant.
- Based on the dimensions above, the following six UCs were proposed to the MR MAP Working Group.

Figure 3: Proposed six MR MAP UCs (as of December 2019)

	FULLY TRAINED HEALTH WORKER (HW)	PARTIALLY TRAINED COMMUNITY HEALTH WORKER (CHW)	SELF ADMINISTRATION
FIXED HEALTH POST (full cold chain capabilities)	1. Delivery by HW in fixed posts RI, catch-up (ANC visit) <i>All geographies**</i>		5. Self-administration with HW assistance RI/PIRI, catch-up (SIA), ORI <i>All geographies**</i>
OUTREACH* (limited cold chain capabilities)	2. Outreach delivery by HW RI/PIRI, catch-up (SIA, school), ORI <i>MICs/LICs</i>	3. Outreach delivery by CHW RI/PIRI, catch-up (SIA, school), ORI <i>MICs/LICs</i>	
ANYWHERE (no cold chain)		4. CHW delivery in "home" community Catch-up (SIA), ORI <i>MICs/LICs</i>	6. Self-administration with no HW assistance RI/PIRI, catch-up (SIA), ORI <i>All geographies**</i>

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 RI = Routine Immunization PIRI = Periodic Intensification of Routine Immunization
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 ANC = Antenatal Care

** All geographies using MR vaccine

Using the six UCs, MMGH also evaluated the value proposition of each UC to confirm its selection and mapped the UCs to the Target Product Profile (TPP) attributes to identify the minimum and critical attributes needed. Based on discussions with the MR MAP Working, MMGH further revised the UCs to expand UC1 to include community health workers (CHWs) and UC2 to include “Anywhere” (e.g., requiring no cold chain).

To further validate and refine the UCs and their definitions, MMGH conducted survey and interviews. This report outlines the methodology, results, conclusions from the surveys and interviews, while also identifying the key next steps to estimate the size of each UC.

II. Survey

The project team worked with the WHO IVB team to identify a list of individuals who were engaging in MR activities at the global, regional, and country levels. The surveys aimed to obtain general perceptions on the set of defined UCs (Figure 3) as well as obtain feedback to refine their definitions and / or identify additional UCs.

A. Survey methodology

111 individuals were sent personalized links through the Qualtrics™ software and an anonymous link was posted on the TechNet website. Respondents were requested to answer six demographic questions related to their type of organization and their current role in within their organization, current country location, countries referring to when responding to questions, and familiarity with MR control and elimination strategies and MR MAPs.

Respondents were then requested to answer a series of predefined questions related to a country’s ability to achieving its MR control and elimination goals by: (i) identifying key vaccine delivery challenges and influential factors, (ii) evaluating the importance of the six MR MAP UCs and where they could be utilised; (iii) identifying where MR MAPs would have the most contribution. Respondents were also requested to submit additional programmatic situations where MR MAPs could be used.

For questions relating in sections (i) and (iii) respondents were asked to rate each of the proposed answer using a 5-point Likert scale of “Strongly Disagree” to “Strongly Agree” or “Not [Important / Familiar] at all” to “Extremely [Important / Familiar]”. For certain questions, the option of “Don’t know” was also given. A mean was calculated for each criterion based by applying points of 1 for “Strongly Disagree” or “Not [Important / Familiar] at All” to 5 for “Strongly Agree” or “Extremely [Important / Familiar]”. The questions related to section (ii) were matrix questions that evaluated when and where the six UCs would be beneficial. Respondents were provided different types of vaccination programs and World Bank income group classifications and asked to evaluate if MR MAPs would contribute to the achievement of MR goals by UC. The responses were evaluated by calculating a percentage of the number of individuals indicating MR MAPs would contribute versus the number of total respondents.

The respondents were also given the opportunity to provide additional thoughts for each of the questions. The qualitative responses were individually reviewed and if needed, new categories / topics were created.

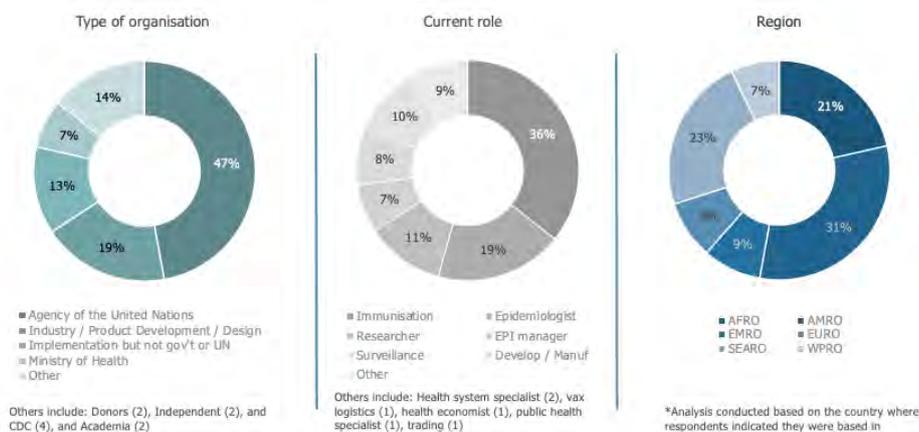
An additional stratified analysis was conducted using Microsoft Excel to evaluate any difference in trends in responses based on whether the individual was located at the global level, regional/country level, or from industry.

See Annex A for the survey questions.

B. Survey response rates and demographics

Seventy individuals partially or fully completed the survey. Figure 4 provides the demographics of the respondents by type of organisation, current role, and region. Approximately 47% of the respondents represent an agency of the United Nations followed by 19% who represented industry, product development or design, 13% working in implementation, but not for the UN or a country government, 7% working for Ministry of Health, and 14% as Other. Over 35% of the respondents identified themselves as Immunisation specialists followed by 19% as Epidemiologists and ~7-10% each representing the other categories of Researchers, EPI managers, Surveillance officers, individuals working in development or manufacturing, and Other. Lastly, survey respondents were asked which country they were based in, with the largest portion indicating their current country within the Americas region (31%) followed by Southeast Asia and African region at 23% and 21%, respectively, and approximately 7-9% for Eastern Mediterranean, European, and West Pacific regions.

Figure 4: Demographics of survey respondents



Respondents were also asked their level of familiarity with MR control and elimination strategies and MR MAPs. Figure 5 provides an overview of the responses with over 70% of respondents indicating Extremely or Very familiar with MR control and elimination strategies while only 17% indicated they were extremely familiar with MR MAPs followed by 26% and 23% indicating Very or Moderately familiarity with MR MAPs, respectively.

The MMGH project team separately reviewed the responses (N=5) for those that selected “Not Familiar at All” to MR MAPs and deemed that these responses did not significantly affect the overall outcomes or messages. Thus, these responses were maintained in the analysis.

Figure 5: Level of familiarity with MR control and elimination strategies and MR MAPs



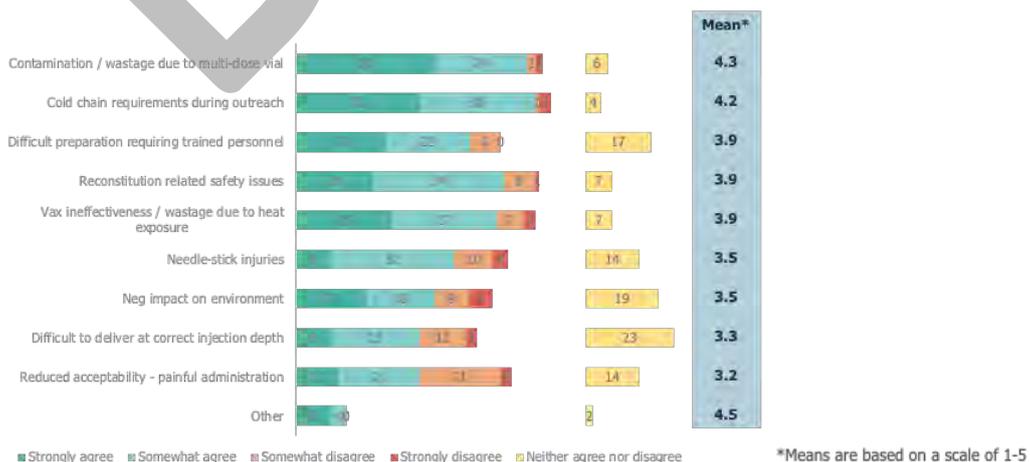
C. Survey results

70 individuals responded to what were the key MR vaccine delivery challenges that impact a country’s MR control and elimination goals. While the majority agreed on all of the factors listed, **contamination or wastage due to the multi-dose vial and cold chain requirements during outreach** ranked as the top two challenges with the most agreement amongst the stakeholders. The next three challenges included: difficult preparation requiring trained personnel, reconstitution related safety issues and vaccine ineffectiveness or wastage due to heat exposure. Although difficult preparation ranked as the third biggest vaccine delivery challenge based on the means, 17 respondents also indicated “neither agree or disagree”.

Further, a number of individuals indicated “neither agree or disagree” for negative impact on environment and difficult to deliver at the correct injection depth. Finally, reduced acceptability due to painful administration received the highest number of “somewhat disagree” and ranked as the lowest vaccine delivery challenge. Figure 6 provides the breakdown of the MR vaccine delivery challenges.

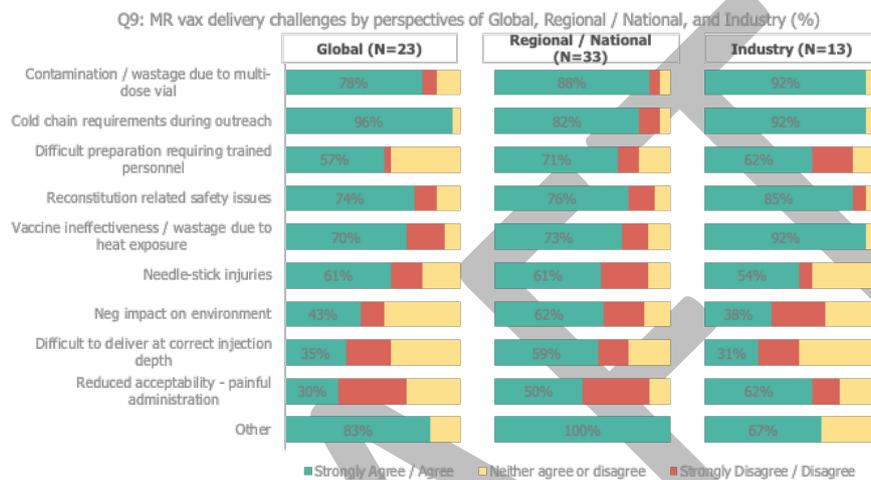
Respondents were also requested to identify additional challenges, and 5 respondents indicating cost (e.g., cost of goods, cost of SIAs, availability of government financing, etc) and four respondents highlighted logistics and transportation issues (e.g., difficulty in transporting the vaccine to health facilities and logistic challenges of bundled supplies). Two respondents also indicated the need to reduce the number of injections during a visit and one respondent indicated challenges due to the need to ensure careful planning to avoid vaccine wastage.

Figure 6: MR vaccine delivery challenges (Number of respondents)



The stratified analysis for this question indicated a difference in opinions on four challenges related to difficult preparation requiring trained personnel, vaccine ineffectiveness / wastage due to heat exposure, negative impact on the environment, difficulty to deliver the vaccine at the correct injection depth, and reduced acceptability due to painful administration. The general trend indicated that regional and country perspectives felt that these were more pertinent challenges affecting their achievement of MR control and elimination goals compared to those with industry perspectives.

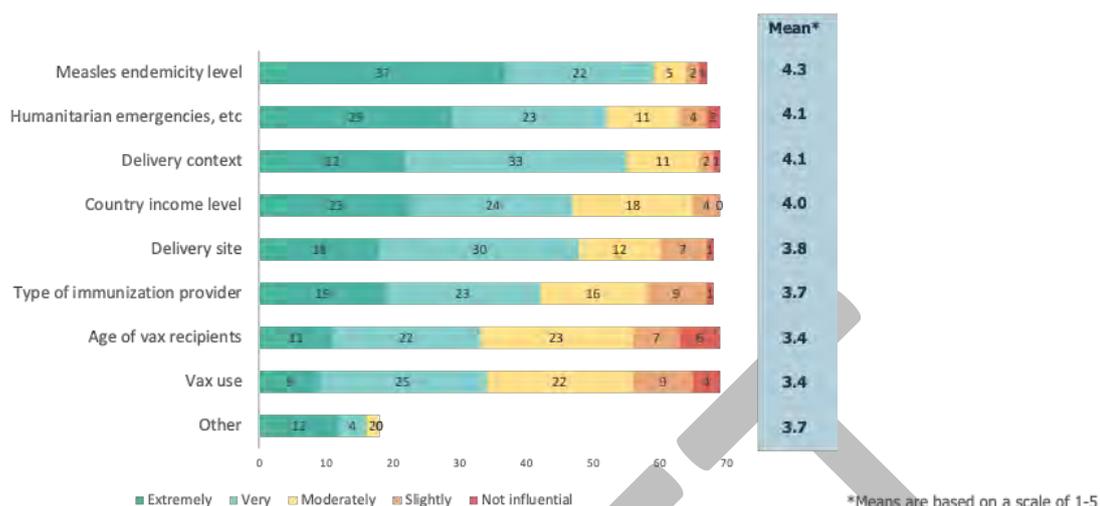
Figure 7: MR vaccine delivery challenges by stratified perspectives (percentage of respondents)



69 individuals responded to how influential are the following factors to achieving MR control and elimination goals. The top four influential factors identified by respondents included **Measles endemicity levels, humanitarian emergencies, delivery context** (e.g. routine, campaigns, outbreak response, etc), and **country income level**. The other four factors of delivery site (e.g. hospital, fixed health post, outreach, etc), type of immunisation provider (health worker, community health worker etc.), age of vaccine recipients, and vaccine use (e.g. standalone, co-administered) were also considered to have very to moderate influence by the majority of respondents.

Individuals provided additional comments with 8 individuals indicating **inadequate number of trained human resources and strength of the healthcare system**. Four individuals cited the **political will** as key influencing factor, 3 individuals each cited **vaccine supply / availability and vaccine hesitancy / communication**, and one individual cited surveillance. Figure 8 provides an overview of the influential factors. Please see Annex B for the stratified analysis.

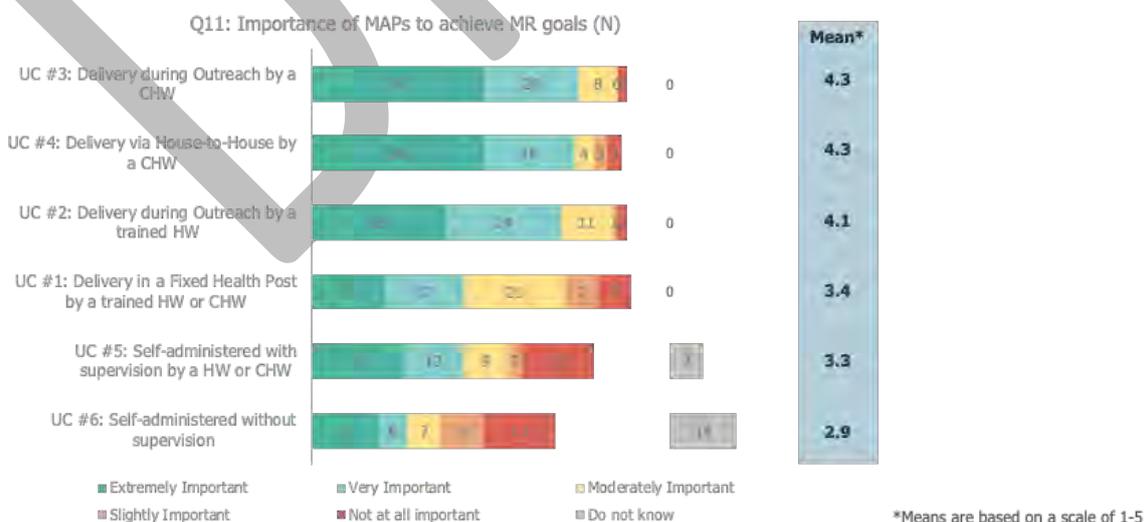
Figure 8: Factors that influence a country’s ability to achieve its MR control and elimination goals (Number of respondents)



The respondents were then asked to rate the importance of the predefined six UCs. **UC3, UC4, and UC2 received the highest level of importance** per the respondents. UC1 and UC5 received moderate importance and UC6 received the lowest level of importance with highest level of discordant options where ~47% of respondents stated that UC6 was only slightly important or not at all important. UC5 also received a high number of individuals that rating it as not important at all (25%).

Respondents provided their own ideas related to new UCs, these responses included the use of MR MAPs in schools or universities, in emergency rooms, as part of mass gatherings, in outbreak or humanitarian settings, as part of missed opportunity, as part of multi-age campaigns, by parents to child and in travellers. As these suggestions were covered within the six predefined UCs, the MMGH project team utilised the feedback to clarify and refine the existing definitions. Figure 9 provides additional details on the level of importance the respondents assigned to MAPs.

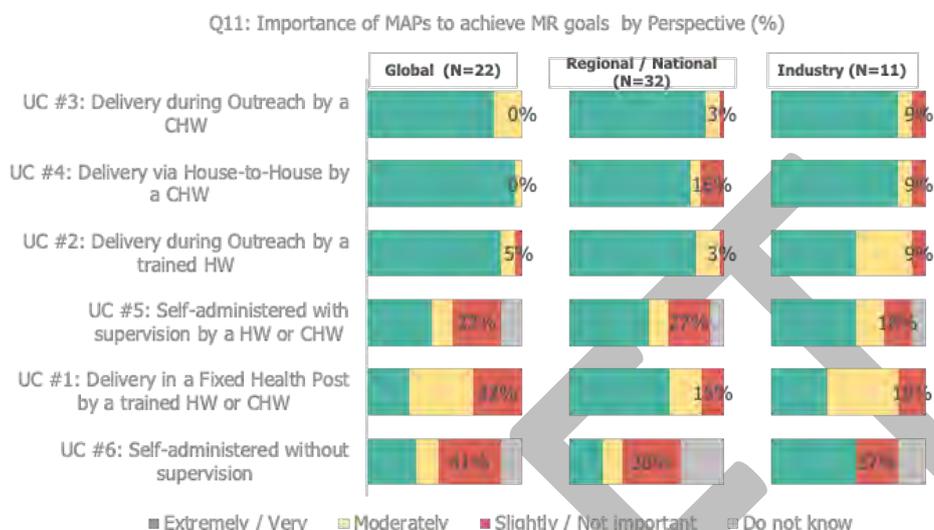
Figure 9: The importance of MAPs to achieve a country’s control and elimination goals by predefined UCs (Number of respondents)



When the results were stratified, there was general agreement amongst the different perspectives for UC2, UC3, and UC4. However, opinions differed particularly for the UCs

utilising self-administration (UC5 and UC6) and the delivery in a fixed health post (UC1), with those from the Industry rating these UCs as more important than those representing the Global and Regional/National levels.

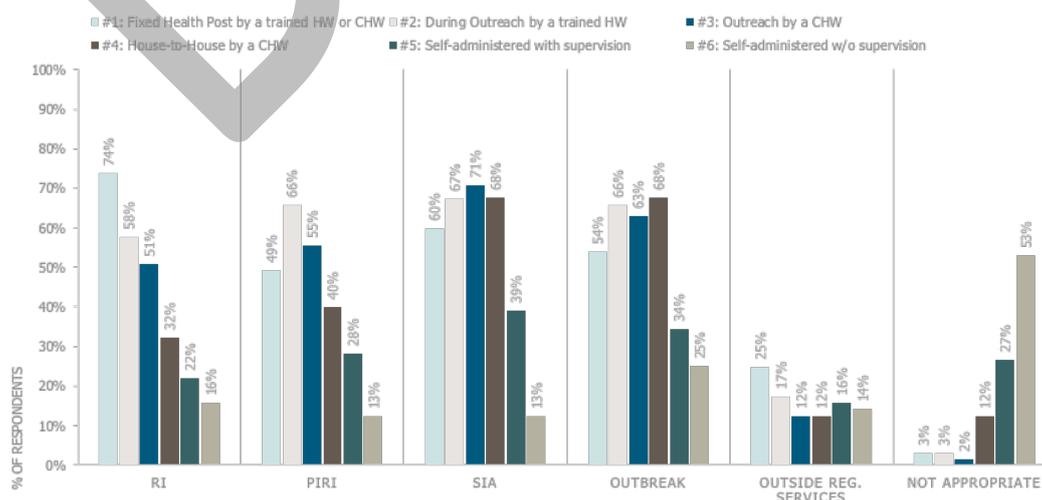
Figure 10: The importance of MAPs to achieve a country’s control and elimination goals by predefined UCs (percentage of respondents)



65 respondents provided their input on which vaccination programmes would receive the most benefit from MR MAPs by the predefined UCs. The majority (more than 50%) felt that **UC1, UC2, and UC3 would be useful for routine immunisation, periodic intensification of routine immunisation (PIRI), supplementary immunisation activities (SIA), and outbreak response.** For **UC4**, the majority of respondents felt this was only useful during SIAs and outbreak activities.

For both **UC5 and UC6**, the percentage of respondents that believed the vaccination programme would benefit from MR MAPs use was below 50 percent. However, more respondents felt UC5 has more potential than UC6 to benefit the vaccination programmes, particularly during SIAs and outbreak response. Lastly, 27% and 53% of the respondents indicated UC5 and UC6 were not appropriate, respectively. Figure 11 provides the percentage of respondents who felt the predefined MR MAP UCs would benefit the vaccination programmes and Annex C provides the stratified analysis.

Figure 11: MR MAP benefit to vaccination programmes



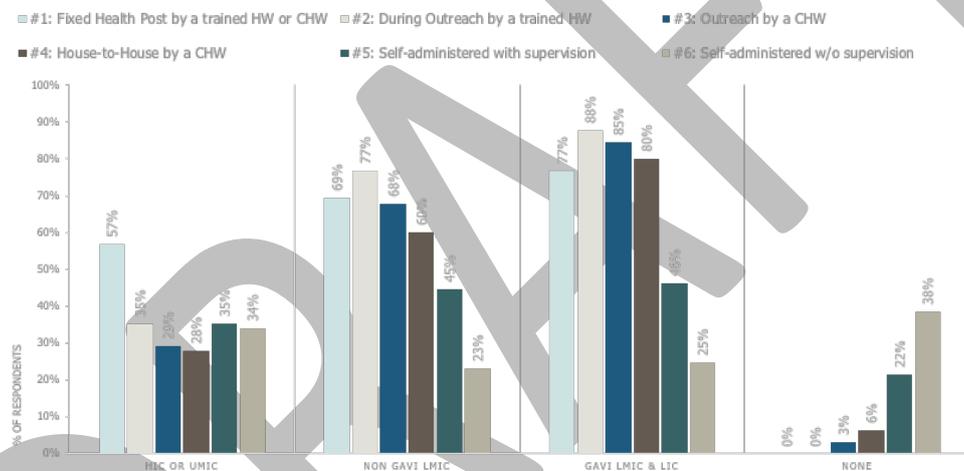
The respondents were asked to select the country income groups where MR MAPs would contribute to MR control and elimination goals. While the majority of respondents indicated that UC1 could be used by all countries, the opinions differed for the other UCs.

Between 28% to 35% of the respondents felt that high income countries (HICs) and upper-middle income countries (UMICs) could use MR MAPs for UCs 2 to 6.

The trends from the respondents for non-Gavi lower-middle income countries (LMIC) and Gavi LMICs and low-income countries (LICs) were roughly similar. A high percentage (between 60-88%) of the respondents saw MR MAPs being used by non-Gavi LMICs and Gavi LMICs and LICs for UC2, UC3, and UC4. Approximately 45% and 25% of the respondents felt UC5 and UC6, respectively, could be used by Non-Gavi LMICs and Gavi LMICs and LICs.

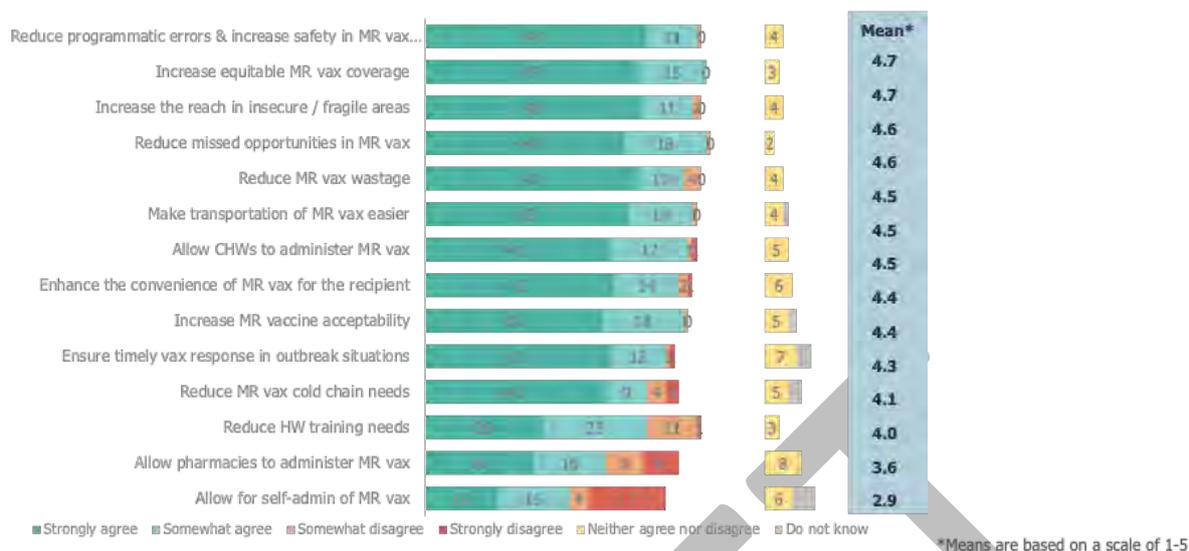
There seemed to be **high acceptability of UC1, UC2, UC3, and UC4**, with only a limited number of respondents indicating that no countries would utilise these UCs. However, **UC5 and UC6 still contained the highest percentage of respondents who felt that no countries would use these UCs at 22% and 38%, respectively**. Figure 12 provides additional information and Annex B provides the stratified analysis.

Figure 12: Countries that can use MR MAPs by UC



Lastly, 65 respondents provided their feedback on whether MR MAPs could contribute to MR control and elimination goals. In general, the respondents agreed that MR MAPs could have a positive effect and help to achieve different goals and objectives. Areas where respondents did not agree were largely related to self-administration with 62% and 50% agreed with allowing pharmacies to administer MR vaccine and allow for self-administration of MR vaccination, respectively. Figure 13 provides additional details on the feedback of how MR MAPs can help.

Figure 13: MR MAPs can contribute to the following (number of respondents)



D. Survey discussion

Per the results of the survey, the top challenges identified by respondents are related to the current vaccine presentation and the requirements to ensure an effective and safe vaccine is delivered (e.g., contamination and wastage due to a high dose vial, cold chain requirements, requirement of trained personnel and reconstitution/safety issues). Thus, it is not surprising that **MR MAPs are expected to reduce programmatic errors and increase safety, increase coverage, particularly if there are no cold chain requirements** as this could facilitate outreach activities even in fragile and insecure areas.

As respondents highlighted that the most influential factors to achieving MR control and elimination goals were measles endemicity level and humanitarian emergencies. This highlights an important point **that MR MAPs must be as efficacious and effective as the current presentation to ensure its acceptability and use**. Linked to this, ease of **transportation and administration** are likely key drivers to whether MR MAPs will be utilised by countries.

While UC1, UC5 and UC6 had the most discordant opinions regarding their level of importance, there was still sufficient evidence to indicate that **there may be potential opportunities, particularly for UC1 and UC5**. This required a further deep dive through the interviews to understand the opinions and identify potential barriers.

Further, the data from the survey indicates that **there may be demand from HICs and UMICs**, even if they use MMR / MMRV in their routine schedules. This will also need to be further explored during the interviews. While there is a slightly higher perception that MR MAPs will be mainly used for Gavi countries, there is no significant difference between Gavi countries and non-Gavi LMICs.

The stratified analyses indicate a difference in perceptions regarding MR MAP UCs, **particularly for those individuals working in the industry**. Thus, it is important to continue to keep open communication channels between those working on MR programmes and those working on product development.

While the survey provided an overview of key trends and thoughts regarding the MR MAP UCs, it is important to utilise the interviews and further explore and understand the rationale behind these trends. The key issues that require further exploration include

whether UC5 and UC6 are viable options, why were there discordant opinions regarding UC1 and if HICs or UMICs are interested in using MR MAPs and if yes, how would they use MR MAPs. Finally, the number of survey respondents working for or directly with Ministries of Health (N = 5) was limited, it is of utmost importance that their voices and input is captured to further refine or develop the UC scenarios.

III. Interviews

The interviews were conducted after the survey (June-July 2020) and aimed to obtain country level perspectives by conducting deep dives into how MR MAPs could be used in specific country context and where would MR MAPs be the most beneficial. The interviews were also used to delve deeper into the rationale of the key trends identified from the survey related to UC1, UC5, UC6, and HICs / UMICs utilizing MR MAPs.

A. Interview methodology

MMGH, in consultation with WHO IVB, selected a set of countries to target for interviews. It was agreed that the countries should be selected based on the following factors:

- The 10 most populous countries;
- The 10 countries with the most unimmunized children, using WUENIC MCV1 (2019);
- Countries that were previously selected for the Vaccine Innovation Prioritization Strategy (VIPS) deep dive;
- Countries that represent the high-priority countries for Gavi and Measles & Rubella Initiative;
- A selection of countries that are classified as middle- or high-income countries per World Bank (2019) and
- A selection of countries that are currently experiencing protracted crises.

Based on the criteria above, 49 countries were selected for interviews. MMGH contacted 49 individuals EPI managers or equivalent and interviews were conducted by teleconference using a semi-structured interview guide. Each interview lasted approximately 30 minutes, with the interviewer transcribing the feedback and input. In the situation where MMGH was unable to receive a response from the EPI managers, the WHO immunisation focal points were contacted.

The respondents answered a series of predefined questions related to: (i) their current technical MR vaccine delivery challenges; (ii) whether the proposed UCs would be appropriate for the country and why; (iii) identified any additional UCs; and (iv) indicated how MR MAPs would help resolve the previously identified technical vaccine delivery challenges and contribute to the achievement of their MR goals. Questions were sent in advance and, if needed, tailored to the participant. Interviewers documented responses in real time as verbatim as possible.

The senior MMGH team members reviewed all interview transcripts and using an iterative process discussed these to identify the key results and emerging themes. MMGH also utilized TextiQ™ from Qualtrics™, a text analysis tool which assigns topics to qualitative feedback and performs a sentiment analysis (e.g., assigns a positive, neutral, mixed, or negative sentiment to the qualitative feedback). The project team members developed the

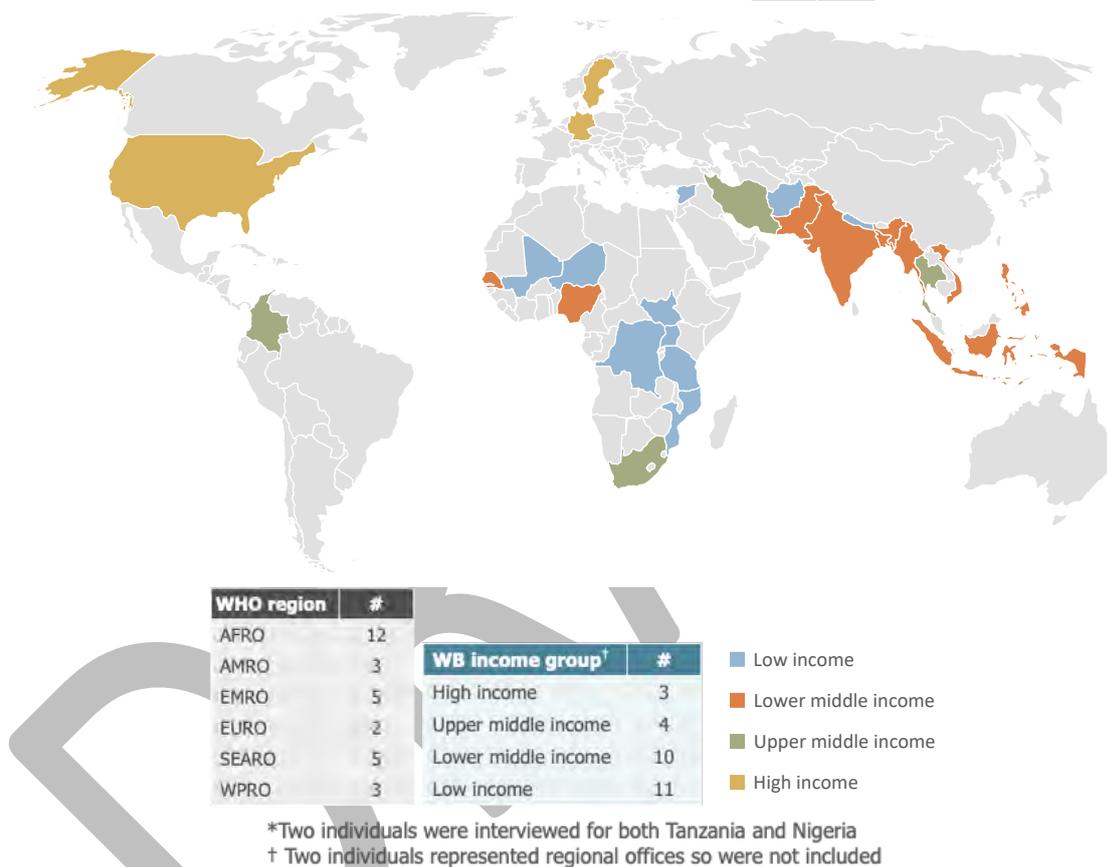
topics and sub-topics together and reviewed all of the assigned sentiments, correcting any that were inaccurate. Finally, the project team discussed the results of both analyses to arrive at a consensus and identify the results and emerging themes.

See Annex C for a full list of the interview questions.

B. Interview response rates and demographics

MMGH interviewed 30 individuals across the WHO regions and World Bank Income Group classifications, including 2 WHO regional representatives and 26 countries*. The interviewees comprised of 16 EPI managers and 14 WHO immunisation focal points at the country or regional levels¹. The figure below provides a map and additional details of the individuals interviewed.

Figure 14: Map of interview respondents



C. Interview results

The interviewees were asked to identify and discuss their top three technical vaccine delivery challenges. The majority of respondents (N=22) cited **logistics and transportation** challenges e.g., difficult to conduct outreach activities, inability to prepare vaccines in advance when conducting outreach activities, insufficient number of health facilities, lack or insufficient cold chain, and the inability to access hard-to-reach or security compromised areas or vulnerable populations.

The second most identified challenge related to vaccine **acceptability**, including challenges in communication, fear of needles / crying children, overcrowded vaccination schedules. The third and fourth most identified challenge included **human resources** and

¹ MR regional focal points for PAHO and AFRO were interviewed

administration. Respondents referred to human resources as either the lack of quality vaccinators or insufficient number of individuals to deliver the vaccine and administration as reconstitution and safety issues. Other challenges that were identified low coverage or high drop-out rates, adverse events following immunisation (AEFI), and high wastage or costs.

The figure below provides a graphical representation of the technical vaccine delivery challenges.

Figure 15: Technical vaccine delivery challenges identified by the interviewees



Respondents were provided an overview of the six UCs and asked to provide their feedback on whether their country or region would utilise MR MAPs, considering that MR MAPs would become available in 10 years or 2030. In general, respondents felt that **UC1, UC2, UC3, and UC4 could be used by the country but with caveats.**

Such caveats included that some countries felt that UC1 and UC2 would not be relevant for their countries as they utilise MMR or MMRV in their routine schedule or already have strong systems in place and would not want to upset their existing system, which could trigger additional implications for other vaccines.

For UC3 and UC4, some individuals indicated that this would not be accepted as their countries recently experienced serious AEFIs related to MR or there may be legal constraints on who can administer vaccinations. Further to this, a few respondents indicated the need to roll-out MR MAPs in fixed health posts with formally educated health workers to increase acceptance and trust prior to providing MR MAPs to community health workers. Linked to these ideas, the respondents also indicated that UC4 was less likely than UC3 unless appropriate supervision was put into place.

Regardless, the majority of the individuals did believe that UC3 (82%) and UC4 (70%) could be utilised in their countries as they saw the benefits of an **expanded workforce** to deliver vaccines, with a few respondents indicating that polio is delivered with volunteers and MR MAPs could follow suit. Many also saw the benefits to **improve access of hard-to-reach or security compromised areas, the chronic unimmunized, and insecure areas.**

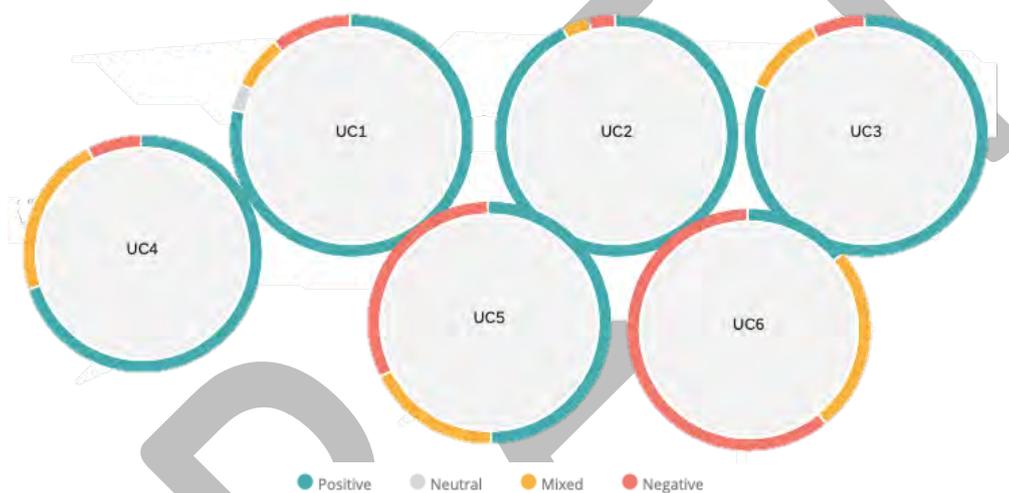
Although the respondents were **initially cautious towards UC5 and UC6**, upon further discussion, it became clear that both could have roles to play. The majority of respondents cited two key barriers to self-administration – **the inability to record and report vaccination and the inability to monitor for AEFIs.**

Regardless, **~50% of the respondents had a positive view of UC5**, citing that older age groups could self-administer MR MAPs under the supervision of a health worker or MR

MAPs could be used in hard-to-reach, security compromised, or remote areas. Some countries cited a preference for UC5 (e.g., Indonesia, DRC, and Mozambique) while others cited the current global pandemic of COVID-19 as providing potential opportunities to utilise UC5 (e.g., provide the mother the MR MAP and she can administer under the supervision of a HW).

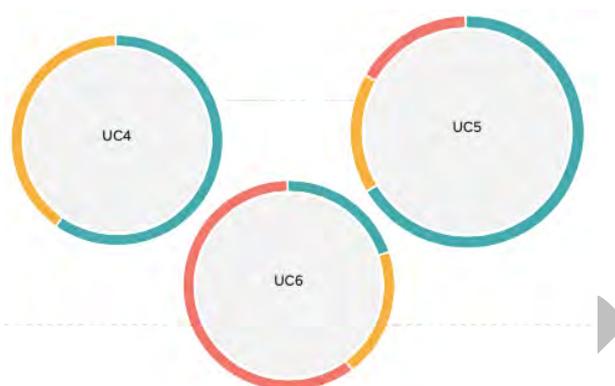
UC6 remained the most divisive with some countries indicating that it would be possible if **appropriate advocacy and communications** were conducted and the community felt responsibility and pride in utilising a new innovative technology. Another respondent indicated that MR MAPs could be a **powerful tool against hesitancy** as the parents could be administering the vaccine themselves ultimately participating in the process and feeling more empowered. While another country indicated that it would not be possible given the linkages of vaccination with infant and child health checks. The figure below provides an overview of the sentiments towards the six UCs.

Figure 16: Appropriateness of UCs



As countries with MMR or MMRV in their routine programme were interviewed, a stratified analysis of the above was conducted to better understand the appropriateness of UC4, UC5, and UC6. UC1, UC2, and UC3 were not separately evaluated as many stated they would want to not replace MMR / MMRV with a MR vaccine. The figure below provides the stratified analysis of countries utilising MMR / MMRV in their routine immunisation schedule (N = 7 countries). These countries saw a role for MR MAPs, particularly in **specific populations such as vaccine hesitant, asylum seekers, travellers, older age catch-up immunisation or isolated communities**. A few also indicated the possibility to conduct self-administration of MR MAPs through pharmacies if there was an ongoing outbreak.

Figure 17: Countries using MMR / MMRV in their routine immunisation schedule (only UC4 and UC6)



When asked how MR MAPs could impact their MR programmes, all respondents responded in a positive manner. All of the individuals indicated that MR MAPs would **increase their efficiency**, citing the reduction in reconstitution errors, increased ease of administration, and expansion of the types of individuals able to administer the vaccine. Further, ~30% cited that MR MAPs would help them save time either in delivering the vaccine faster or in reducing their preparation and planning time. Others also cited the reduction in waste management and wastage.

~80% of the respondents stated that MR MAPs would help to **increase MR coverage and reduce inequities** (e.g., reducing drop-out rates, increasing the ability to access hard-to-reach areas or migrant populations) Almost 60% of the respondents cited **decreased logistics and transportation** (e.g., no cold chain requirements and ease of transportation) as an important aspect of MR MAPs. Lastly, 40% of the respondents indicated that MR MAPs would **increase vaccine acceptance** by reducing the number of injections and reducing pain and fear. Figure 18 provides an overview of the impact MR MAPs could have.

Figure 18: How MR MAPs could impact MR programme and goals



The respondents were also queried to provide any additional UCs. The additional ideas included pre-emptive use of MR MAPs in humanitarian crises, use during door-to-door outbreak investigations, and airport administration before traveling to high risk countries. These were incorporated into the existing UCs.

Although not explicitly asked, the feedback received from the interviewees highlighted a number of key needs that must be met for MR MAPs to be utilised. These include the following:

Vaccine characteristics:

- **Safety and efficacy:** must be demonstrated and needs to be comparable, if not better, than the needle and syringe (e.g. what are the side effects, will there be a delayed anaphylaxis?)
- **Thermostability:** This was a key assumption applied during all the interviews and is a needed characteristic of MR MAPs, including a vaccine vial monitor (VVM)

Pre-implementation:

- **Studies and pilots:** many individuals indicated that they would prefer to pilot MR MAPs prior to larger scale use. Some also highlighted the need for local studies not only for National Immunisation Technical Advisory Groups (NITAG) and policy makers, but also to improve community acceptance of MR MAPs
- **Costing analyses:** An in-depth analysis must be done, considering total systems costs. This includes understanding cold chain implications, AEFIs from programmatic errors, wastage, waste disposal, and transport costs
- **Information and communications:** Excellent communications are needed at two levels: (i) NITAG and National Immunisation Programmes (NIP) to ensure appropriate policy and programmatic decision making; and (ii) Communities to improve acceptance and counteract rumours

Implementation / post-implementation:

- **Training:** Intensive training with clear detailed instructions must be developed (e.g., location of the administration site, length of application time, etc)
- **Monitoring:** any coverage improvement, even if only minimal, must be measured, documented, and communicated

D. Interview discussion

Unsurprisingly, whether a country can utilise MR MAPs according to the UCs largely depends on their own contextual factors and challenges. The discussions with the interviewees **validated that all six UCs could potentially be used in the future if certain barriers were removed and all of the critical components were addressed.**

Similar to the results of the surveys, the majority of the respondents found **UC2, UC3, and UC4 as having the most potential.** The interviews were able to provide additional insight into why some respondents felt UC1 may not be appropriate, which was largely due to the current vaccine in the routine schedule and existing health systems. However, for countries currently utilising MMR / MMRV in their routine schedules, MR MAPs could be used for specific populations or during specific contexts. This would also help them to maintain high MR coverage and increase equity. One individual also stated that MR MAPs would help them to sustain their MR control and elimination goals rather than reach them.

The interviewees viewed **UC5 and UC6 with more positive attitudes** compared to the surveys. The differences in the perceptions of UC5 and UC6 when compared to the survey could be driven by the ability to discuss in-depth the respondents' rationale and pose follow-up questions, which has led to the identification of two key barriers (e.g., inability to monitor for AEFIs and inability to record and report vaccination). If those barriers are addressed, then it is conceivable that UC5 and potentially UC6 will be utilised by countries. However, it is impossible to ignore the impact of the ongoing global pandemic of COVID-19, which may have shifted thinking (since the surveys) as some respondents cited specific

examples considering implications of COVID-19. For example, provide a MR MAP to a mother, who can administer the MAP to her child but under the supervision of a health worker, who remains a safe distance away.

The feedback from the interviews also indicated that the type of vaccination programme which would use MR MAPs was not necessarily relevant by UC and that all vaccination programmes could benefit.

Although not a main objective of the interviews, the feedback obtained from the respondents indicated a fairly low tolerance for a higher cost of MR MAPs. This conclusion is driven by respondents who indicated high wastage and its associated costs as a key challenge to achieving their MR goals, but they were not interested in switching to the 5-dose vial as the perception was the cost is too high. The 2020 wastage adjusted price per fully immunised \$2.34 for the 5-dose vial versus \$2.19 for the 10-dose vial². Thus, use of MR MAPs will depend heavily on costing analyses evaluating total systems costs that can communicate the benefits of MR MAPs beyond vaccine price (e.g., cold chain requirements, transportation costs, time savings, etc.).

IV. Conclusion and next steps

The results and conclusions were presented to the MR MAPs WG in late July for their feedback and guidance. The group discussed the following key points:

- Potential implications of using MR MAPs to strengthen the 2nd year of life platform
- The importance of having appropriate conversations with industry and countries related to the price and willingness to pay, including what are the trade-offs of needle and syringe presentation versus MAPs presentation that extend beyond the price per dose.

The group was also requested to submit additional feedback in writing, below contains a summary of key points:

- As MAPs advance over time, they may not only be judged against the needle and syringe presentation but also against other technologies in the pipeline, particularly the dual chamber or auto-reconstitution devices which may hold similar benefits to MAPs.
- The group was requested to complete short survey on Qualtrics™ to provide additional guidance. Ten responses were received that agreed to the following:
 - Continue assuming that MR MAPs are thermostable, but only 40% indicated yes and 40% indicated maybe.
 - Agreed to continue exploring UC5 and UC6 (self-administration with and without supervision) with 80% indicating their agreement.
 - Agreed to include HICs and those countries utilising MMR or MMRV in their routine programmes as part of the sizing exercise with 70% indicating their agreement.

The group also provided additional suggestions to continue disseminating information related to MR MAPs to key stakeholders, including EPI managers and guidance on additional areas of consideration given the COVID-19 situation. MMGH will work with WHO IVB to discuss the additional suggestions provided by the MR MAP working group related to disseminating information and COVID-19 considerations.

² <https://www.gavi.org/our-alliance/market-shaping/product-information-vaccines-cold-chain-equipment>. Accessed on 22 July 2020

Based on the feedback from the MR MAP WG, surveys, and interviews, the UC definitions have been revised to the following:

Figure 19: Final defined UCs for MR MAPs

	HEALTH WORKER (HW)	COMMUNITY HEALTH CARE WORKER (CHW) [†]	SELF ADMINISTRATION
FIXED HEALTH POST (full cold chain capabilities)	1. Delivery by HW or CHW in Fixed Post		5. Self-administration with HW or CHW assistance
OUTREACH (reduced cold chain capabilities)	2. Outreach delivery by HW	3. Outreach delivery by CHW	
OTHER SETTINGS (no cold chain)		4. Delivery by CHW in their "home" community	6. Self-administration without assistance*

[†]Community health worker provide health education, referral and follow-up, case management and basic preventive health care and home visiting services to specific communities. They provide support and assistance to individuals and families in navigating the health and social services system. Occupations included in this category normally require formal or informal training and supervision recognized by the health and social services authorities (Source: www.who.int/hrh/statistics/workforce_statistics)

*This may include community member assistance (e.g., teachers, elders, etc) who have not been trained in MAPs but can monitor and document the administration

- **UC1: Delivery by health worker (HW) or community health worker³ (CHW) in a fixed health post.** Fixed health post is defined as a permanent structure which has full cold chain capabilities, examples include hospitals, and health facilities at all service delivery levels.
- **UC2: Outreach delivery by HW in settings that have reduced or no cold chain capacities.** Includes delivery in areas that do not have access to a fixed health post conducted by health workers and with reduced or no cold chain capacities. Examples may include regular outreach by HWs to remote or hard-to-reach areas in the catchment area of fixed health posts, school vaccination, reactive or pre-emptive vaccination, outbreak response immunisation, etc.
- **UC3: Outreach delivery by CHW in settings that have reduced or no cold chain capacities.** Includes delivery in areas that do not have access to a fixed health post conducted by community health workers and with reduced cold chain capacities. Examples may include regular outreach by CHWs to remote or hard-to-reach areas in the catchment area of fixed health posts, including school vaccination, reactive or pre-emptive vaccination, outbreak response immunisation, etc.
- **UC4: Delivery by CHW in their "home" community in settings that have no cold chain capacities.** The CHW residing in a specific area is given a stock of MR MAPs and can deliver them within their own community as needed. Examples may include areas that are remote, security compromised or inaccessible during specific times due to annual weather patterns (e.g., flooding).
- **UC5: Self-administration with HW or CHW assistance.** The MR MAP is self-administered by the individual with the assistance or under supervision of HW or CHW, who is able to monitor for AEFI and record and report who has received the vaccination. It is anticipated that this occurs in either a fixed health post or during

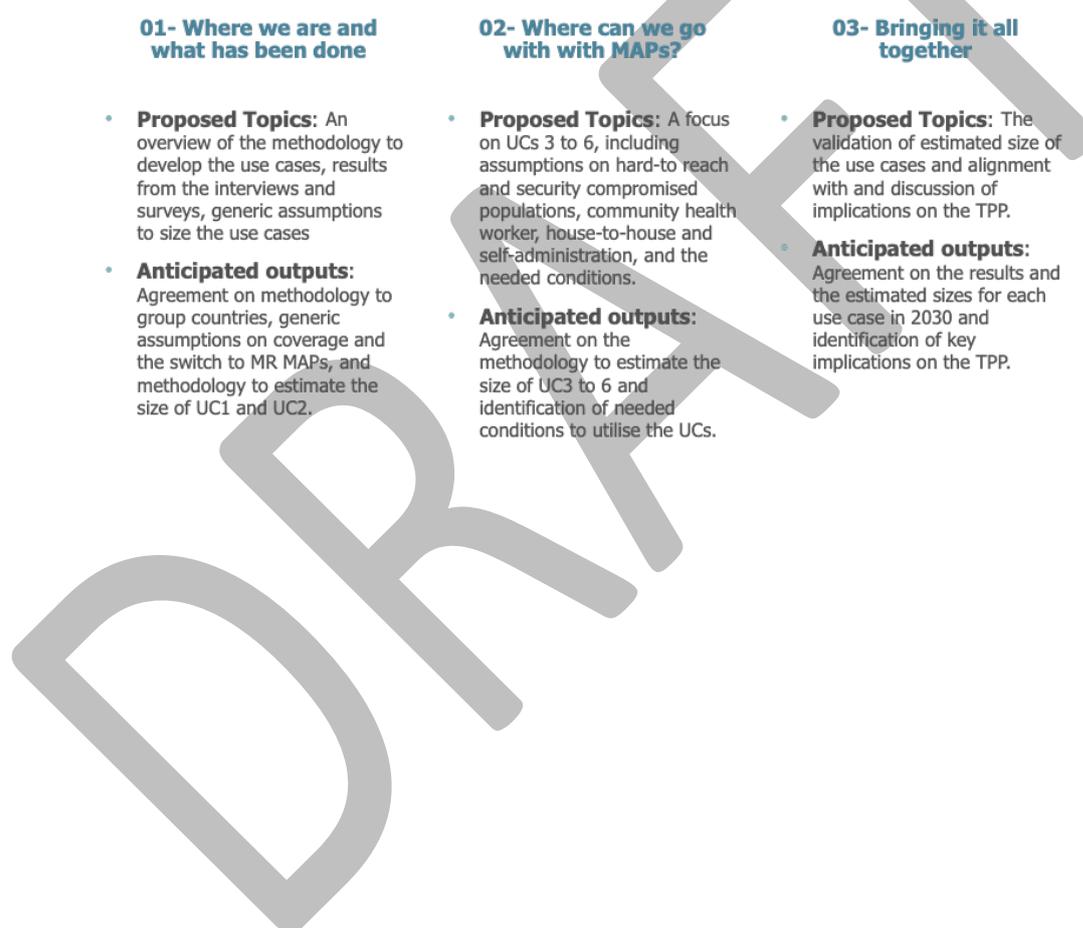
³ Community health worker provide health education, referral and follow-up, case management and basic preventive health care and home visiting services to specific communities. They provide support and assistance to individuals and families in navigating the health and social services system. Occupations included in this category normally require formal or informal training and supervision recognized by the health and social services authorities (Source: www.who.int/hrh/statistics/workforce_statistics)

outreach . Examples may include school vaccination, outbreak vaccination, vaccination during COVID-19 social distancing situation, parent-to child, etc.

- **UC6: Self-administration without HW or CHW assistance.** The MR MAP is self-administered by the individual . The vaccination would be monitored and supervised by another individual who has received minimal training, e.g., teacher or local community leader. Other examples of this UC may include vaccination in pharmacies. A reporting system would need to be set up.

As the next step, WHO IVB will convene a set of virtual meetings in late September and October to discuss the assumptions and methodology to estimate the size of the UCs for 2030. The experts invited to these meetings will include selected individuals from the MI4A Advisory Group and MR MAPs Working Group. The figure below outlines the proposed topics and anticipated outputs for each of the meetings:

Figure 20: Proposed topics and anticipated outputs for meetings to discuss and develop the methodology to size the MR MAP UCs



Annex A: Survey questionnaire

Overview

MM Global Health (MMGH) would like to thank you for participating in this survey, commissioned by the World Health Organization, Department of Immunisation, Vaccines and Biologicals (WHO IVB) with the goal of defining the most appropriate use cases for Microarray Patch-based Measles-Rubella vaccines (MR-MAPs). "Use Case" in this context means *"the specific situations in which MR-MAPs could potentially be used to accomplish a Measles Control and Elimination goal"*.

This survey is aimed at the TechNet members who are knowledgeable about and interested in identifying the most relevant contributions of MR-MAPs to increase equitable coverage, specifically in hard-to-reach populations. The insights collected via this survey will be used to finalize the definition of MR-MAPs use cases and to prioritize the areas where the added value of MR-MAPs will be greatest compared to that of other vaccines and interventions. The results will be used by WHO IVB to validate assumptions on product characteristics and preferences and will provide input into the MR-MAP value proposition and ongoing demand forecast analyses.

When responding to this survey please think prospectively about the use of MR-MAPs at the moment of their possible country introduction, which is at the earliest 10 years from now.

Privacy Policy

In addition to your expert views, we will be collecting some demographic information such as your organization, location, and your level of familiarity with the MAPs technology to allow for stratified analyses. The information will be stored in data servers with MMGH's provider of cloud services (Microsoft) and the survey platform (Qualtrics). These service providers are compliant with the European Union's General Data Protection Regulations (GDPR). Upon completion of the project, all demographic information will be deleted.

MMGH respects your trust and values your privacy, and therefore will never share any of the data collected with any third party, other than WHO IVB for the purpose of this project. Furthermore, all information collected will be anonymized and aggregated prior to the inclusion into analyses and reports. The same data treatment (full anonymization and disclosure of aggregated data only) will apply in the event of publication of the results of this project.

By completing this survey, you agree that MMGH will process your responses in line with its privacy policy. If you have any questions you can contact the MMGH Data Protection Officer Melissa Ko (kom@mnglobalhealth.org)

Privacy policies references:

MMGH's privacy policy: <https://mmglobalhealth.org/privacy-policy/>

WHO privacy policy: <https://www.who.int/about/who-we-are/privacy-policy>

Microsoft's privacy policy: <https://privacy.microsoft.com/en-us/privacystatement>

Qualtrics's privacy policy: <https://www.qualtrics.com/privacy-statement/>

This survey contains six demographic and seven content questions and requires approximately 10 minutes to complete.

Your responses will be automatically saved in the cloud and you will need to click the "submit" button at the end of the survey. The survey can be interrupted at any time and will remain active for one week from first login. At the subsequent login you will be taken back to where you left off. Once you click "submit", you will be able to print your answers.

Depending on the speed of your internet connection, the page transition may take some time, so we kindly ask for your patience.

You can now start the survey by moving to the clicking the arrow button below.

Q1. What kind of organization do you work for? (Please select the one that applies)

- Ministry of Health
- Agency of the United Nations
- Implementation agency other than government or United Nations
- Academia
- Industry
- Other (please specify)

Q2. What role do you have in your organization? (please select your primary role)

Epidemiologist

- EPI manager
- Health systems specialist
- Immunisation specialist
- Researcher
- Surveillance specialist
- Other, please describe below

Q3. What country are you based in?

▼ Afghanistan (1) ... Other not listed (199)

Q4. Please select the country(ies) that you are referring to when responding to this survey. To select more than one country, please press the "ctrl" button.

▼ Afghanistan (1) ... Other not listed (199)

Q5. How familiar are you with the Measles and Rubella Control and Elimination strategies?

- Extremely familiar
- Very familiar
- Moderately familiar
- Slightly familiar
- Not familiar at all

Q6. How familiar are you with the Microarray Patch (MAP) vaccine technology?

- Extremely familiar
- Very familiar
- Moderately familiar
- Slightly familiar
- Not familiar at all

What are MAPs? Microarray Patches (MAPs) consist of hundreds or thousands of tiny projections that deliver dry vaccine into the skin, with some MAPs applied like a bandage and others requiring an applicator for delivery. MAPs have the potential for enhanced heat stability and freeze resistance, increased ease-of-use, for being less painful than an injection and for being sharps-free, thus improving safety.

As such, Measles Rubella MAPs (MR-MAPs) are perceived to significantly ease delivery of MR-containing vaccines, however, they have not yet advanced to clinical development.

The questions below aim at obtaining your input regarding MR-MAPs.

Q7. In your opinion, do the following delivery challenges impact a country's Measles-Rubella control and elimination goals? Potential responses: Strongly agree, somewhat agree, neither agree nor disagree, somewhat disagree, strongly disagree.

- Contamination or wastage due to multi-dose vial
- Vaccine ineffectiveness or wastage due to heat exposure
- Reconstitution related safety issues
- Cold chain requirements during outreach
- Needle-stick injuries
- Difficult preparation requiring trained personnel
- Negative impact on the environment due to waste disposal practices
- Reduced acceptability due to painful administration
- Difficult to delivery at correct injection depth
- Other (please specify below)

Q8. In your opinion, how influential are the following factors on a country's ability to achieve its Measles-Rubella control and elimination goals? Potential responses: Extremely, Very, Moderately, Slightly, Not influential at all, Do not know.

- Measles endemicity level
- Country income level
- Age of vaccine recipients
- Delivery site (e.g., hospital/dispensary, fixed health post, outreach, mobile, etc)
- Type of immunisation provider (e.g., Health worker, Community Health Worker, etc)
- Delivery context (e.g., routine, campaigns, outbreak response, etc)
- Vaccine use (e.g., stand-alone, co-administered)
- Humanitarian emergencies
- Other, please describe below

Q9. Please describe any other factors that could influence a country's ability to achieve its Measles-Rubella control and elimination goals

Q10. In your opinion, how important would MR-MAPs be in achieving the Measles-Rubella control and elimination goals in the country or region in which you work, when considering the following potential uses? Potential responses: Extremely important, Very important, Moderately important, Slightly important, Not important at all, Do not know.

- Delivery in a Fixed Health Post (e.g., clinic) by a trained Health Worker (HW) or Community Health Worker (CHW)
- Delivery during Outreach by a trained HW
- Delivery during Outreach by a CHW
- Delivery via House-to-House by a CHW
- Self-administered with supervision
- Self-administered without supervision

Q11. Are there additional programmatic situations in which MR-MAP vaccines could potentially be used? Please describe up to two (2) additional situations, if possible. If you do not know of additional situations, please leave this question blank.

Q12. For each situation in which MR-MAPs could be used, please indicate what type of vaccination programme would most benefit from their use. Potential responses: Routine Immunisation, Periodic Intensification of Routine Immunisation,

Supplementary Immunisation Activities, Outbreak Response Immunisation, Delivery outside regular services (e.g., self-administration or pharmacies, etc), Not appropriate to be used in any delivery context, Do not know.

- Delivery in a Fixed Health Post (e.g., clinic) by a trained Health Worker (HW) or Community Health Worker (CHW)
- Delivery during Outreach by a trained HW
- Delivery during Outreach by a CHW
- Delivery via House-to-House by a CHW
- Self-administered with supervision
- Self-administered without supervision

Q13. Please select all of the country context(s) where MR-MAPs could contribute to the achievement of Measles-Rubella control and elimination goals. Potential responses: High-income or upper middle-income countries, Non-Gavi lower middle-income countries, Low income & Gavi lower middle-income countries, None, Do not know.

- Delivery in a Fixed Health Post (e.g., clinic) by a trained Health Worker (HW) or Community Health Worker (CHW)
- Delivery during Outreach by a trained HW
- Delivery during Outreach by a CHW
- Delivery via House-to-House by a CHW
- Self-administered with supervision
- Self-administered without supervision

Q14: Would you agree that MR-MAPs will contribute to the following? Potential responses: Strongly agree, somewhat agree, neither agree nor disagree, somewhat disagree, strongly disagree, do not know.

- Increase equitable MR vaccine coverage
- Reduce missed opportunities in MR vaccination
- Reduce programmatic errors, and therefore increase safety in MR vaccine administration
- Make transportation of MR vaccines easier
- Reduce MR vaccine cold chain needs
- Reduce MR vaccine wastage
- Reduce Health Worker training needs
- Increase MR vaccine acceptability
- Allow Community Health Workers to administer MR vaccines
- Allow pharmacies to administer MR vaccine
- Allow for self-administration of MR vaccine
- Enhance the convenience of MR vaccine for the recipient
- Increase the reach in insecure / fragile areas
- Ensure timely vaccination response in outbreak situations

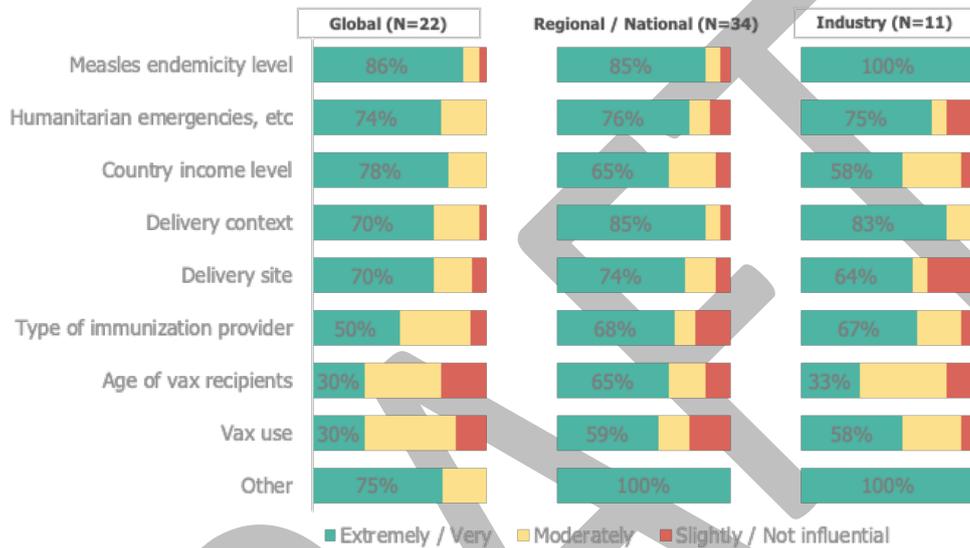
Q15. Please provide any additional comments or feedback.

Annex B: Additional stratified analysis for survey results

This annex contains additional stratified analyses from the survey results.

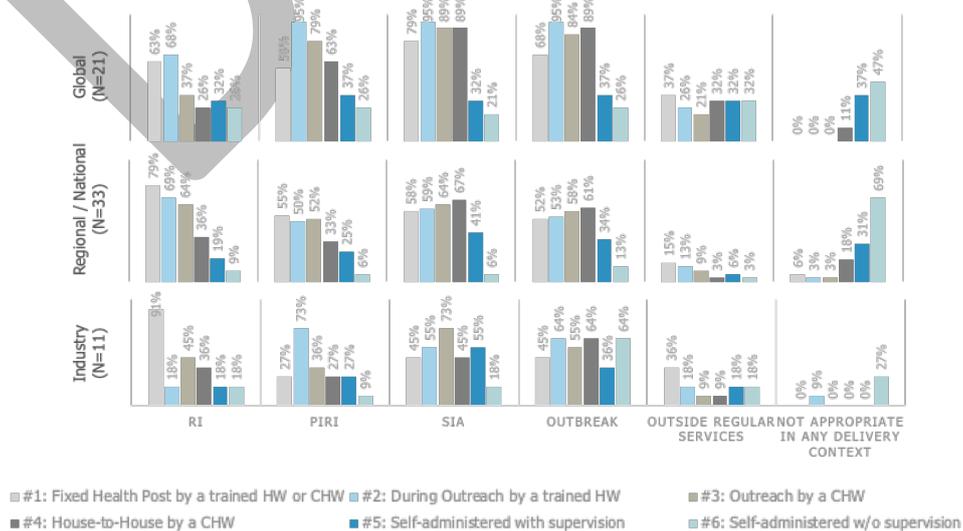
With regards to which factors influence a country’s ability to achieve their MR control and elimination goals, the stratified analysis showed differences in opinions related to country income level, type of immunisation provided (e.g., health worker, community health worker, etc), age of the recipients, and vaccine use (e.g., standalone or co-administered). The figure below provides additional details of the responses.

Figure 21: Influential factors affecting the ability to achieve MR control and elimination goals by perspective



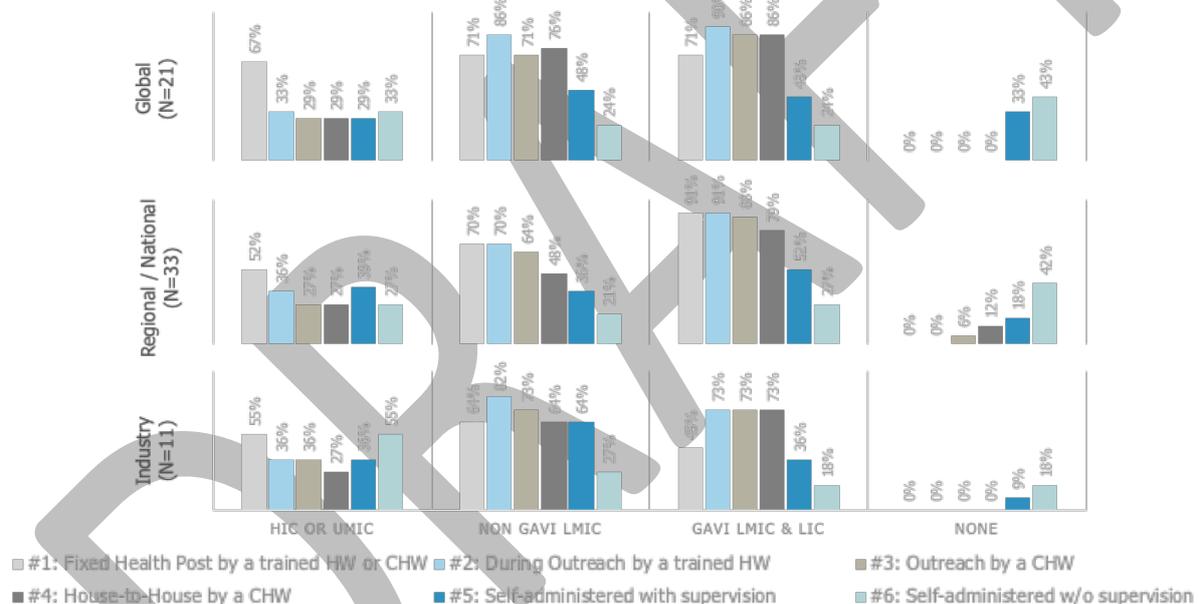
The figure below provides the stratified analysis of which vaccination programmes would benefit from the different UCs. Across all of the UCs, the Global perspectives were more positive on the benefit that MR MAPs could bring to different types of vaccine programmes, particularly for SIAs and outbreak response, compared to those located at Regional / National and Industry levels. Further, more individuals representing the Global and Regional / National perspectives saw UC5 and UC6 (self-administration) as not appropriate in any delivery context compared to the industry perspectives.

Figure 22: MR MAP benefit to vaccination programmes by perspective



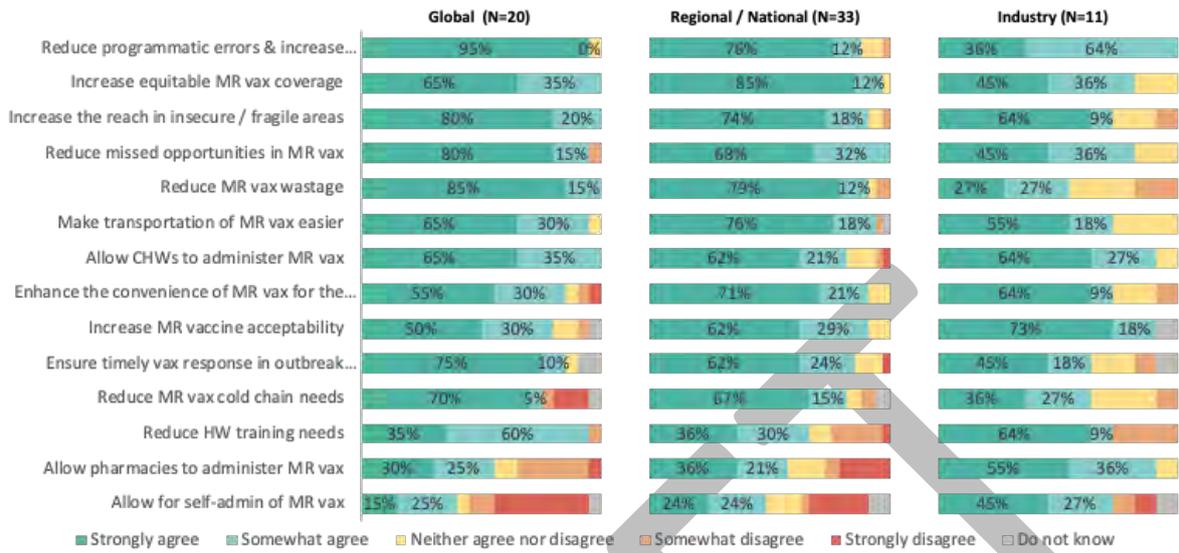
The figure below provides the stratified analysis by perspectives when respondents were asked which country income groups would utilise MR MAPs by use cases. For HICs, UMICs and non-Gavi LMICs, there was not much difference between the perspectives with similar percentages across all six UCs. A higher percentage of respondents felt that HICs and UMICs would utilise UC1 compared to the other UCs. However, the feedback was mixed on UC6 (self-administration without supervision) with the Industry respondents indicating this had a higher likelihood compared to those located at the Global, Regional / National levels. There were no significant differences between the percentage of individuals who felt that UC1, UC2, UC3, and UC4 could be used by non-Gavi LMICs. However, more Industry respondents felt that UC5 could be appropriate compared to the other two perspectives. For Gavi LMICs and LICs, there was a difference in opinion particularly for UC1, where those located at the regional / national levels rated this as appropriate compared to those with global and industry perspectives. The appropriateness of the roughly other UCs were similar. Finally, it should be noted again that those with Industry perspectives were more accepting of UC5 and UC6 compared to the other perspectives. However only 18% of the individuals at the regional/national level felt that UC5 would not be used by any countries.

Figure 23: MR MAP use by country income groups and perspectives



The figure below provides the results of the stratified analysis on what MR MAPs can contribute to. There is general agreement between the different perspectives across all of the factors provided, however, the Industry perspective had more neutral responses. The key areas where the opinions differed includes reduction of cold chain needs, allowing pharmacies to administer MR vaccination, and allowing for self-administration of MR vaccination. In each of these, more respondents from the Global and Regional/National levels indicted strongly disagree compared to those with the Industry perspective.

Figure 24: MR MAPs can contribute to the following (percentage of respondents) by perspective



DRAFT

Annex C: Interview questionnaire

Overview

We would like to thank you for participating in this interview, commissioned by the World Health Organization, Department of Immunisation, Vaccines and Biologicals (WHO IVB) with the goal of defining the most appropriate use cases for measles rubella microarray patch-based vaccines (MR-MAPs). "Use Case" in this context means "the specific situations in which MR-MAPs could potentially be used to accomplish the regional measles and rubella Elimination/Control goals".

Together with an earlier survey, the insights collected via this interview will be used to finalize the definition of MR-MAP use cases and to prioritize use cases for which MR-MAPs would provide the greatest added-value. Further, the results will be used by WHO IVB to validate assumptions on product preferences and to identify critical product attributes for MR-MAP. More broadly, it will inform an ongoing demand forecast analyses and provide input into the MR-MAP value proposition.

Background information on MAPs

Microarray patches (MAPs) consist of hundreds or thousands of tiny projections that deliver dry vaccine just below the skin surface, with some MAPs applied like a bandage and others requiring an applicator for delivery. MAP presentations are single dose, thereby reducing vaccine wastage and missed opportunities for vaccination. They remove the need for reconstitution and are needle free, thus improving safety by reducing potential programmatic errors, and removing sharps waste. They have the potential for enhanced heat stability and freeze resistance and may be less painful than an injection. As such, MR-MAPs are perceived to significantly ease delivery of MR-containing vaccines and may significantly enhance equitable coverage of MR. However, they have not yet advanced to clinical development.

When responding, please think prospectively about the use of MR-MAPs at the moment of their possible country introduction, which is approximately 10 years from now.

Privacy Policy

Information from this interview will be stored in data servers with MMGH's provider of cloud services (Microsoft). These service providers are compliant with the European Union's General Data Protection Regulations (GDPR). Upon completion of the project, all demographic information will be deleted. MMGH respects your trust and values your privacy, and therefore will never share any of the data collected with any third party, other than WHO IVB for the purpose of this project. Furthermore, all information collected will be anonymized and aggregated prior to the inclusion into analyses and reports. The same data treatment (full anonymization and disclosure of aggregated data only) will apply in the event of publication of the results of this project. By participating in this interview, you agree that MMGH will process your responses in line with its privacy policy. If you have any questions you can contact the MMGH Data Protection Officer Melissa Ko (kom@mmglobalhealth.org)

Privacy policies references:

- MMGH's privacy policy: <https://mmglobalhealth.org/privacy-policy/>
- WHO privacy policy: <https://www.who.int/about/who-we-are/privacy-policy>
- Microsoft's privacy policy: <https://privacy.microsoft.com/en-us/privacystatement>

Interview Questions

This interview with 5 main questions will last approximately 20 minutes.

Q1. What organization do you work for and what is your current role? Which country or country groups will your responses be referring to?

Q2. How familiar are you with the: (i) Regional measles and rubella elimination or control strategies and (ii) the microarray patch (MAP) vaccine technology?

Q3. In your opinion, what are the top 3 technical vaccine delivery challenges that hinder your country's* ability to achieve its Measles-Rubella elimination or control goals?

* the country/ groups referred to in Q1.

Q4a. How would your country / country group use MR-MAPs?

Where? (e.g., Fixed health post, outreach, other)	Who? (e.g., trained individual, untrained individual, self, other)	In what context? (e.g., RI, PIRI, SIAs, ORI, outside regular services, other)
•		

Summary of six MR-MAPs use cases

← CURRENT USE CASES FOR MR VACCINES →			
<i>Use cases are not considered mutually exclusive</i>	FULLY TRAINED HEALTH WORKER (HW)	PARTIALLY TRAINED COMMUNITY HEALTH WORKER (CHW)	SELF ADMINISTRATION (OR BY PARENTS / CARETAKERS)
FIXED HEALTH POST (full cold chain capabilities)	1. Delivery in Fixed Post with trained HW or CHW RI, catch-up (ANC visit) All MR-using geographies		5. Self-administration with HF staff or CHW assistance
OUTREACH* (limited cold chain capabilities)	2. Outreach delivery by trained HW RI/PIRI, SIA, ORI MICs/LICs	3. Outreach delivery by CHW RI/PIRI, SIA, ORI MICs/LICs	RI/PIRI, SIA, ORI All MR-using geographies
ANYWHERE (without cold chain)		4. H2H CHW delivery SIA, ORI MICs/LICs	6. Self-administration (possibly with community member assistance) RI/PIRI, SIA, ORI All MR-using geographies

* This includes school-delivery, mobile outreach, house-to-house, etc.
 RI = Routine Immunization
 ORI = Outbreak response immunization (also in conflicts and humanitarian emergencies)
 ANC = Antenatal Care
 PIRI = Periodic Intensification of Routine Immunization
 SIA = Supplementary Immunization Activities

Q4b. In your opinion, which of the above Use Cases for MR-MAPs, are best suited to contribute to achieving your country's* Measles-Rubella elimination or control goals? * the country/ groups referred to in Q1.

Q4c. What is the rationale for your choice?

Q4d. Are there sub-national areas within your country where MR-MAPs would be more useful? If so, please provide specific situations and rationale for why a MAP would be better than the current presentation.

Q4e. For the chosen Use Cases, in what way(s) do you think MR-MAPs can address the vaccine delivery challenges that you previously identified in Q3?

Q5. What would you expect to be the most important programmatic impact of MR-MAPs in your country? And why?

3 categories of potential programmatic impact:

- **Higher coverage and increased acceptance** (e.g., increase equitable MR vaccine coverage, reduce missed opportunities in MR vaccination, enhance convenience of MR vaccine for the recipient, reduce fear of needles)
- **Ease of delivery** (e.g., reduce programmatic errors, allow community health workers to administer MR vaccines, reach fragile / insecure areas, ensure timely outbreak response)
- **Increase effectiveness and efficiencies** (e.g., reduce wastage, make transportation of MR vaccines easier, reduce MR vaccine cold chain needs, reduce health worker training needs, allow other potential administration options such as pharmacy or supervised self-administration)

Q6. Do you have any additional comments or any feedback, which you would want to raise at this point?

The VIPS Prioritisation Process: Methodology and Outcomes

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INTRODUCTION

Rationale for VIPS

Innovative approaches are needed to help to address immunisation barriers and achieve immunisation coverage and equity goals. Vaccine product innovations offer important means to simplify logistics, increase the acceptability and safety of immunisation, minimise missed opportunities, and facilitate outreach. There is increasing recognition of the need to employ targeted solutions to extend vaccine access to reach the unreached. This may require the use of differentiated vaccine products or technologies for these focused efforts and a willingness to pay a price premium to reduce vaccine coverage inequities. Work by industry; individual technology developers; academic institutions; and governmental, non-governmental, and international agencies has contributed to the advancement of specific vaccine product innovations yet it has often been insufficiently coordinated, focused on higher income markets, and/or lacking in the market shaping efforts required to ensure that promising technologies reach those who need them most.

VIPS Background and Goal

In the 2016-2020 Supply and Procurement Strategy, Gavi, the Vaccine Alliance reaffirmed innovation as one of three priorities¹ in shaping markets to better meet country needs and support Alliance goals on immunisation coverage and equity. In 2017, the Gavi Secretariat convened an Alliance Working Group (WG) including the World Health Organization (WHO), Bill & Melinda Gates Foundation (BMGF), United Nations Children's Fund (UNICEF), and PATH, that developed a single integrated framework to drive priority vaccine product innovations forward.

The resulting Vaccine Innovation Prioritisation Strategy (VIPS) represents an unprecedented three-year collaboration amongst the aforementioned organisations, involving in-depth research, stakeholder consultations, and development and application of a framework capable of evaluating a variety of technologies at different stages along the product development pipeline continuum. The work required understanding countries' needs to consider the expected financial and non-financial impacts of innovations; developing common principles across the Alliance to measure the long-term benefits of product innovations; and convening a platform to articulate a clear and aligned perspective on priority product innovations. By prioritising innovations in vaccine products and communicating these priorities, the goal of VIPS is to provide greater clarity to manufacturers and partners to inform and influence investment decisions. VIPS outcomes will also represent a first step to mobilise key decision-makers and funders and chart a strategic pathway forward for the prioritised innovations.

Purpose of this Document

This document describes the methodology developed by VIPS to prioritise vaccine product innovations as well as the outcomes.

¹ Other priorities included ensuring adequate and secure supplies and reducing prices to appropriate and sustainable levels.

STRUCTURE OF VIPS

Alliance Working Group

VIPS is a close Alliance-wide collaborative effort that leverages the existing capabilities and comparative advantages of five key organisations that cover the entire product development to uptake spectrum, from research and development to policy, procurement, access and impact, and have complementary roles along this continuum. The VIPS Alliance Working Group (WG) consists of representatives from the five organisations (BMGF, Gavi, PATH, UNICEF and WHO), who worked collaboratively to identify the scope of innovations to be considered, conducted in-depth background research on each innovation, developed and executed the methodology for prioritising the innovations, consulted with relevant stakeholders, determined final outcomes (informed by recommendations from the Steering Committee), and communicated the progress along the way. The work would not have been possible without the strong commitments from each organisation and dedication of resources to create a sophisticated and coherent process for evaluation and decision-making.

Steering Committee

A VIPS Steering Committee (SC) was formed in June 2018 to offer independent and expert advice to the VIPS WG across multiple dimensions and provide recommendations regarding the prioritised innovations. The committee is comprised of 16 members with strong technical, programmatic and/or global health expertise. Members bring independent and broad-ranging perspectives on the issues pertinent to VIPS analyses, the innovations under consideration and prioritisation. Members are not expected to represent their affiliated institutions' positions and recused themselves from making recommendations if potential conflicts of interest were identified.

The SC members (see Appendix A) have expertise in the following domains:

- National immunisation programme financing and immunisation service delivery challenges, including supply chain and logistics, with a focus on understanding lower- and middle-income country (LMIC) needs
- Coverage and equity barriers and challenges
- Infectious disease epidemiology/vaccine-preventable disease control (especially with regard to increasing coverage rates and reducing morbidity and mortality)
- Health impact analysis/modelling
- Vaccine innovations, pipeline developments related to vaccine manufacturing and delivery technologies, and development of value propositions for new products.

As the VIPS SC operates on an existing foundation established by the WHO's Immunisation Practices Advisory Committee (IPAC) and the Product Development for Vaccines Advisory Committee (PDVAC) and to ensure alignment with existing initiatives, half of the SC members are also members from these two committees. Two SC subgroups were also formed and provided feedback on the evaluation methodology and country consultations.

Stakeholder Engagement

The VIPS evaluation process included broad stakeholder engagement to inform the prioritisation process, obtain input and alignment with other ongoing initiatives, and raise awareness.

Country stakeholders were consulted via surveys and in-person interviews to ensure that VIPS prioritised innovations could best address barriers to immunisation faced by countries.

Technology developers were asked to review and comment on documents about innovations relevant to their product pipeline and portfolio to verify the data presented.

Vaccine industry representatives were consulted to ensure the accuracy of the assumptions on technologies that impacted vaccine products through a series of meetings and interactions with the Delivery Technologies Working Group (DTWG) that is co-chaired by WHO and PATH. DTWG members include vaccine manufacturers from both the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and the Developing Countries Vaccine Manufacturers Network (DCVMN). In addition, meetings were held with IFPMA and DCVMN representatives to provide regular updates on the VIPS process.

Regulators and regulatory consultants were engaged to obtain feedback on and validation of assumptions related to the regulatory pathway for each innovation and the clinical development pathway where relevant.

International agencies and other interested parties were kept informed about VIPS throughout the prioritisation process via presentations and regular updates including to the WHO Strategic Advisory Group of Experts on Immunization, IPAC, and PDVAC as well as to the Coalition for Epidemic Preparedness Innovations and other stakeholders.

Further details on these consultations can be found in the Phase I and Phase II descriptions below.

OVERVIEW OF THE VIPS PROCESS

Description of Phases and Timeline

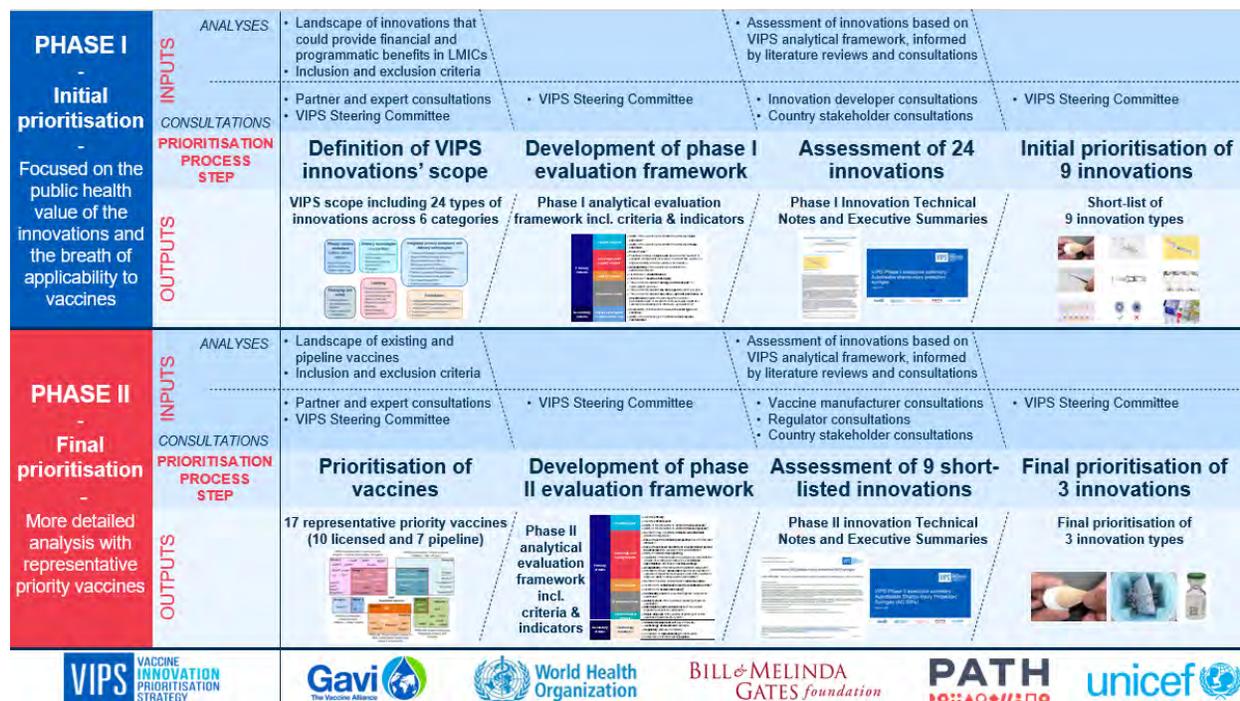
The VIPS prioritisation process is summarised in Figure 1 and consisted of:

- **A preparatory phase** from January to November 2018 that focused on work planning and resourcing during which an innovation landscaping and an initial landscaping of vaccines was conducted, the scope of innovations was defined, and the SC's terms of reference and membership were finalised. The innovation landscaping exercise, informed by partner and expert consultations, as well as SC recommendations, enabled the identification of 24 innovations for consideration in phase I that fit within the scope of VIPS. These included existing and potential future vaccine product innovations that could provide measurable financial or programmatic benefits to LMICs. During the preparatory phase, the VIPS WG also

designed a country consultation approach to better understand country immunisation barriers that could be addressed by vaccine product innovations.

- **A phase I** from December 2018 to June 2019 during which the initial list of 24 innovations were evaluated based on their characteristics or design features and potential public health value, as well as their potential 'breadth of use' (applicability to several antigens) resulting in a short list of 9 innovations that progressed to phase II.
- **A phase II** from July 2019 to May 2020 during which the 9 shortlisted innovations were analysed in more detail and in the context of a set of priority vaccines to identify the final list of vaccine product innovations determined to have the highest potential to address immunisation issues and improve coverage and equity.

Figure 1: VIPS Prioritisation Process



Scope of Innovations

The scope of vaccine product innovations included in VIPS is defined as completely new products or adaptations to existing products that provide measurable financial or programmatic benefits to LMICs, such as increased coverage and equity (e.g., by overcoming a 'last mile' barrier) or vaccine effectiveness. The scope was informed by partner and expert consultations.

The 24 innovations that were defined as in-scope can be grouped into 6 categories:

- **Primary vaccine containers:** The immediate receptacles in direct contact with the vaccine as distributed for sale.
- **Delivery technologies (not prefilled):** Stand-alone technologies used to administer a vaccine by a specific vaccine administration route.
- **Integrated primary containers and delivery technologies:** Prefilled devices that act both as the primary container and delivery device.
- **Packaging and safety:** The containers that enclose or protect vaccine products for distribution or items that facilitate safe administration but are not the actual delivery device.
- **Labelling on primary packaging:** Text, symbols, data or other visual cues provided on the primary packaging of a vaccine.
- **Formulations:** This category only included formulation improvements with the objective of improved thermostability.

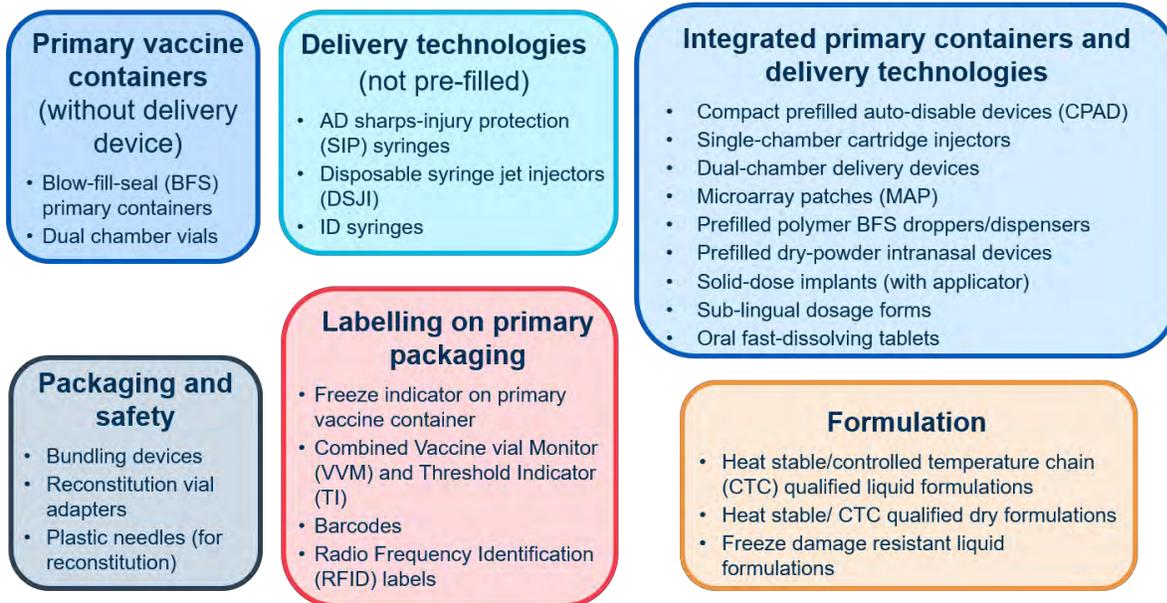
Innovations determined to be out of scope included supply chain innovations and cold chain equipment as these categories are covered by other mechanisms, global working groups, and market-shaping efforts including the Cold Chain Equipment Optimisation Platform. Innovations that relate to the type of antigen or vaccine (subunit, virus-vector, nucleic acid etc.) or immuno-enhancers were also determined to be out of scope as these are vaccine-specific and covered by PDVAC and the Gavi Vaccine Investment Strategy.

In addition, three exclusion criteria were defined and applied to focus the scope of innovations:

1. **Innovations were excluded, if WHO Programmatic Suitability for Vaccines Prequalification criteria for the innovation already exist but were not met by the innovation.** For example, prefilled syringes that are not compact or lack auto-disable features.
2. **Innovations that already have a mechanism for product development and will come to market without Alliance interventions were excluded.** For example, innovations that are already widely available including: prefilled syringes, intranasal spray nozzles, prefilled intranasal spray dispensers, and prefilled, preformed containers for oral/intranasal vaccines.
3. **Innovations for which development has been discontinued were excluded** including dry-powder jet injectors.

Figure 2 lists the initial 24 innovation categories that were evaluated in phase I of VIPS.

Figure 2: Innovations Assessed in Phase I



PHASE I

Overview of the VIPS Phase I Evaluation Framework

A VIPS evaluation framework was developed by the VIPS WG with oversight and guidance from the VIPS SC. The framework was meant to:

- Objectively and transparently assess and compare the added value of different types of innovations taking into consideration financial and non-financial trade-offs for countries to the extent possible,
- Allow for an aligned prioritisation across different stakeholders, and
- Achieve a balance between granularity and rigor on one hand, and simplicity on the other.

The evaluation framework included primary and secondary criteria as shown in Figure 3.

Figure 3: VIPS Assessment Criteria Definitions

Primary criteria	Health impact	Beneficial impact of a vaccine product innovation on health of the population receiving the vaccine.
	Coverage and equity impact²	Beneficial impact of a vaccine product innovation regarding increased access and utilisation of the vaccine for all populations.
	Safety impact	Potential impact of a vaccine product innovation on the safety of the population administering or receiving the vaccine.
	Economic costs	Potential impact of the vaccine product innovation on costs such as price of the vaccine and delivery technologies, cold chain, transport and health worker time costs, and introduction and recurrent costs.
	Environmental impact	Potential impact of vaccine product innovation on waste treatment management used in resource-limited settings (incineration/disinfection).
Secondary criteria	Potential breadth of innovation use	Potential breadth of an innovation’s applicability to vaccines based on technical feasibility.
	Technology readiness	Readiness and complexity of a vaccine product innovation from clinical, technological, regulatory & manufacturing perspectives.
	Commercial feasibility	Commercial feasibility of an innovation in terms of market size, interests and barriers.

Indicators were then created for each of the criteria categories as described in Figure 4.

² Although coverage and equity measures are typically a subset of the health impact criteria, given the importance of improved coverage and equity as one of the ultimate objectives of VIPS, it was decided to have Coverage and Equity as a separate criterion.

Figure 4: VIPS Phase I Criteria Indicators

Primary criteria	Health impact	<ul style="list-style-type: none"> • Ability of the vaccine presentation to withstand heat exposure³ • Ability of the vaccine presentation to withstand freeze exposure
	Coverage and equity impact	<ul style="list-style-type: none"> • Ease of use⁴ • Potential to reduce stock outs based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities • Acceptability of the vaccine presentation to patients/caregivers
	Safety impact	<ul style="list-style-type: none"> • Likelihood of contamination • Likelihood of needle-stick injury
	Economic costs	<ul style="list-style-type: none"> • Total economic cost of storage and transport of commodities per dose • Total economic cost of the time spent by staff per dose • Total economic cost of one-time / upfront purchases or investments required to introduce the vaccine presentation and of recurrent costs associated with the vaccine presentation (not otherwise accounted for)
Secondary criteria	Potential breadth of innovation use	<ul style="list-style-type: none"> • Applicability of innovation to one or several types of vaccines • Ability of the technology to facilitate novel vaccine combination

Parameters were then defined to qualitatively measure each innovation against each indicator. Due to the diversity of innovations being evaluated under VIPS, direct comparisons across innovations were difficult (e.g., comparing compact prefilled auto-disable devices to barcodes). To overcome this issue, each innovation was assessed for each primary criteria parameter using a comparator. The comparator represented the best or standard practice that most closely matched the innovation in terms of features, attributes, and use. When the comparator included existing vial presentations of liquid or lyophilised vaccines, single dose vials, rather than multi-dose vials were used for the comparator, because in most cases the innovation being considered was a single-dose presentation. Using single-dose vials made the incremental gains/losses easier to compare. *For example, the comparator for the dual chamber delivery device includes all the*

³ Improved heat stability can also be used to increase shelf life, hence no indicator on shelf-life extension is included in the framework.

⁴ Ease of use can prevent missed opportunities resulting from the complexity of preparation and administration procedures, hence no indicator on missed opportunities from that perspective is included in the framework. Ease of use also affects timeliness of vaccination (vaccine doses given within the recommended age range); however, it was decided that timeliness of vaccination should be captured under vaccine effectiveness based on country data.

components required to reconstitute and deliver a lyophilised vaccine, i.e., a single dose vial of lyophilised vaccine, diluent vial, reconstitution syringe, and auto-disable syringe. In this manner, each assessment against each parameter resulted in a score, using a magnitude of impact where possible, that rated the innovation in comparison to best or standard practice. The scoring methodology, although qualitative, ultimately allowed the innovations to be compared and ranked. The secondary criteria parameters were also assessed qualitatively; however, they were not assessed against a comparator but in an absolute manner. Secondary criteria were used to provide additional contextual information for each innovation.

In some cases, sub-categories of innovations needed to be assessed when the product attributes of one sub-category resulted in a different scoring outcome than the product attributes of another sub-category. For example, four types of compact prefilled auto-disable devices (CPADs) were evaluated: preformed, Blow-Fill-Seal (BFS) pre-assembled, BFS user-assembled, and other types. Assessments were made at the level of the technology category (or sub-category), not at the level of individual products.

Evaluation of the 24 Innovations in Phase I

Country Consultation to Inform the Phase I Evaluation

Country stakeholder inputs were critical in guiding the VIPS phase I evaluation. An online survey⁵ was therefore launched, requesting inputs from country representatives on immunisation implementation barriers and vaccine product attributes countries value the most. The survey was fully completed by 500 country representatives across a total of 61 Gavi-supported and non-Gavi-supported countries, including immunisation programme managers, procurement staff, logistics/supply chain staff, data managers, senior policy makers, healthcare service providers, implementing partners, UNICEF and WHO country/regional office staff, and in-country research/university partners.

Survey respondents were asked to select their top 5 priority implementation barriers to immunisation that could be addressed by vaccine product innovations, and top 5 most valuable vaccine product attributes, across three different use-settings: routine facility-based immunisation, routine community-based immunisation and campaigns. Based on the analysis of the results, the VIPS WG assigned qualitative levels of importance to the phase I indicators of the evaluation framework that were taken into account during the prioritisation process.

Technical Notes and Executive Summaries

Each innovation was assessed using the phase I evaluation framework and the assessments were consolidated into documents called **phase I Technical Notes**. These detailed notes not only consolidate the evidence (or expert opinions) behind the scoring on each parameter but also provide background and other relevant information on the innovations.

⁵ Survey results are reflected in the Executive Summaries of each innovation and a detailed publication on all VIPS country consultations will be published in Q3 2020.

Literature reviews were conducted on each innovation category using publicly available sources and databases (such as PubMed, manufacturer websites, clinical trial databases) and additional information was gathered from Alliance partners and international experts. Where needed, manufacturers and technology developers were queried with targeted questions to fill data gaps. In all cases, data sources were referenced, and only non-confidential data were used that could be transparently shared.

The phase I assessments, documented in the Technical Notes, were drafted by technical experts from the VIPS WG and consultants with background in the innovation being assessed.

Regular consultations and rigorous review of the Technical Notes by VIPS WG members and independent technical experts helped to ensure alignment and consistency in application of the scoring methodology across the 24 innovations. In addition, the content of each Technical Note without the scoring was reviewed by up to 3 relevant technology developers or manufacturers to ensure accuracy of the information upon which the scoring was based. Once all Technical Notes were developed, a final consistency check was conducted for all indicators across the innovations to ensure they were assessed in a consistent manner.

Key findings from the phase I Technical Notes were summarised in **phase I Executive Summaries** for each innovation.

All Technical Notes and Executive Summaries for the 24 innovations assessed in Phase I can be found on the following link: <https://www.gavi.org/our-alliance/market-shaping/vaccine-innovation-prioritisation-strategy>.

At the end of phase I, the VIPS WG held a series of meetings to analyse the findings of the phase I assessment and develop initial recommendations to present to the SC. These initial recommendations are reflected in the phase I Executive Summaries.

Selection of Innovations Shortlisted for Phase II

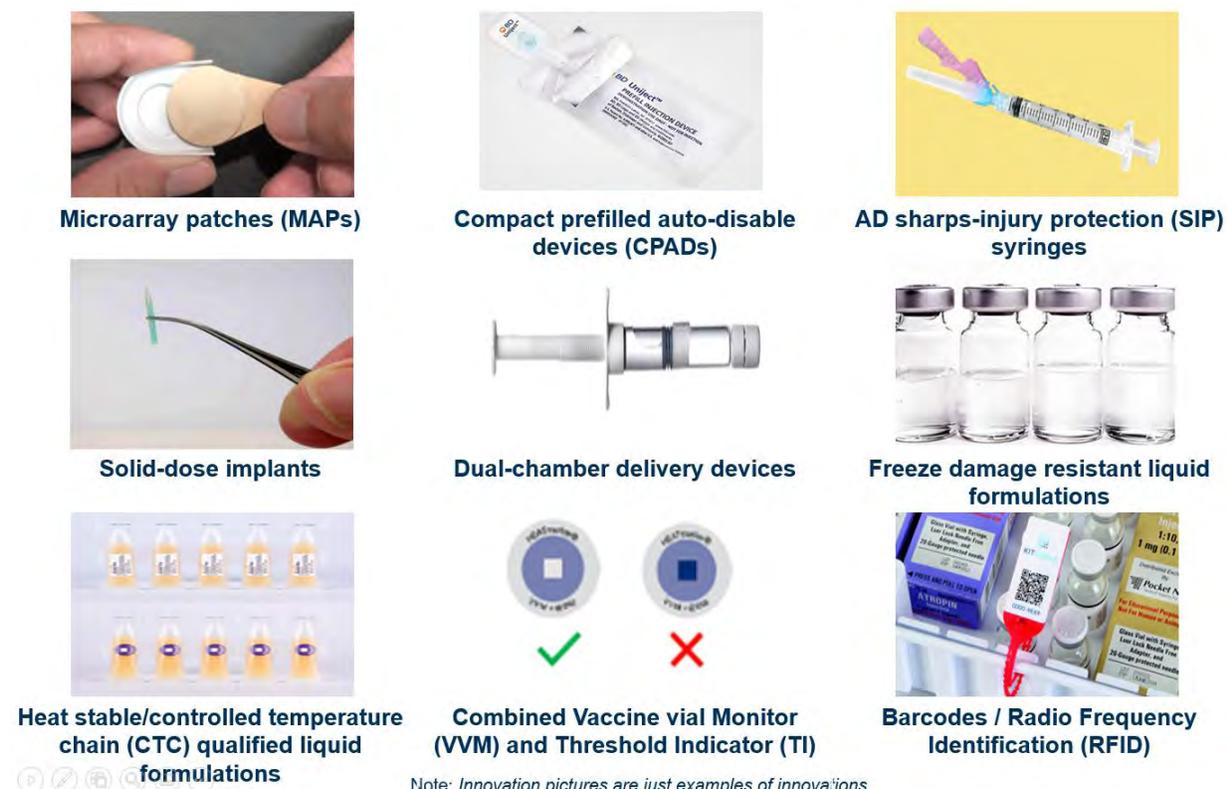
A two-day VIPS SC meeting was held in June 2019 during which the results of the phase I evaluation were discussed, and recommendations were made for innovations to be further assessed in phase II. The process was informed by several steps of analysis and discussions:

1. Assessing the potential public health benefits of each innovation using the primary criteria and indicator scores, while paying attention to the indicators that were given more importance by countries, and prioritising innovations with the highest or broadest potential public health benefits.
2. Applying the insights from secondary criteria, especially the breadth of antigen applicability based on technical feasibility.
3. Analysing the relative benefits across innovations, i.e., comparing innovations with similar benefits and prioritising those with the broadest benefits or applicability.

4. Leveraging additional insights and expert knowledge from the group that may influence the prioritisation.

The SC then recommended proceeding to phase II with 9 innovations (see Figure 5) and these were endorsed by the WG.

Figure 5: 9 Innovations Shortlisted for Further Analysis in Phase II



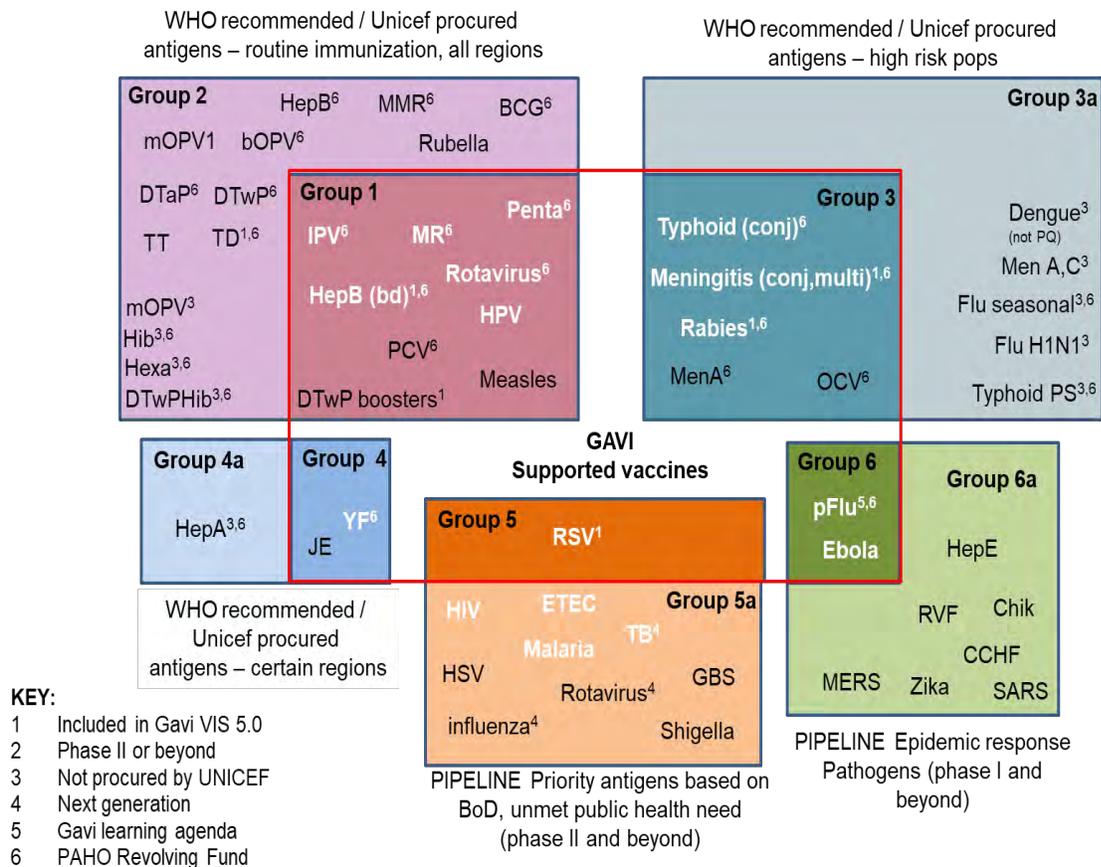
PHASE II

Overview of the Phase II Evaluation Framework

In the second phase of VIPS, the 9 shortlisted innovations were further assessed in the context of specific vaccines they could be applied to and the vaccine-specific implementation challenges and issues they could potentially address in combination with those vaccines. As it was not possible to analyse the innovations in combination with the full vaccine landscape, a list of 10 licensed vaccines and 7 pipeline candidates were identified as ‘priority vaccines’ to be analysed in phase II to provide a representative picture of the broader vaccine universe based on vaccine type, formulation and presentation. These 17 vaccines are shown in white text in Figure 6. Note

that Ebola vaccine was subsequently licensed in November 2019. However, the VIPS analysis continued to refer to it as a pipeline vaccine as this was its status for the majority of the process.

Figure 6: Prioritised 17 Representative Vaccines and Categorisation



These vaccines were selected by the VIPS WG based on a thorough four-stage process that included applying specific inclusion and exclusion criteria: (1) landscaping to define a preliminary long list of all licensed vaccines, (2) categorisation of vaccines by characteristics, (3) application of primary inclusion criteria as proposed by the VIPS SC, and (4) application of secondary inclusion and exclusion criteria based on additional analysis and considerations. A landscape of pipeline vaccines was also assessed based on the WHO PDVAC and R&D Blueprint priority pathogens.

As in phase I, phase II assessed a diversity of innovation types, making direct comparisons across innovations very difficult. To overcome this issue, each vaccine-innovation combination was assessed against a comparator presentation to allow a direct comparison for each indicator. For

phase II, the comparator presentation chosen for each vaccine included the single dose vial presentation, but also included comparison to the multi-dose vial presentation in cases where it is the most-commonly procured presentation by LMICs. This enabled an assessment of the innovations against both ‘best practices’ but also ‘current practices’.

The phase I analytical framework was further expanded for the phase II assessment (see Figure 7) given that the phase II assessment was conducted for each vaccine-innovation combination which allowed for greater specificity and deeper analysis. An additional primary criterion was added on environmental impact aimed at assessing the potential impact of vaccine product innovations on waste management. Two new secondary criteria were also added: technology readiness and commercial feasibility. The technology readiness criterion assessed the innovation’s development status (i.e., clinical development status and regulatory, technological and manufacturing complexity), while the commercial feasibility criterion assessed the commercial opportunity for the innovation (i.e., potential market, country stakeholder interest, existence of partnerships). As in phase I, secondary criteria were not assessed against a comparator but in an absolute manner and were used to provide additional contextual information for each innovation.

Figure 7: VIPS Phase II Criteria Indicators

Primary criteria	Health impact	<ul style="list-style-type: none"> • Vaccine efficacy • Vaccine effectiveness • Ability of the innovation to withstand heat exposure⁶ • Ability of the innovation to withstand freeze exposure⁶
	Coverage and equity impact	<ul style="list-style-type: none"> • Number of fully or partially immunised individuals (relative to target pop) • Ease of use from a clinical perspective based on product attributes⁷ • Ease of use based on the ability of a lesser trainer person to administer the vaccine or self-administration⁷ • Ability to facilitate dose sparing • Availability of the innovation in a single-dose presentation or multi-dose with preservative to avoid missed opportunities and reduce vaccine wastage • Acceptability of the innovation to patients/caregivers⁶ • Potential to reduce stock outs based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities⁶

⁶ Same indicators as for Phase I but further assessed under Phase II due to the antigen/vaccine pairing

⁷ This indicator is re-assessed in Phase II only when the comparator for a specific vaccine is a multi-dose vial, requiring a new evaluation – The comparator single-dose vial is assessed in Phase I

	Safety impact	<ul style="list-style-type: none"> • Number of vaccine product-related adverse events • Likelihood of contamination and reconstitution errors⁶ • Likelihood of needle stick injury⁶
	Economic costs	<ul style="list-style-type: none"> • Commodity costs of a vaccine regimen⁸ (per person vaccinated) • Delivery costs of the vaccine regimen⁸ (per person vaccinated) • Introduction and recurrent costs of the vaccine regimen⁸ (per person vaccinated)
	Environmental impact	<ul style="list-style-type: none"> • Waste disposal of the vaccine regimen (per person vaccinated) and delivery system
Secondary criteria	Technology readiness	<ul style="list-style-type: none"> • Clinical development pathway complexity • Technology development challenges • Regulatory pathway complexity • Complexity of manufacturing the innovation • Robustness of the innovation pipeline
	Commercial feasibility	<ul style="list-style-type: none"> • Potential breadth of market size • Existence of partnerships to support development and commercialisation • Known barriers to global access to the innovation • Stakeholders’ interest

As in phase I, specific parameters were developed to enable scoring for each indicator and the scoring methodology used a magnitude of impact where possible. The difference in phase II was that each vaccine-innovation combination was assessed for each parameter against the relevant comparator.

Evaluation of the 9 Innovations in Phase II

Country Consultations

In phase II, two country consultations, an online survey and in-depth interviews, were conducted to support the final prioritisation of the VIPS 9 shortlisted innovations and to complement the first online survey conducted in phase I.

Phase II online survey:

An online survey⁹ was conducted to identify and evaluate vaccine-specific immunisation challenges that could be addressed by VIPS innovations and to collect additional information on

⁸ Vaccine regimen cost refers to the vaccine product and innovation cost times number of doses for complete immunisation

⁹ Results are reflected in the Executive Summaries of each innovation and a detailed publication on all VIPS country consultations will be published in Q3 2020.

the use of electronic recordkeeping systems for vaccine inventories or patient vaccination records to support the barcode analysis. The survey was targeted to experts in vaccination strategies and existing vaccine products in both Gavi-supported and non-Gavi supported-countries as well as global experts. Participants were provided with a standard list of challenges developed by global experts for the 10 licensed vaccines analysed through VIPS and were asked to select the top three challenges for all vaccines they had knowledge about. 209 participants responded to the survey across a total of 54 Gavi-supported and non-Gavi-supported countries.

The top five challenges for each vaccine based on the frequency of selection (the number of times a challenge was selected as a top three challenge by respondents from a list of 11 challenges) were reported in the assessments as ‘vaccine problem statements’. These vaccine problem statements were mapped to the VIPS phase II evaluation indicators and for all vaccine-innovation combinations the assessments of indicators that relate to the problem statements were highlighted. For the pipeline vaccines, problem statements were defined by the VIPS WG based on current knowledge of the vaccine presentation and/or expected use case and delivery setting.

As detailed in the phase II Technical Notes and Executive Summaries, the online survey helped to clarify and highlight each innovation’s ability to address the most important problem statements identified by countries for each vaccine. It also brought visibility to problem statements that apply to multiple vaccines in the VIPS analysis.

Phase II in-depth interviews:

In-depth face-to-face interviews⁹ were also conducted to collect feedback on the 9 shortlisted VIPS innovations from country decision makers, i.e., stakeholders with decision-making authority or influence over vaccine purchase decisions (national and regional levels), and immunisation staff (health care workers, district and frontline staff, and logistics staff). 84 respondents were interviewed across 6 countries: Ethiopia, Mozambique, Nepal, Nigeria, Senegal and Uganda.

Interviewees were first briefed about each innovation (with no information provided on benefits and challenges), and then, per innovation, were asked open-ended questions about foreseen benefits and challenges and specific vaccines for which each innovation could be particularly useful. Lastly, they were asked to select the top three innovations that have the greatest potential to address their immunisation programme challenges.

The in-depth interviews provided perspective from country stakeholders on the perceived relevance of VIPS innovations for their immunisation programmes. In particular, the results helped in understanding which innovations could help address current challenges faced by immunisation programmes (innovation’s ranking), how each innovation could help (perceived benefits) and which challenges they may bring (perceived challenges). Country stakeholders also identified which vaccines they thought would benefit the most from each innovation (vaccines’ ranking). The results were used to inform the assessment of the VIPS phase II secondary criteria on commercial feasibility in terms of country interest and feedback for each innovation.

Industry consultations

The VIPS WG also conducted a series of consultations with the WHO- and PATH-led Delivery Technologies Working Group (DTWG), consisting of a broader set of immunisation stakeholders including industry experts. The objective of these consultations was twofold: to update these stakeholders on VIPS and to collect feedback on the specific innovations. The key features of each innovation were presented, and detailed background information was shared. DTWG members were then asked to complete an on-line survey focused on the technology readiness and commercial feasibility of each innovation and this feedback was used to inform the assessment of these VIPS phase II secondary criteria.

Regulator consultations

As recommended by the VIPS SC, the VIPS WG also engaged in early consultations with several regulators and regulatory consultants to inform the secondary criteria on technology readiness. The input collected informed the assessment of the regulatory pathway complexity indicator. Two types of consultations were held:

- **Consultations with United States Food and Drug Administration (FDA), European Medicines Agency, African Vaccine Regulatory Forum, and Paul Ehrlich Institute officials:** VIPS technical experts gathered feedback/validation on assumptions related to endpoints/surrogate markers for vaccines and the complexity of clinical development used in evaluation of vaccine-innovation products.
- **Consultations with ex-FDA officials:** VIPS technical experts gathered feedback from ex-FDA consultants on VIPS assessments of technical development and manufacturing challenges on a vaccine innovation product basis from a regulatory perspective.

Technical Notes and Executive Summaries

As in phase I, phase II assessments were documented in detailed **phase II Technical Notes** which consolidated all the information collected relevant to the 9 shortlisted innovations. These documents include the assessment of vaccine-innovation combinations against the comparator presentations and provide consolidated evidence behind the scoring of indicators as well as additional relevant information not easily captured by scores.

To develop the Technical Notes, the VIPS WG conducted additional literature reviews where needed to identify relevant data to assess the indicators added to the evaluation framework in phase II. Technical Notes also include data collected from consultations with countries, industry, and regulatory agencies as described in detail above – that informed relevant criteria and associated indicator scoring.

As in phase I, the Technical Notes went through a rigorous review process where all VIPS technical experts conducted multiple reviews of the indicator assessments and scores to ensure consistency and manage subjectivity of scoring. Additionally, the essential information from the Technical Notes was summarised in **phase II Executive Summaries** that crystallise essential findings along the following dimensions:

- **Potential public health impact of the innovation:** Expected applicability of the innovation to the VIPS priority vaccines (licensed and pipeline), public health benefits (assessed along the VIPS primary criteria indicators), and vaccine problem statements addressed by the innovation (identified via the country survey data).
- **Barriers to realise the innovation’s potential impact:** Cost considerations, technology readiness and commercial feasibility (assessed along the VIPS secondary criteria indicators) and countries’ feedback on the innovation (based on in-depth interviews with countries).

All Technical Notes and Executive Summaries for the 9 short-listed innovations further analysed in Phase II can be found on the following link: <https://www.gavi.org/our-alliance/market-shaping/vaccine-innovation-prioritisation-strategy>.

Selection of Innovations for Final Prioritisation

The VIPS WG again held a series of meetings and deliberations following the review of the final results, documented in the Technical Notes and Executive Summaries, of the phase II assessments of the 9 innovations. Proposed guiding principles were also developed for the SC including suggestions to consider:

- Prioritising innovations that may increase coverage and equity for priority vaccines that have an elimination or eradication agenda, i.e., measles-rubella, inactivated polio, and human papillomavirus vaccines.
- De-risking the portfolio of VIPS prioritised innovations by including both lower risk and higher risk innovations.
- The effort/complexity/feasibility and resources required to ensure access of the innovation to LMIC markets and the trade-offs in terms of expected public health impact.
- Highlighting specific synergistic pairings of innovations which may add incremental value.
- The impact/risks of not prioritising a specific innovation through VIPS.
- Seeking ‘win-win’ scenarios by prioritising innovations with potential to both increase equitable coverage for existing vaccines, particularly during post-COVID-19 catch-up immunisations, and be valuable for COVID-19 vaccine delivery. The WG was cognizant that the COVID-19 pandemic might create potential funding opportunities for innovations that are relevant for both COVID and other priority vaccines and could accelerate their product development and/or implementation.

At the VIPS SC meeting held in May 2020, the SC selected and recommended 3 innovations to be prioritised and these were endorsed by the WG.

VIPS OUTCOMES

Prioritised innovations

Three innovations were ultimately selected (listed below in order of priority) for which VIPS will engage in advancing their development and access:

1. Upstream novel delivery devices – **Microarray patches (MAPs)**: MAPs are seen as truly ‘transformational’ innovations that have the potential to address many immunisation barriers identified by countries due to their improved thermostability; better ease of use; avoidance of reconstitution and the associated errors and risks; improved safety (as they are sharps-free); and the fact that they are single-dose presentations, thereby avoiding missed opportunities due to the reluctance to open a multi-dose vial. Additionally, MAPs are applicable to a number of use cases including routine, supplemental, house-to-house and outbreak immunisation. Therefore, the development of MAPs should be encouraged for use with several vaccines, including pipeline vaccines and those with elimination and eradication agendas. They are also innovations that may have a positive impact on ‘life-course’ immunisation for broader populations beyond children, including adolescents, adults and older adults. While MAPs are unlikely to be ready for implementation with the first COVID-19 vaccines developed in response to the current pandemic, they could be co-developed with vaccines to be positioned for future emergency response, or for use with COVID-19 vaccines in the longer term. However, it was noted that there are still significant technical, biological and commercial barriers to overcome before MAPs can be implemented, particularly for vaccines intended for use in low resource settings, which will require substantial funding. Additionally, it is not known whether the prices for vaccines on MAPs will be acceptable to end-users, despite the expectation that they may reduce costs at the delivery level and assist with overcoming immunisation barriers.
2. A combined formulation, regulatory, and programmatic approach to vaccine management – **Heat stable and Controlled Temperature Chain (CTC)¹⁰ qualified vaccines**. Thermostability was identified as the top priority by countries consulted on barriers to immunisation and this innovation directly addresses equity concerns by virtue of improving access to harder to reach communities and alleviating cold chain constraints for health care workers. As such, the Alliance has prioritised heat stable and CTC-qualified vaccines, including both liquid and dry formulations. Enhanced thermostability is a desirable feature for all vaccines to improve vaccine effectiveness and, where possible and appropriate, to enable higher temperature storage and transport in a CTC. Vaccine candidates for CTC use, whether liquid or dry, should have the following attributes: adequate heat stability to achieve regulatory and WHO prequalification for CTC with the longest CTC duration possible (e.g., days, weeks or months), contexts of use that benefit from CTC, and formats that do not increase vaccine wastage or safety risks when used in a CTC. Dry formulations are of interest if coupled with

¹⁰ CTC-qualified vaccines are approved by regulatory authorities and WHO for use up to a specified threshold temperature for a **minimum** of 3 days prior to administration.

technologies that offer additional benefits such as removing the issues associated with manual reconstitution – as would be the case with dual delivery chamber devices, solid dose implants or MAPs. This innovation category is also synergistic with VVM-TIs to facilitate temperature monitoring. VVM-TIs could be further evaluated as part of a future scope. This innovation may be a relatively ‘quick win’ for existing thermostable vaccines and emerging pipeline vaccines. However, thermostability represents a higher hurdle for existing vaccines that require reformulation; in such instances greater heat stability and/or CTC could be pursued if vaccines undergo reformulation for another reason.

3. A programme implementation and system technology – **Barcodes on primary packaging:** Track and trace is considered a priority for vaccines on secondary packaging by Gavi and UNICEF and 2D barcodes on primary packaging would allow for greater accuracy in tracking vaccine products, especially when they are removed from their secondary packaging at lower levels of distribution. It would also support the eventual transition to electronic record keeping, in line with the objectives of advancing digital health in Primary Health Care. Barcodes on primary packaging are seen as highly valuable in terms of tracking inventory and immunisation coverage, and follow-up of AEFIs, and this is particularly true for deployment of novel vaccines. While this is a mature technology in general, an analysis of the implications of barcodes on primary packaging and a ‘push’ for implementation based on the analysis of the implications could build upon the existing efforts to place barcodes on vaccine secondary packaging and spur wider implementation of systematic monitoring and surveillance systems. The COVID-19 pandemic may provide an opportunity to leverage investment to catalyse manufacturing of vaccines with barcodes and it was felt that VIPS may be the right avenue to help advocate and support the advancement of this technology. Implementation of barcodes for COVID-19 vaccines is likely not feasible for the current pandemic and the first vaccine deployments, but they may be for later phases of vaccine deployment; and while it will take time to ensure country readiness, a few countries with advanced electronic recordkeeping could benefit from their availability on secondary packaging almost immediately and on primary packaging in the coming years. There is a clear recognition that barcodes themselves are not an innovation but part of a broader innovation ecosystem that will need coordination and integration within the realms of vaccine standards, manufacturing, regulatory, procurement, distribution, and in-country recordkeeping. It was noted that in order to capture the full benefits from barcodes on primary packaging, electronic inventory and health records transitioning will be required in LMICs which could be a challenging and lengthy process in many countries.

Shortlisted innovations

While VIPS has the capacity to focus on only a few innovations in the coming years, the 6 short-listed innovations that were not prioritised have strengths and merit and remain of high interest to VIPS. The intention is to continue to monitor their status for future consideration. These are (in alphabetic order):

Auto-disable sharps injury protection syringes (AD-SIPs): These devices are broadly available and improve safety by reducing the likelihood of needlestick injury and transfer of bloodborne pathogens to patients, health workers and the community after vaccine administration. VIPS supports WHO's intention to require use of syringes with SIP features in the expanded programme of immunisation in the near future.

Combined vaccine vial monitor and threshold indicators (VVM-TIs): VVM-TIs are particularly useful for vaccines used in a controlled temperature chain (CTC). The technology offers increased ease of use, fewer components, and saving of staff time in comparison to current use of VVMs with separate TIs to monitor higher temperature exposure of vaccines used in a CTC. Their adoption is likely to be determined by the size of the incremental price premium.

Compact prefilled auto-disable devices (CPADs): CPADs have many potential public health benefits, broad applicability to liquid parenteral vaccines, and proven utility in facilitating vaccine outreach. They have the benefits of greater ease of use, single-dose presentations, and can be synergistic with CTC if filled with appropriately licensed vaccines. Previous concerns regarding high cost may be overcome by new manufacturing techniques, including blow-fill-seal (BFS). The current efforts of the US government to advance and scale up BFS compact prefilled devices (although without AD features that would be required in LMICs) may help to advance this technology platform. Overall, CPADs warrant close monitoring given the potential value of this innovation.

Dual chamber delivery devices: Dual chamber delivery devices offer some of the same safety benefits as MAPs since they are appropriate for vaccines that must be formulated dry. They ease the process of reconstitution and dosing, largely eliminate reconstitution errors, and for some formulations may enable vaccines to be heat-stable until immediately prior to administration. They can also be used with vaccines that have liquid components that require mixing. Most dual chamber device formats are early in development and face significant technical and manufacturing challenges. This innovation was not selected in this VIPS cycle primarily given the need to limit the number of innovations that are early in development. Future adoption is also likely to be determined by the eventual cost of these devices.

Freeze damage resistant liquid formulations: Exposure of freeze-sensitive vaccines (particularly those with aluminium-salt-based adjuvants) to freezing temperatures during storage and distribution continues to be an important issue for countries and this was verified in the VIPS country consultations. The addition of low-cost excipients to these vaccines can prevent freeze-damage. There are some technical and clinical development hurdles yet to be overcome, as well as potentially significant acceptability issues associated with adding an excipient. As with heat stability improvements, reformulating existing vaccines was flagged as a challenge and pipeline vaccines could represent a better opportunity. In addition, VIPS recognised that alternative measures exist to address the freeze exposure problem, including improved cold chain equipment and temperature monitoring as well as vaccine management training. The prioritisation of heat stable and CTC qualified vaccines also may address some challenges related to freeze sensitivity by enabling end users to reduce a vaccine's exposure to the cold chain.

Solid dose implants: These devices have the potential to address many of the same barriers to immunisation as MAPs and dual chamber delivery devices, and might not be associated with the same degree of local reactogenicity as MAPs (though data are needed on this point). However, they have other drawbacks such as the need for a separate applicator and are earlier in development than MAPs. They were also viewed as less favourable in the VIPS country consultations than other innovations – including MAPs and dual chamber delivery devices – which also deliver dry vaccines. Solid dose implants could represent an alternative to MAPs and dual chamber delivery devices and manufacturers are encouraged to continue to generate new data, especially on country/user acceptability.

Conclusion and next steps

The VIPS partners (BMGF, GAVI, PATH, UNICEF, WHO) will now focus on defining end-to-end strategies including clear action plans to accelerate the advancement of the 3 prioritised innovations. This work will be informed by targeted consultations with technology developers and manufacturers to address key roadblocks and gaps to innovation development and uptake and will build on the ongoing efforts by VIPS partners and other stakeholders. Additionally, VIPS Alliance partners will work to create an enabling environment for vaccine innovation in terms of policy, procurement and programme implementation, and continuous learning/evaluation in alignment with Gavi's 2021 to 2025 strategy.

APPENDIX A: VIPS STEERING COMMITTEE MEMBERS

Member	Affiliation	Title
Alejandro Cravioto	Facultad de Medicina Universidad Nacional Autónoma de México	Professor; SAGE Chair
David Robinson	Bill and Melinda Gates Foundation	Deputy Director of Vaccine Development and Surveillance, Chemistry Manufacturing and Controls
Christopher Morgan	Jhpiego (from June 2020) <i>and</i> Burnet Institute	Senior Technical Advisor (Immunization) <i>and</i> Honorary Senior Principal Research Fellow
David Kaslow	PATH	Vice president, Essential Medicines
Jean-Pierre Amorij	UNICEF Supply Division	Vaccine Technology Specialist
Jerome Kim	International Vaccine Institute	Director General
Jon Abramson	Wake Forest School of Medicine	Professor of Paediatric Infectious Diseases
Kelly Moore	Vanderbilt University School of Medicine	Adjunct Associate Professor of Health Policy
Mark Jit	London School of Hygiene and Tropical Medicine	Professor, Vaccine Epidemiology
Mark Papania	Global Immunization Division, Centers for Disease Control	Medical Epidemiologist
Michael Free	Independent	Independent Consultant; Senior Advisor Emeritus, PATH
Nora Dellepiane	QRB Consultants Sàrl	Independent consultant
Ramanan Laxminarayan	Center for Disease Dynamics, Economics and Policy	Director
Ruth Karron	John Hopkins University	Professor, International Health
Samir Sodha	WHO	Routine Immunisation Officer
Shelley Deeks	Public Health Ontario	Chief, Health Protection Officer

Member of the Immunization Practices Advisory Committee (IPAC) – WHO

Member of the Product Development for Vaccines Advisory Committee (IPAC) - WHO

VIPS Phase II executive summary: Microarray patches (MAPs)

March 2020

Microarray patches (MAPs)

About MAPs

- MAPs consists of **an array of micro-projections on a patch**. The micro-projections are coated with or are composed of, vaccine in a dry formulation. When a MAP is applied to the skin, the vaccine is delivered into the dermis and/or epidermis layers.
- MAPs can be administered **without an applicator**, by applying pressure with fingers, or using **an integrated applicator**.
- Like solid-dose implants (SDIs), MAPS are sharps-free devices that could potentially be used with all injected vaccines (once they have been reformulated). However, development of MAPs is more advanced than SDIs and current MAPs do not have a separate applicator, which will likely be needed for SDIs.

Vaxxas, 15 May 2019



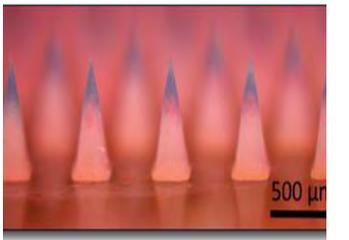
microbiomedical.com^b



Stage of development

- Various formats of MAPs are **being developed for vaccine delivery** by several different developers.
- Three developers have tested **influenza vaccine MAPs in phase I clinical trials**, and **preclinical development** is underway with **other vaccines, including measles-rubella (MR)**.
- MAPs for delivery of non-vaccine products, such as teriparatide (for osteoporosis) and Zolmitriptan (migraine), have been evaluated **in phase II and III trials** respectively.

WHO^c



Summary of key insights (1/2)

Potential public health impact of innovation



Applicability to vaccines

- MAPs could be used with **all or most vaccines** that are currently injected. However:
 - Vaccines that are currently adjuvanted **might need to be formulated without adjuvant** to reduce local reactogenicity and/or facilitate manufacturing.
 - MAPs have a relatively **limited payload** which might not be sufficient for use with some vaccines.



Public health benefits

- MAPs potentially offer a broad range of public health benefits for a range of vaccines including:
 - **Resistance to heat exposure** which may facilitate **use within the controlled temperature chain**;
 - **Easier to use**, allowing **lesser trained staff** to administer vaccines and potentially enabling self administration;
 - Single-dose presentation, **reducing missed opportunities** and **contamination risks** associated with multi-dose vials;
 - **Improved safety** by **avoiding reconstitution errors** and avoiding **needle-stick injuries**.
 - **Improved acceptability to caregivers/parents**;
 - Fewer components than needle and syringe (N&S) delivery **reducing the risk of stock-outs**.



Vaccine problem statements

- MAPs could potentially **address many or all of the top 5 problem statements** identified for HepB birth dose, HPV, MR, MenA, IPV, rabies, TCV, and yellow fever vaccines, particularly those related to:
 - **Heat-stability** of vaccines and **cold-chain requirements**;
 - **Reconstitution** of lyophilised vaccines and **missed opportunities** due to use of preservative-free multi-dose vials;
 - **Ease of use** and **safety**.

Summary of key insights (2/2)

Barriers to realise the innovation's potential impact



Costs

- The **commodity costs** for MAPs are **unknown but are likely to be higher** than for vials and N&S.
- **Delivery and distribution costs are also unknown** and will depend on the size of the MAP and possibly the 'wear-time' of the MAP.



Technology Readiness

- Development of MAPs faces **significant technical and manufacturing challenges** including:
 - The need to develop and scale-up **novel manufacturing** processes;
 - Formulation without adjuvants (to reduce reactogenicity) **might reduce vaccine immunogenicity**;
 - Formulations need to provide vaccine stability and allow rapid and efficient delivery into the skin.



Commercial feasibility

- The **commercial feasibility** of MAPs in low to middle income countries (LMICs) is **uncertain**, especially as the cost of the devices is likely to be higher than N&S. A dual-market in high income countries (HICs) might be needed.
- There is **demonstrated interest** from countries and several MAP developers have programs supported by global health funders. There are however **no or few established commercial partnerships** between vaccine manufacturers and MAP developers.



Countries interest

- Based on the VIPS country interviews, there appears to be **strong interest in MAPs both from immunisation staff and decision makers**, with an overall ranking of **number 1** amongst the 9 tested.

MAPs have a broad applicability to vaccines



	VIPS Phase II vaccines	Vaccine Type	Presentation	Route
Vaccines technically compatible with MAPs and analysed in Phase II.	Hepatitis B (birth dose)	Adjuvanted sub-unit	Liquid	IM ¹
	HPV	Adjuvanted sub-unit	Liquid	IM
	MR (or MCV)	Live attenuated,	Lyophilised	SC ²
	N. Men A (or N. Men A,C,W,Y,X)	Polysaccharide-protein conjugate, adjuvant in diluent	Lyophilised	IM
	Polio, IPV	Whole inactivated	Liquid	IM or ID ³
	Rabies	Whole inactivated	Lyophilised	IM or ID
	Typhoid, conjugate (TCV)	Polysaccharide-protein conjugate	Liquid	IM
	Yellow fever (YF)	Live attenuated	Lyophilised	SC
Pipeline vaccines	Ebola (rVSV-ZEBOV) ⁷	Live vector	Liquid (FROZEN)	IM
	HIV (ALVAC prime only) ⁸	Live recombinant virus	Lyophilised	IM
	Influenza (pandemic, VAL-506440)	Lipid nanoparticle, modified RNA	Liquid	IM
	MTb (next gen., VPM1002)	Live recombinant BCG	Lyophilised	ID
	RSV (Pre-F)	Recombinant protein	Lyophilised	IM
Vaccines not technically compatible with MAPs & not analysed in Phase II	Penta (or DTP containing)	Adjuvanted inactivated subunit plus polysaccharide-protein conjugate	Liquid	IM
	Rotavirus (Oral)	Live attenuated virus	Liquid	Oral
	ETEC (ETVAX)	Whole inactivated organism	Liquid vaccine, lyophilised buffer and adjuvant	Oral
	HIV (bivalent subtype C gp120 boost only) ⁸	Adjuvanted recombinant protein	Liquid	IM
	Malaria (RTS,S)	Adjuvanted recombinant protein	Lyophilised, liquid adjuvant	IM

13 vaccines (out of 17 in scope) are technically compatible with MAPs and have therefore been assessed in Phase II.

Vaccine applicability:

- **Most or all parenteral vaccines are candidates for use with MAPs.**
- Vaccines with adjuvants are likely to have a **more challenging** development pathway. Some of these have been excluded as they are likely to be particularly challenging.
- Technical feasibility was assessed based on data, when available, and expert opinion. Key considerations included the natural route of infection, vaccine type, use of adjuvants and preservatives, and context of use.

Comparators:

To assess innovations against both 'best practice' and 'current practice', comparators were defined as:

- **Single dose vial (SDV)⁴ presentation** and auto-disable (AD) N&S⁵,
- If available, the **MDV⁶ presentation** commonly procured by LMICs.

¹ Intramuscular; ² Subcutaneous; ³ Intradermal; ⁴ Single-dose presentation; ⁵ Auto-disable needle & syringe; ⁶ Multi-dose presentation; ⁷ At the time of the assessment, Ebola vaccine was not yet licensed and has been analysed as a pipeline vaccine; ⁸ HIV vaccine consists of two different components: a virus vector for priming doses and a subunit protein plus adjuvant. The prime and boost were therefore assessed separately.

Vaccines technically compatible with MAPs and analysed in Phase II.

Vaccines not technically compatible with MAPs & not analysed in Phase II

Beyond the 17 vaccines analysed through VIPS, MAPs should be compatible with a range of other vaccines

*Pipeline vaccines



VIPS vaccines compatible with MAPs	Vaccine type	Other vaccines likely to be compatible with MAPs
HepB	Subunit, liquid, adjuvant	dT; TT; DTwP; DTaP; hexavalent; <i>non-replicating rotavirus; GAS; next generation malaria; CEPI vaccine platform (clamp); Shigella; ETEC</i>
HPV	VLP or inactivated virus, liquid, adjuvant	JE (inactivated); hepA; <i>non-replicating rotavirus; RSV; improved or universal influenza; influenza (pandemic)</i>
IPV	Inactivated virus, liquid	Influenza (seasonal); RSV
Men A	Polysaccharide-protein conjugate, lyophilised	Men ACWY(X)
MR; YF; HIV (ALVAC prime)	Live attenuated virus, lyophilised	MCVs; JE (live atten.); dengue; influenza (seasonal); <i>CEPI vaccine platforms (live recombinant vectors); chikungunya, HSV; next generation malaria; RSV</i>
Rabies	Inactivated virus, lyophilised	<i>R&D Blueprint vaccines</i>
Typhoid	Polysaccharide-protein conjugate, liquid	Pneumococcal conjugate vaccine; Hib, Men ACWY (liquid); GBS; <i>Shigella</i>
Ebola	Live vector, liquid	<i>CEPI vaccine platforms (rVSV); R&D Blueprint vaccines; HSV; next generation malaria; RSV</i>
Flu (pandemic)	Nucleic acid, liquid	<i>CEPI vaccine platforms (DNA, RNA), HSV</i>
RSV	Subunit, lyophilised, +/- adjuvant	<i>Mtb (next generation, M72)</i>
<i>Mtb (next generation)</i>	Live attenuated, lyophilised, ID admin	BCG, other vaccines for ID administration e.g. IPV, rabies



Overview of MAPs public health benefits based on Phase II analysis

Public health benefits

Comparator: MDV

Vaccine with an elimination agenda

VIPS Criteria		Indicators	Hep B BD	HPV	MR	Men A	IPV	Rabies	TCV	YF	Ebola	HIV ⁶	Influenza ⁵	M. Tb ⁷	RSV ⁸		
Primary criteria	Health impact	Vaccine efficacy	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	
		Vaccine effectiveness	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		Ability of the vaccine presentation to withstand heat exposure	No data	Better	Better	No data	Better	No data	No data	No data	No data	No data	No data				
		Ability of the vaccine presentation to withstand freeze exposure	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
	Coverage & Equity impact	Number of fully or partially immunised (relative to target population)	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		Ease of use: clinical perspective based on product attributes	Better	Better	C. better	C. better	Better	C. better	Better	C. better	Better	C. better	C. better	Mixed	C. better	C. better	
		Ease of use: ability of a lesser trainer personnel to admin. / self-admin.	Better	C. better	C. better	C. better	Better	C. better	C. better	C. better	C. better	C. better	C. better	C. better	Better	C. better	
		Ability to facilitate dose sparing	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		Avoid missed opportunities and reduce vaccine wastage ¹	Better	C. better	C. better	C. better	Better	C. better	C. better	C. better	Neutral	Neutral	Neutral	Neutral	C. better	Neutral	
		Acceptability of the vaccine presentation and schedule ²	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better
	Safety impact	Potential to reduce stock outs ³	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	
		Number of vaccine product-related AEFIs	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		Likelihood of contamination and reconstitution errors	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	
	Economic costs	Likelihood of needle stick injury	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	
		Commodity costs of the vaccine regimen ⁴	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		Delivery costs of the vaccine regimen ⁴	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
Environmental impact	Introduction & recurrent costs of the vaccine regimen ⁴	Worse	Worse	Worse	Worse	Worse	Worse	Worse	Worse	Worse	Worse	Worse	Worse	Worse	Worse		
	Waste disposal of the vaccine regimen ⁴ and delivery system	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better	Better		

7 ¹ Based on availability of the innovation in a single-dose presentation or multi-dose with preservative. The score would be neutral for all vaccines if the comparator was a SDV; ² To patients/caregivers; ³ Based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities; ⁴ per person vaccinated; ⁵ VAL 506440; ⁶ ALVAC prime; ⁷ VPM 1002; ⁸ Pre-fusion F protein



Phase II confirms MAPs' broad potential public health benefits for a range of compatible vaccines

Based on the assessment using VIPS primary indicators applied to MAPs with specific vaccines, MAPs can **potentially address many immunisation challenges for a range of compatible vaccines.**

- **Resistance to heat exposure** and facilitating **use within the controlled temperature chain** assuming the MAP formulation confers sufficient heat stability – *data supporting this have been obtained to date with HPV, MR and IPV.*
- **Easier to prepare/use** allowing **lesser trained staff** to administer the vaccines. MAPs score considerably better for vaccines that can be given to adolescents/adults because they **should also enable self administration.** *This includes HPV, RSV and vaccines used in campaigns.*
- Appear painless and safer than N&S to recipients (based on product attributes) so should have **higher acceptance.** Recipients of a non-VIPS vaccine (seasonal influenza) preferred MAPs to N&S injection.
- Single-dose presentation, with the potential to **reduce missed opportunities** due to reluctance to open a multi-dose vial. *Particularly relevant for vaccines with preservative-free multi-dose presentations such as HPV, MR, MenA, rabies, and YF.*
- Do not require reconstitution, so the **risks of reconstitution-related errors and contamination are reduced.** *This is relevant for all lyophilised vaccines, such as MR, MenA, rabies, and YF.*
- Single component, so should **reduce risk of stock-outs** for all vaccines, liquid or lyophilised.
- Needle-free, **avoiding needle-stick injuries and simplifying waste disposal** for all vaccines.



Overview of the ability of MAPs to address vaccine specific problems identified in the VIPS Phase II country consultations¹

Vaccine with an elimination agenda

	Hep B BD	HPV	MR	Men A	IPV	Rabies	TCV	YF	Ebola	HIV ³	Influenza ⁴	M. Tb ⁵	RSV ⁶
Vaccine ineffectiveness/wastage due to heat exposure	2	4	1	3	2	2	1						
Vaccine ineffectiveness/wastage due to freeze exposure	1	1			1		5	3					
Cold chain requirements during outreach ²	3	3	4	2	3								
Vaccine wastage or missed opportunities due to multi-dose vial ²			2	1		4	2	1					
Reconstitution related safety issues ²			3	4				2					
Reduced acceptability due to painful administration ²	5	2			4	3							
Difficult preparation requiring trained personnel ²	4	5				1	4						
Negative impact on the environment due to waste disposal practices ²					5			5					
Needle-stick injuries ²			5	5		5		4					
Contamination risk due to multi-dose vial ²													
Difficult to deliver vaccine to correct injection depth ²							3						

¹ Based on an online survey with 209 global experts and country-level stakeholders across 54 countries conducted in Q4 2019 – Q1 2020, top 5 challenges identified by countries per licensed vaccine were selected as ‘vaccine problem statements’ to be specifically analysed. Numbers in the table refer to the ranking order of top 1 to 5 problem statements. For pipeline vaccines, problem statements were defined by the VIPS WG. ² Scoring based on product attributes. ³ ALVAC prime; ⁴ VAL-506440; ⁵ VPM1002; ⁶ Pre-fusion F protein

No data available for assessment	Mixed	Better than the comparator	Considerably better than the comparator
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MAPs have the potential to address many or all, of the countries' top 5 vaccine problem statements for the applicable vaccines

The overlay of the top 5 problem statements by vaccines with the VIPS primary indicators assessment shows that **MAPs have the potential to address most of the top 5 vaccine problem statements for a broad range of vaccines:**

- **Resistance to heat exposure** and facilitating **use within the controlled temperature chain** – assuming the MAP formulation confers improved heat stability. *Identified as an important problem for the **majority of the 13 vaccines** assessed.*
- Single-dose presentation, potentially **reducing missed opportunities** due to vaccine wastage or reluctance to open a multi-dose vial. *Identified as an important problem for **vaccines in multi-dose presentations like MR, MenA and YF, as well as rabies and TCV.***
- No need for reconstitution, therefore **avoiding reconstitution errors.** *An important problem for **lyophilised vaccines (MR, MenA and YF).***
- **Easier to prepare/use**, saving time and allowing for **lesser trained staff** to administer the vaccines. *Identified as an important problem for **rabies, HepB, TCV, and HPV.***
- MAPs are sharps-free, so **needle-stick injuries should be reduced**, *identified as the problem ranked number 5 for **MR, MenA, rabies** and number 4 for **YF** and **waste-disposal** should be **simpler**, also the problem ranked number 5 for **IPV and YF.***
- MAPs have been **perceived** as being safer and less painful based on the appearance of the device, which might improve acceptability. Limited data, obtained with a non-VIPS vaccine (seasonal influenza), have not found a significant difference in reported pain compared with N&S.



Costs

MAPs will likely have a higher cost than single-dose vial (SDV) and multi-dose vial (MDV) alternatives

Commodity costs^{1, 2}

Unknown, however likely to be higher than for SDV or MDV:

- **There are no data on the cost of goods (COGS) or purchase price of a MAP.**
- However, it is **likely that both will be higher than for vaccines in SDVs and MDVs.**
- Previous costing studies have shown that for the comparators, the 'vaccine + vial' price is larger than the combined cost of delivery devices and safety boxes. **Therefore, the increase in 'vaccine + MAP' price is likely to outweigh savings in other commodity costs components.**

Delivery costs^{1, 3}

Unknown. This will depend on the MAP's volume in the cold chain and vaccinator time for preparing and administering the vaccine:

- **The costs for storage and transport in the cold chain are unknown** because of no volume data for MAPs; but it is most likely larger than a MDV. This will be device-specific.
- **The impact on the vaccinator time costs is unknown** as the **wear time of MAPs is unknown** (and device-specific) and it is not clear whether the vaccinator will have to continue to monitor the vaccines during this time.

Introduction and recurrent costs¹

Introduction costs due to training needs:

- Training would be required to introduce MAPs as would be required with any innovation.
- There are no upfront costs, recurrent or ongoing costs for MAPs.

¹ Of a vaccine regimen (per person vaccinated); ² Includes the purchase cost of a vaccine regimen and delivery devices (injection syringes or other components needed for vaccine preparation and administration) accounting for wastage, and safety box costs; ³ Includes costs of in and out of cold chain storage and transport for a vaccine regimen including delivery technology(ies), time spent by vaccinators when preparing and administering the vaccine and by staff involved in stock management;



MAP development faces significant challenges that will require substantial time, effort and investment to be overcome¹

VIPS Criteria	Indicators	Hep B BD	HPV	MR	Men A	IPV	Rabies	TCV	YF	Ebola	HIV ²	Influenza ³	M. Tb ⁴	RSV ⁵	
Secondary criteria	Technology readiness ¹	High													
	Clinical development pathway complexity	Low	Low	Low	Low	Low	Low	Low	Low	Moderate	High	Low	High	Moderate	
	Technical development challenges	Moderate/High	High	Moderate	Moderate	Moderate	Moderate/High	Moderate	Moderate/High	Moderate/High	Moderate	Moderate/High	High	Moderate	
	Complexity of manufacturing the innovation	High													
	Robustness: multiple developers of the technology	Moderate	Not robust	Moderate	No data	Moderate	Not robust	No data	No data	No data	No data	No data	No data	No data	No data
Robustness: multiple suppliers/manufacturers of the vaccine	High	Moderate	Moderate	Moderate	Not robust	Moderate	Not robust	Moderate	Not robust	Moderate	Not robust	Not robust	Moderate	Not robust	

- MAPs have been evaluated in several clinical trials, but there are **significant challenges** facing the **technical development** and **manufacturing** of MAPs. Some issues are vaccine-specific, but some, particularly manufacturing issues, apply to the platform overall.
- Demonstrating that MAPs can be manufactured at a **pilot scale** (e.g. 1/5 commercial scale) for phase II/III trials is on the **critical path for first vaccine-MAP combination** approval. Establishing a pilot production line will require significant investments (**possibly tens of millions of dollars**).
- The **number** of existing MAP developer – vaccine manufacturer **partnerships is low** (not robust). Vaccine manufacturers have been hesitant to partner with MAPs developers.

¹ VIPS assessment of the Technology Readiness criteria was informed by consultations with the WHO/PATH Delivery Technology - WG, as well as with regulators.

² ALVAC-HIV + bivalent Subtype C gp120; ³ VAL-506440; ⁴ VPM1002; ⁵ pre-fusion F protein

MAPs are highly novel devices with ‘unique’ challenges; scaling up cGMP manufacturing is possibly the most critical issue



Technology Readiness

Regulatory	Technical	Manufacturing	Vaccines
<ul style="list-style-type: none"> • Clinical development. For licensed vaccines, phase III non-inferiority or bridging studies with immunogenicity endpoints are expected to be sufficient. However, for novel vaccines, the same (clinical) endpoints would be required as for N&S or other delivery methods. • Removal of adjuvant means the vaccine may be considered as “new” from a regulatory point of view. • Usability studies might be required, particularly if depth of delivery or wear-time of the MAP is critical. 	<ul style="list-style-type: none"> • Delivery of antigen: MAPs will need to be worn for seconds-to-minutes to transfer antigen to the skin, which might be difficult in LMIC settings. Transfer into the skin will need to be reproducible and efficient. • Quantity of vaccine required: Only limited amounts of antigen can be loaded onto a MAP. This might be insufficient for some vaccines. • Immunogenicity vs. reactogenicity: MAPs initiate immune responses just below the skin surface, so local reactogenicity is expected. It might be necessary to remove adjuvants for this to be acceptable, which might reduce immunogenicity. 	<ul style="list-style-type: none"> • Developing a cGMP manufacturing process: Aseptic manufacture will likely be required. The manufacturing processes (incl. assembly and packaging) will be novel and unique and need to be developed, tested at pilot scale and scaled up. • Bulk antigen: Only small volumes of vaccine can be loaded onto MAPs, therefore bulk antigen will be required at higher than usual concentration. • Quality control: Novel methods for in-process controls and process validation will be required, and possibly novel assays for product release. • Manufacturing time per unit: The process will need to operate at commercial scale and be competitive with the process for other delivery methods, e.g. vials and N&S. 	<ul style="list-style-type: none"> • ‘Best’ vaccines from a development/manufacturing perspective may be MR, MenA, TCV or IPV due to no adjuvant, amount of antigen needed, and low valency. • Hep B birth dose is formulated with adjuvant which might need to be removed. MAPs would be used in neonatal skin, which is physiologically different in some respects to infants and adults. • HPV is adjuvanted & relatively complex, 2-, 4- or 9-valent. • Lyophilised vaccines might be suitable, but new formulations often with reduced amounts of excipients will be needed.



Commercial feasibility

The commercial opportunity for MAPs in LMICs is uncertain and developers and manufacturers will need an upside to create partnerships

VIPS Criteria	Indicators	Hep B BD	HPV	MR	Men A	IPV	Rabies	TCV	YF	Ebola	HIV ²	Influenza ¹	M. Tb ³	RSV ⁴
Secondary criteria	Country stakeholders' interest based on evidence from existing data	No data		Mixed interest	No data									
	Potential breadth of the target market	Large	Large	Large	Moderate	Moderate	Small/ Moderate	Small/ Moderate	Moderate	Small	Large	Small	Large	Large
	Existence of partnerships to support development and commercialisation	Mixed interest	Mixed interest	Mixed interest	No known interest	Moderate interest	Mixed interest	No known interest	No known interest	No known interest	No known interest	No known interest	No known interest	No known interest
	Known barriers to global access to the innovation	No data												

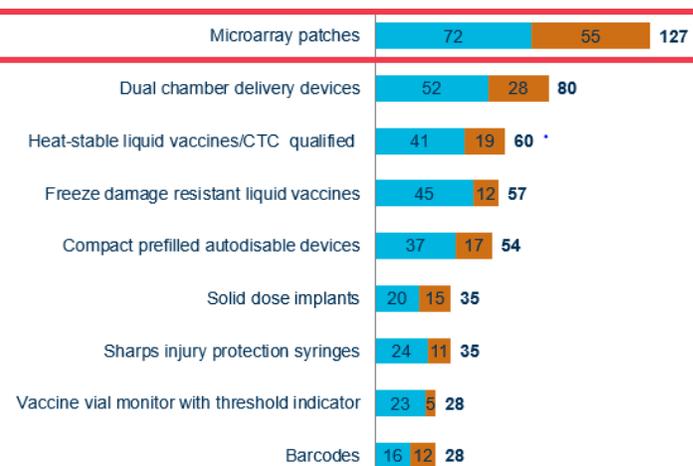
- Published data show **stakeholder interest** in MAPs for use with **MR** in Benin, Nepal and Vietnam.
- Market potential and uptake for MAPs in LMICs is uncertain** and will likely need to be driven by a **dual-market in HICs**:
 - Financial attractiveness of MAPs to vaccine manufacturers is likely to be determined by the **value proposition in HICs**.
 - Higher cost of goods** for MAPs (vs. N&S), at least initially, may drive the selection of the first use case for MAPs in LMICs (e.g. targeted to hard to reach populations vs. broader campaign or routine use, to justify a price-premium).
 - There is potential to leverage **MAPs as a manufacturing platform** to develop a portfolio of vaccines across HICs and LMICs.
- Partnerships to support development and commercialisation will be required**:
 - To provide **investment in manufacturing scale up**; this could include donors/funders.
 - Agreement between vaccine manufacturers and MAP developers** will be needed regarding responsibility for release of the final combination product, royalty sharing and liability during clinical testing.



Based on VIPS country feedback¹, there is strong interest in MAPs

Feedback from in-person country interviews

Innovations' ranking



- MAPs are rated by both immunisation staff and decision makers as the **#1 innovation amongst the 9 tested**, i.e. with the greatest potential impact in helping address their immunisation programme's current challenges.

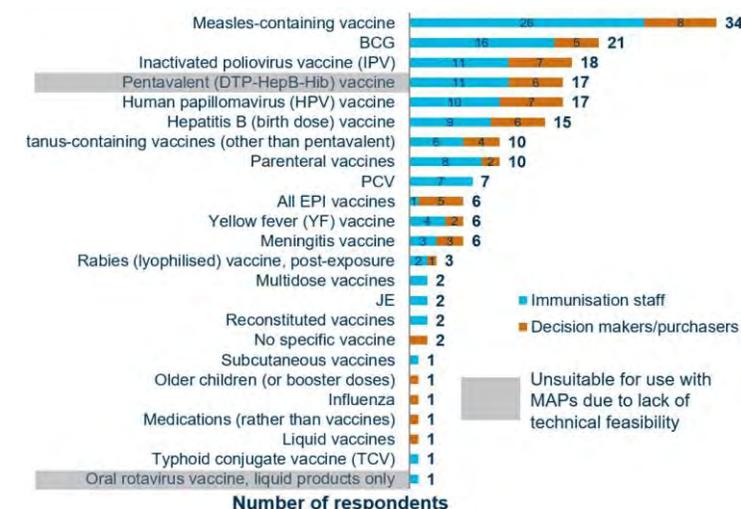
Perceived benefits

- Make preparation and administration of vaccines easier and faster, save health care workers time;
- Increase acceptability;
- Improve safety, i.e. reducing needle-stick injuries, contamination or use of wrong diluents;
- Improve coverage & decrease vaccine wastage;
- Make delivery outside health facility easier & enable lesser trained personnel to deliver vaccines.

Perceived challenges

- Need for community sensitisation to manage acceptability among patients/caregivers;
- Cold chain volume;
- HCWs : time required to use MAPs; complexity of the technology; possibility of skin reaction or different absorption by skin type; no indication that the vaccine has been delivered;
- Decision makers: overall cost and training needs.

Vaccines' ranking for MAPs



¹ Based on in-person interviews conducted in Q4 2019-Q1 2020 with 55 immunisation staff and 29 decision makers across 6 countries to gather feedback on the 9 innovations under final evaluation

Potential impact of VIPS prioritisation



What could VIPS do to accelerate MAPs development for LMICs

If MAPs were prioritised by VIPS, **stakeholder inputs would be sought** to identify follow-up activities that would have the **greatest impact on accelerating MAP development**. These could include:

- **The creation of partnerships** between developers, manufacturers and donors/funders to facilitate access to vaccines.
- **Push funding (possibly)**, e.g. to support pilot-scale manufacturing.
- Developing an **innovative pull-funding mechanism** (possibly).
- **Country and cost analyses** to provide clarity on use-case scenarios in LMICs.

Risks of not prioritising MAPs through VIPS

- There **might not be any immediate downside** of VIPS not prioritising MAPs, beyond a perception that the Alliance does not value MAPs. MAPs **developers might continue as planned**, but they might **not favour products for LMICs**, which **might not be developed or take longer to develop**.
- Vaccine **manufacturers might de-prioritise working with MAP developers**, reducing developers' access to vaccines and delaying programmes.

Session 5:

RTS,S Malaria Vaccine

Malaria Vaccine Implementation Programme

IVIR-AC

21-25 Sept 2020

Rationale and Objective

Data from the MVIP may be reviewed for policy consideration as early as late 2021.

An economic analysis, including the incremental cost-effectiveness benefit of the RTS,S/AS01 vaccine when included as part of a package of malaria control interventions, will inform the policy decision.

In this session, we will:

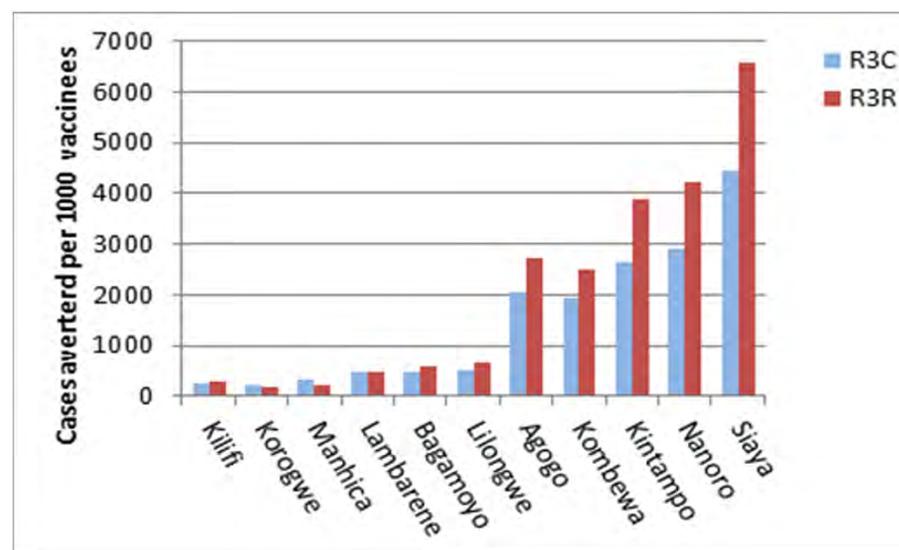
- Present an analytic framework, focusing on a package of malaria control interventions and the added benefit of RTS,S vaccine as part of that package
- Request feedback on whether IVIR-AC agrees with the CHOICE approach as the analytical framework to inform policy on the RTS,S vaccine, including the role of each of the different methods for decision making at different levels

Efficacious vaccine with potential for high impact



5-17 months, 4 doses, 4 years:

- 39% reduction clinical malaria; 29% reduction severe malaria
- 62% reduction in severe malaria anemia; 29% reduction in blood transfusions
- 37% reduction in malaria hospitalization; 18% reduction all cause hospitalizations
- thousands of cases averted/1000 vaccinated in mod/high transmission



Clinical malaria cases averted, 3 or 4 doses, by study site and transmission. *Mal-055 clinical trial, 2009-2014*

Benefits on top of those provided by ITNs

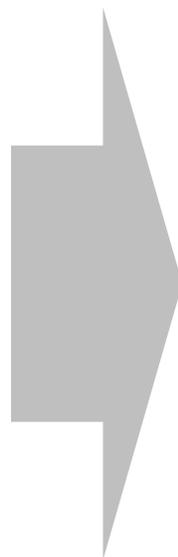
Safety:

- Well tolerated, increased risk of febrile convulsions within 7 days
- Safety signals without established causality: Meningitis (RR 10:1), Cerebral Malaria; higher number female deaths

Summary of modelled health impact using mathematical modelling



200 children
fully vaccinated



Estimated to prevent
233 malaria cases



1 death



Recommendation of pilot phased introductions



EMA provided a positive scientific opinion under Article 58 in 2015

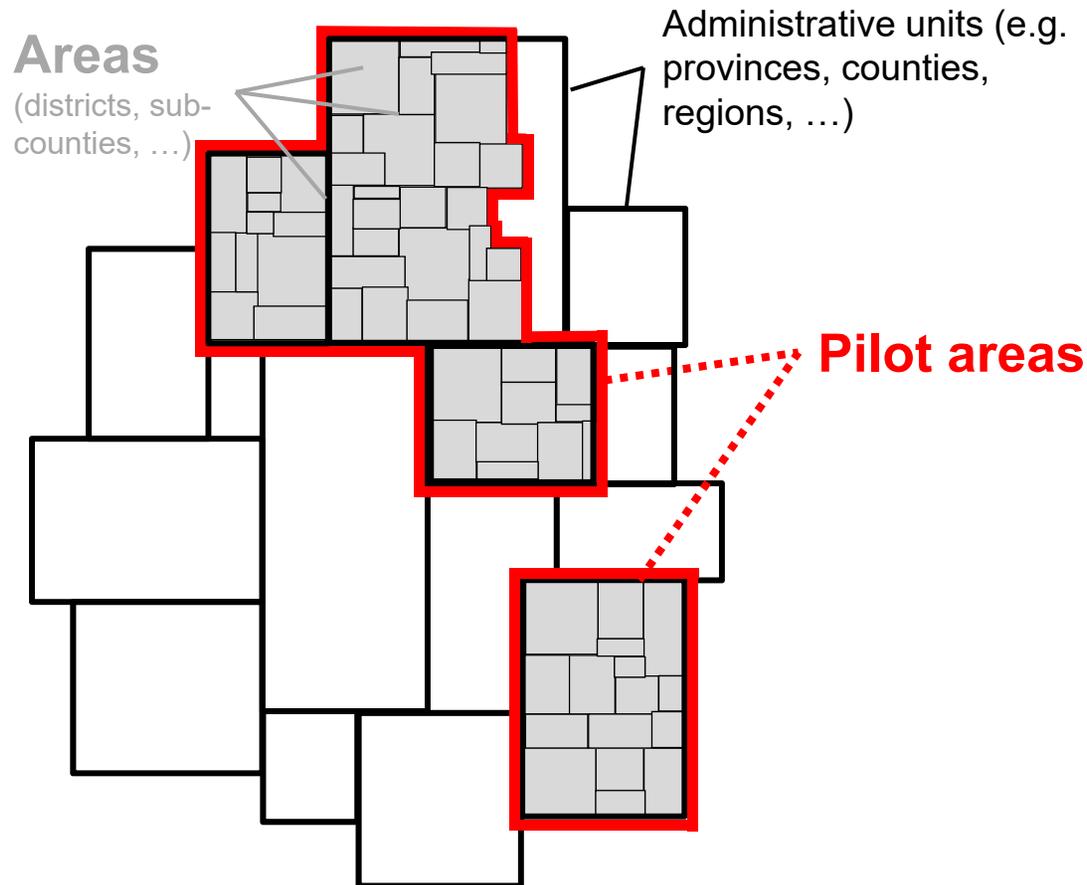
SAGE and MPAC, recognizing potential for high impact, outstanding important questions, recommended pilot phased introduction, in 3-5 countries

- Feasibility of reaching children with 4 doses
- Safety, emphasis on safety signals in Phase 3 trial
- Impact in routine use

Data generated will inform policy on wider use of RTS,S/AS01

Illustration of randomized vaccine introduction through EPI programme

Hypothetical Country



1. Identification of pilot area and units for randomized introduction

2. Set up of standardized monitoring systems in all areas to monitor safety and survival

3. Randomization of areas

 Implement RTS,S

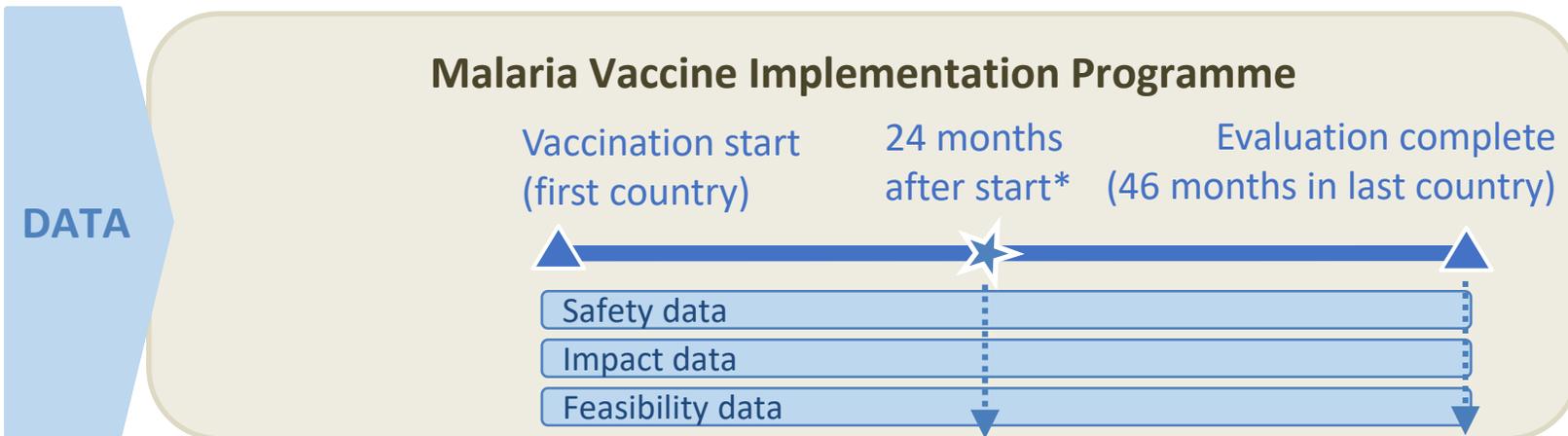
 Comparison areas

Analysis of safety, impact when RTS,S is introduced programmatically



- Primary outcome measures are based on comparison of rate ratios of outcomes of interest among children living in vaccination areas to those living in non-vaccination areas
- Outcome will be a measurement of that difference in the rate ratio in the context of the vaccination coverage reached through the EPI programme
 - e.g. we will measure if there is a higher rate ratio of meningitis in sentinel hospitals among age eligible children living in RTS,S vaccination areas compared with those living in comparator areas, when RTS,S coverage is at X%
- Although we are recording vaccination status, primary outcome measures are not specific to vaccination status

Step-wise approach to policy recommendation



POLICY

1

Policy recommendation for broader use if and when:

- i. Concerns regarding safety signals satisfactorily resolved; and
- ii. Severe malaria data trends assessed as *consistent with a beneficial impact* of the vaccine; or
- iii. Mortality data trends assessed as *consistent with beneficial impact* of the vaccine

2

Adjustments or refinements to policy recommendation if needed based on the final MVIP data set

**Timing dependent on acquisition of and rate of events (among other factors)*

Vaccine implementation



Malawi

23 April 2019 to 30 June 2020



Ghana

1 May 2019 to 30 June 2020



Kenya

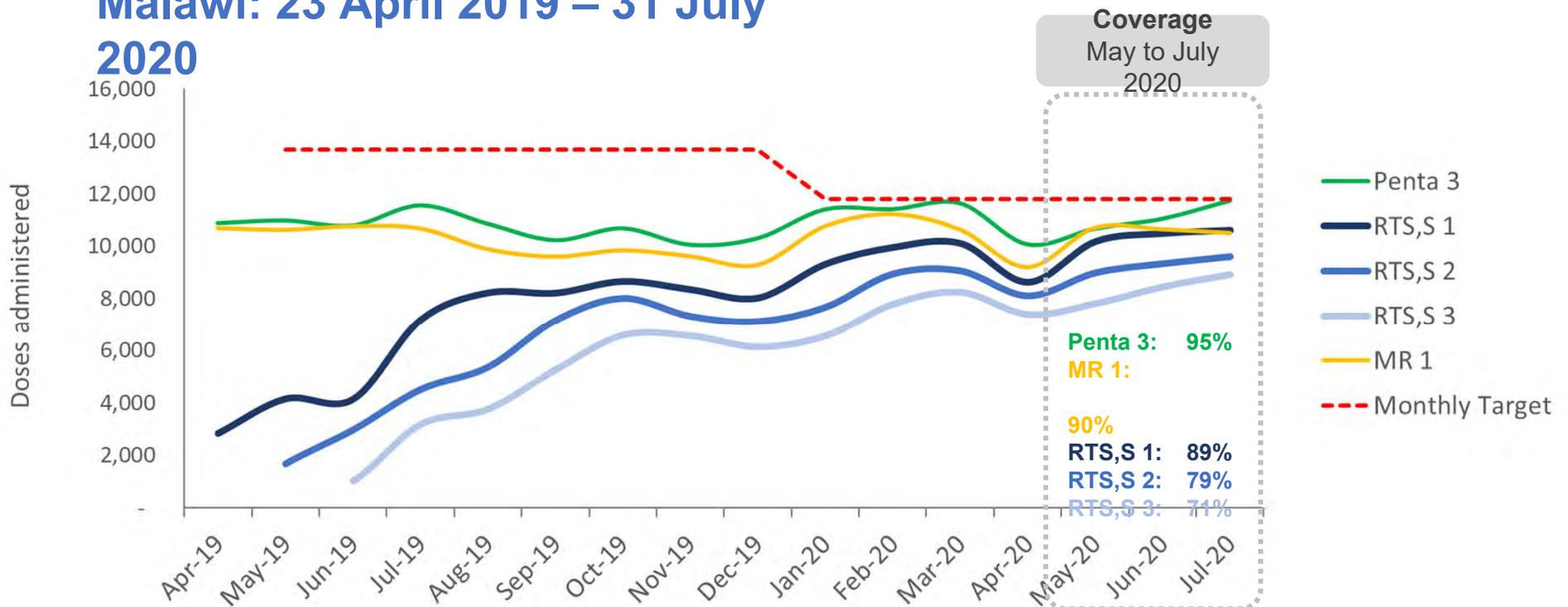
13 Sept to 30 June 2020

~1M– Total number of doses administered
~400K – Children received dose 1

1 VIP Update (WHO)

Malawi: 23 April 2019 – 31 July 2020

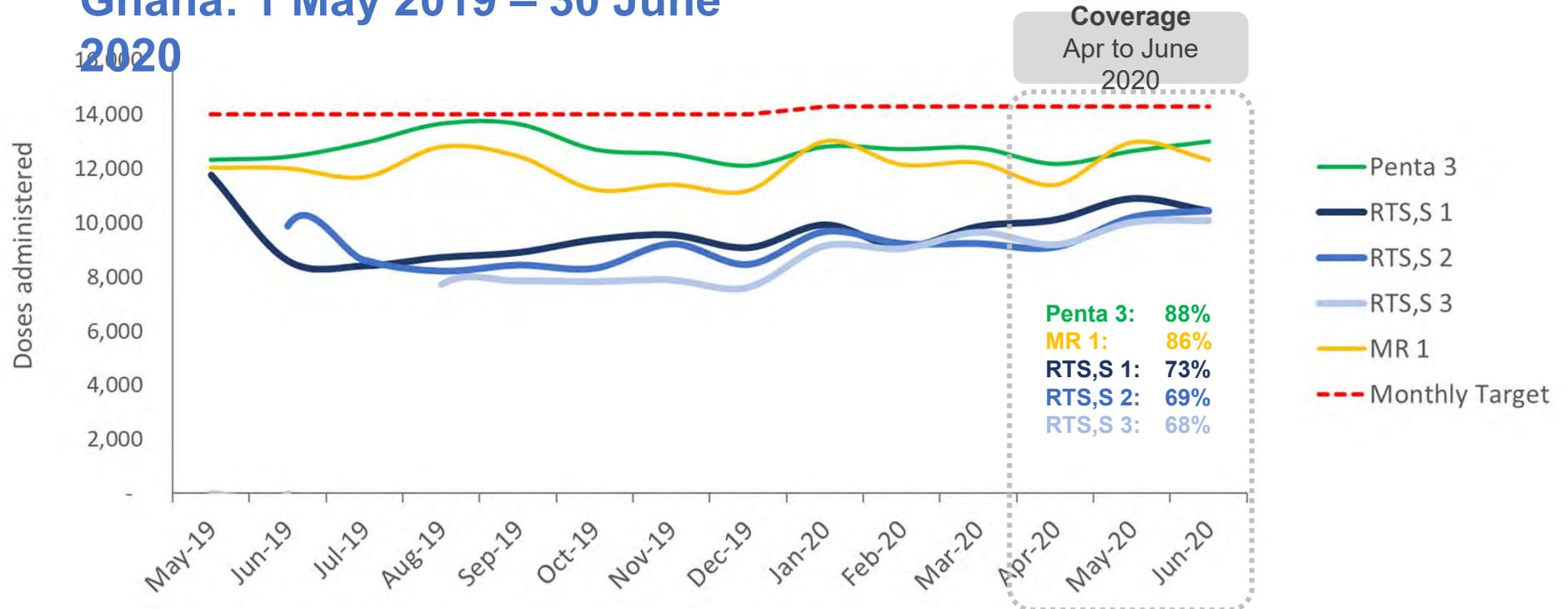
ELIANE/MARY



1 VIP Update (WHO)

Ghana: 1 May 2019 – 30 June 2020

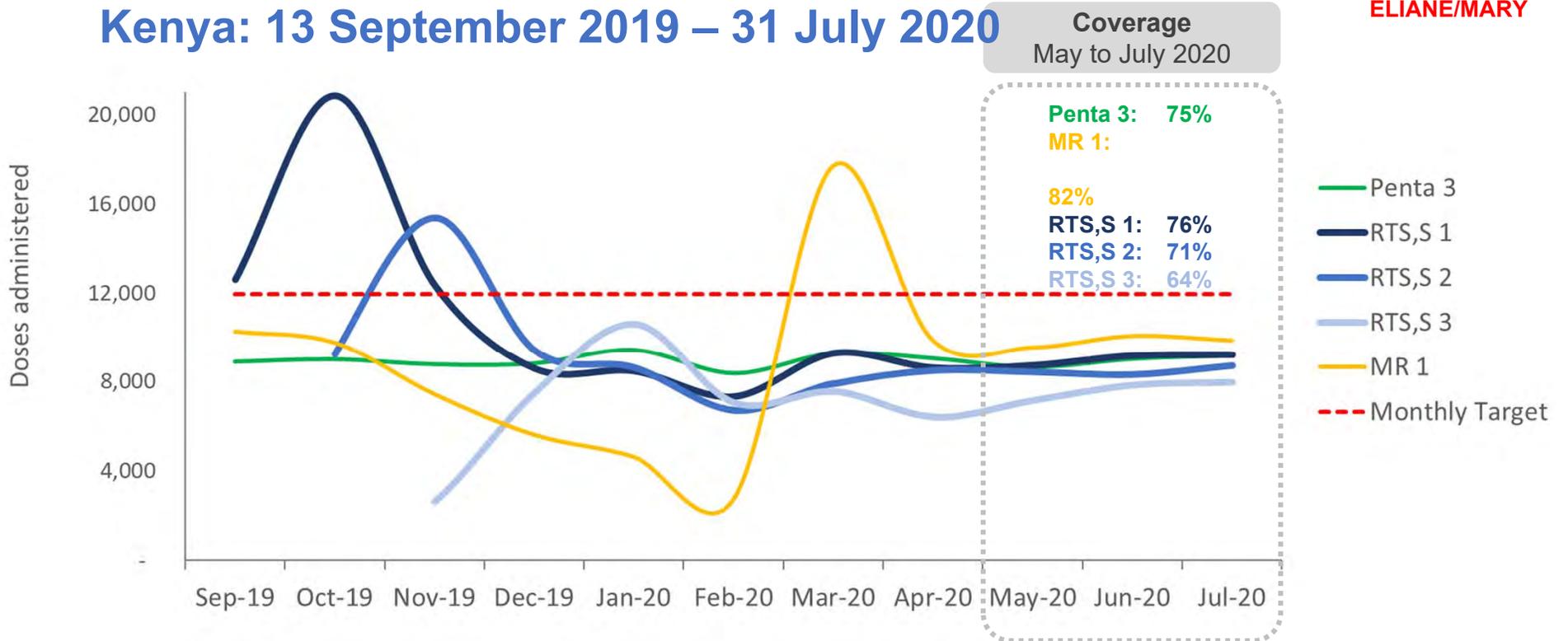
ELIANE/MARY



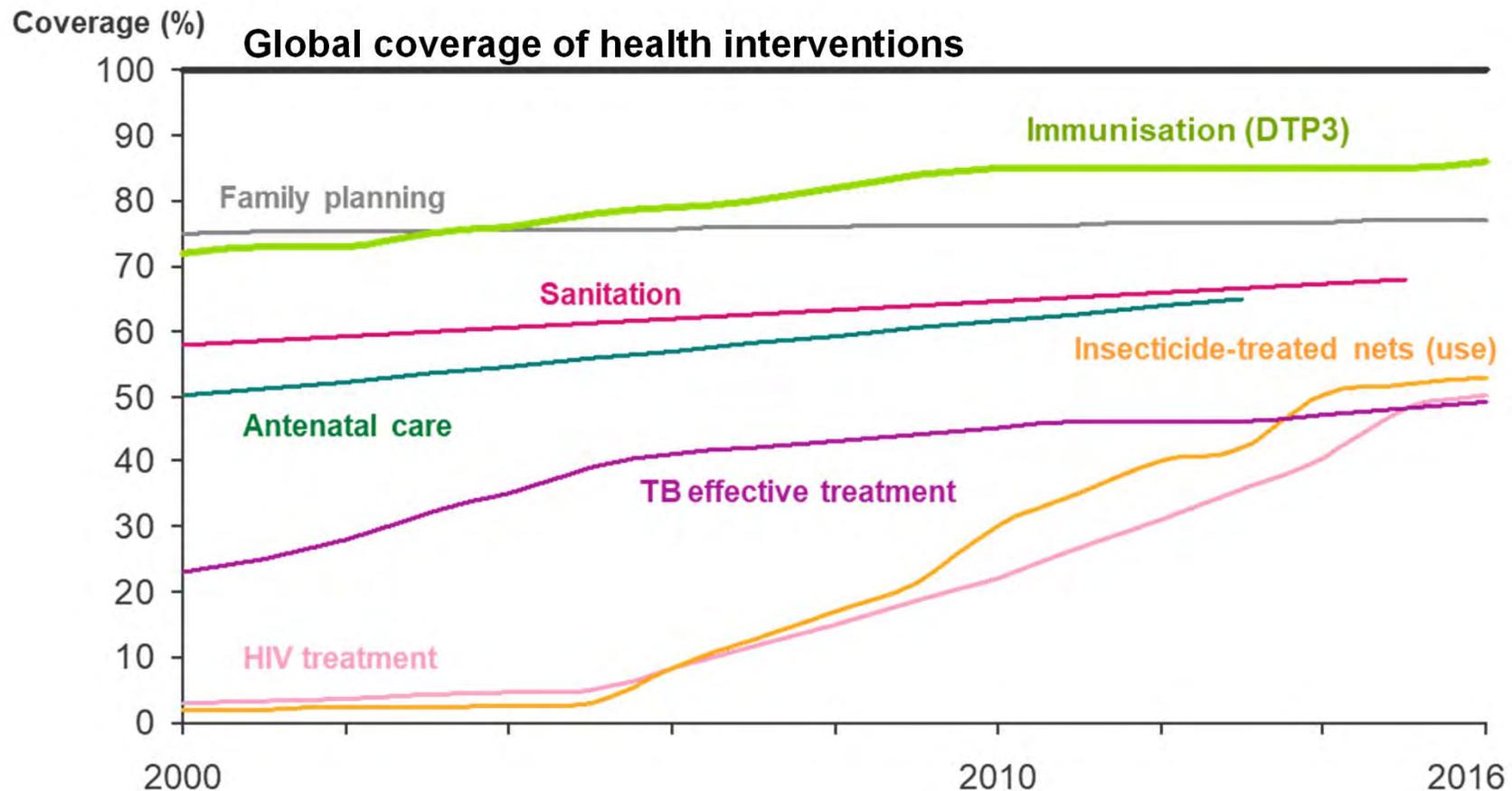
1 VIP Update (WHO)

Kenya: 13 September 2019 – 31 July 2020

ELIANE/MARY



Immunization programmes tend to have greater reach than other health interventions...



High coverage results in reach to children not protected by ITNs

IVIR-AC summary and recommendations Sep 2019



IVIR-AC advised on how to perform economic analysis of RTS,S vaccines in the context of existing preventive malaria interventions, and policy considerations

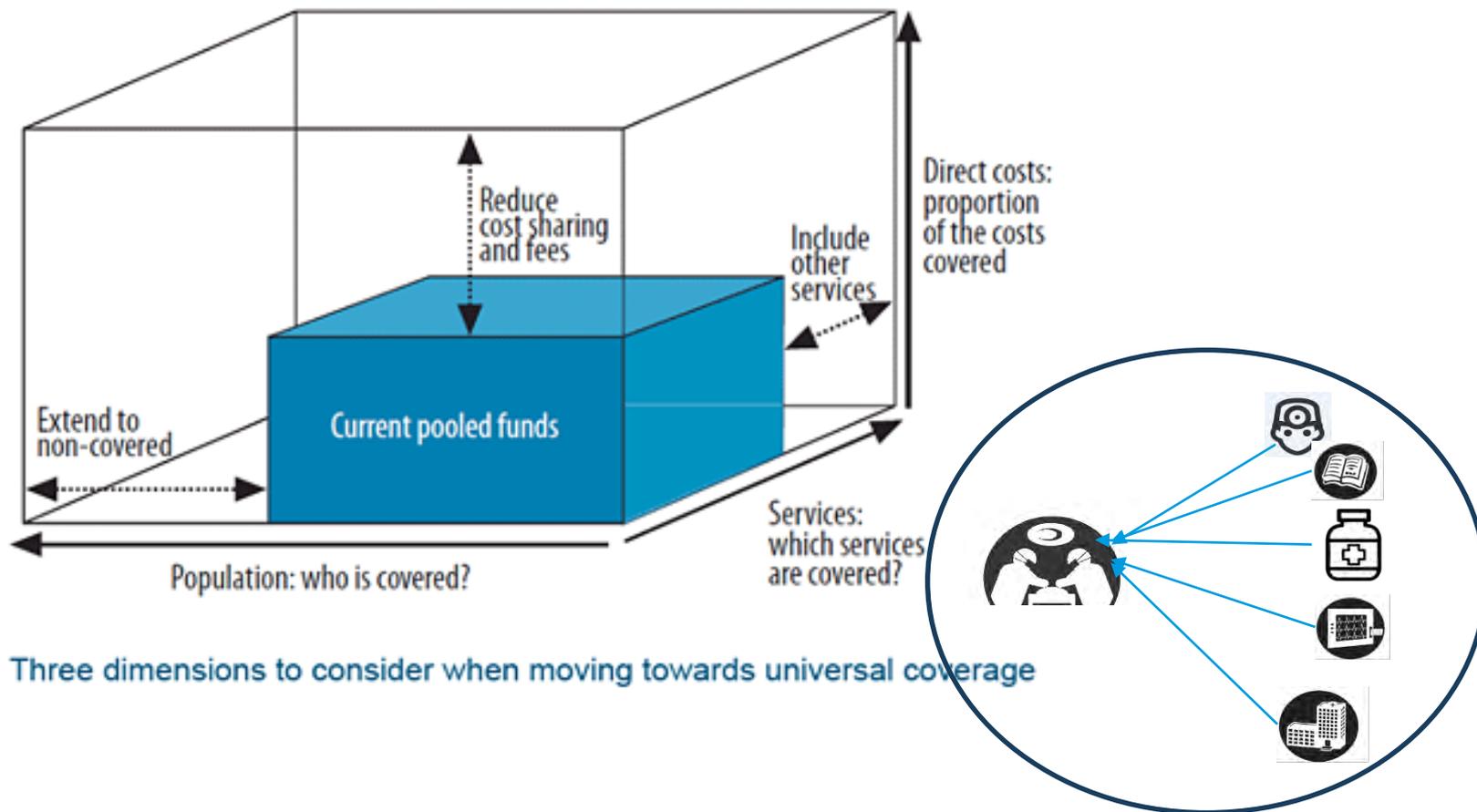
- Current malaria interventions are partially effective and challenging to implement
- Individual interventions should not be assessed as competing interventions or introduced sequentially
 - Malaria interventions should be evaluated within packages of multiple combined interventions
 - Consideration of local health systems and local malaria control and elimination policies
 - Synergistic effects and uncertainty in impact and costs of different preventive interventions (e.g. resistance, LLIN effectiveness, waning vaccine efficacy over time) should be examined
- Vaccine should be evaluated as complementing pre-existing national packages
- Modeling should account for compliance with each intervention
- Efficacy and equity should be considered, in particularly potential reductions in health disparities and provision of financial risk protection, hence economic evaluation should account for heterogeneity in SES for malaria burden, intervention coverage and delivery costs

CHOICE framework & global illustration

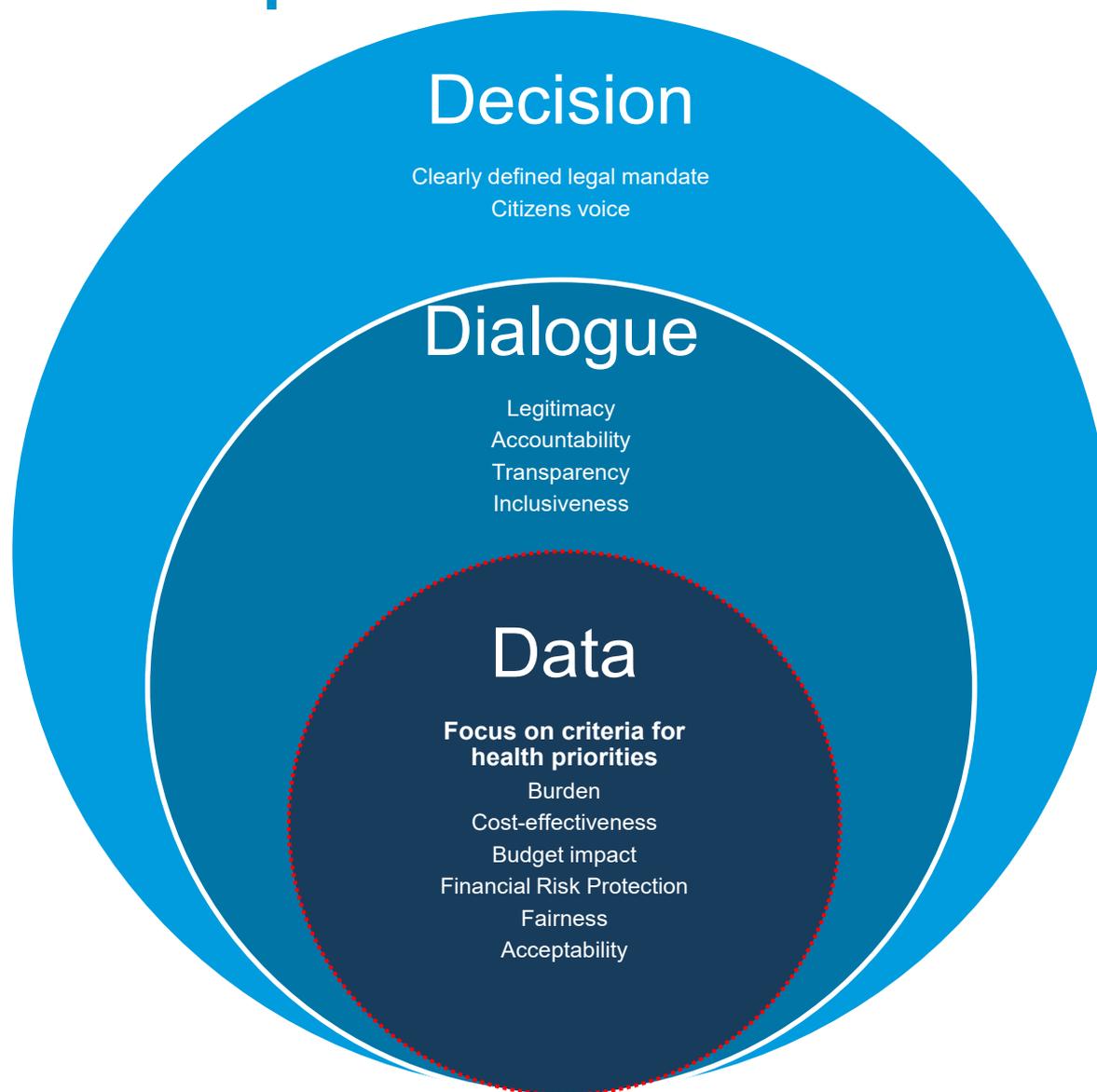
IVIR-AC

21-25 Sept 2020

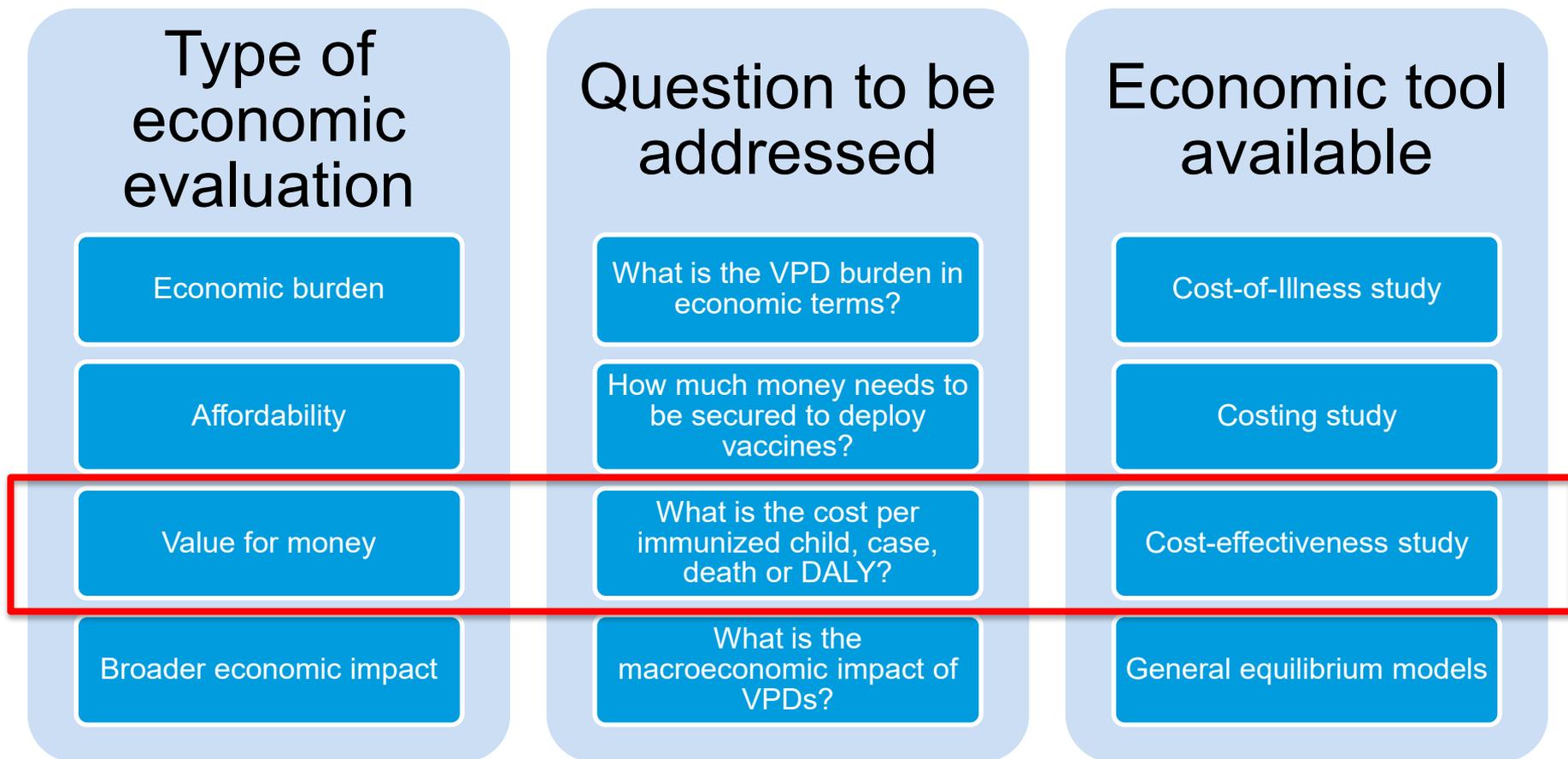
Selecting services for Universal Health Coverage



Service selection processes



Types of economic evaluations, question addressed and analytical tools

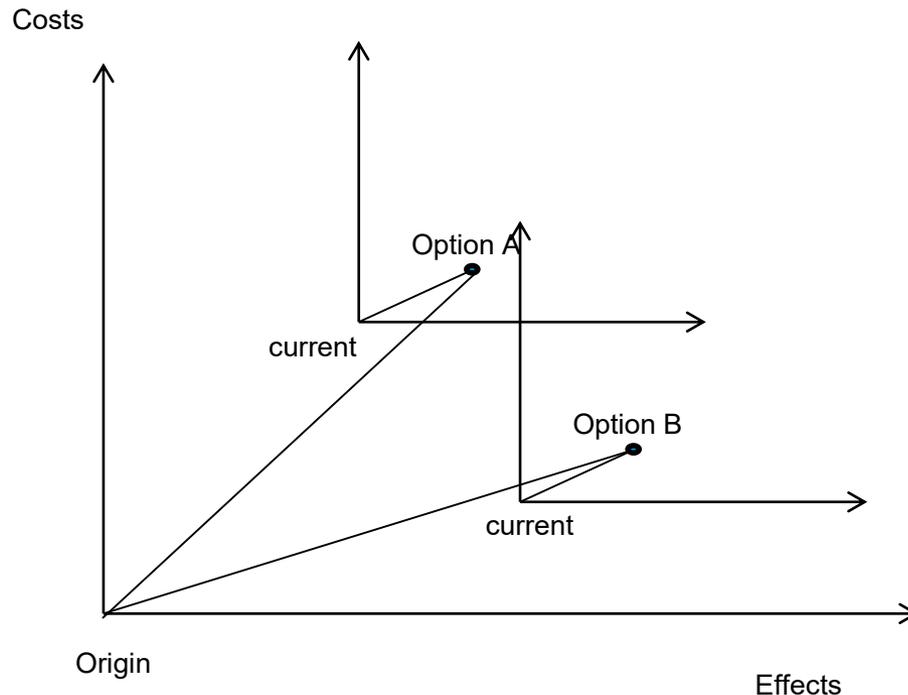


WHO CHOICE: A brief introduction



- Uses a specific form of cost-effectiveness analysis called generalised cost-effectiveness analysis
- GCEA uses a “do nothing” comparator and expresses the result as an average cost-effectiveness ratio (ACER)
- This allows comparison of all interventions in terms of value for money of in across disease areas
- Allows for measurement of the efficiency of the existing package
- Uses a common methodology and pricing database across all interventions
- Promotes standardisation of CEA to ensure it is fit-for-purpose for decision making

Generalized vs Incremental CEA

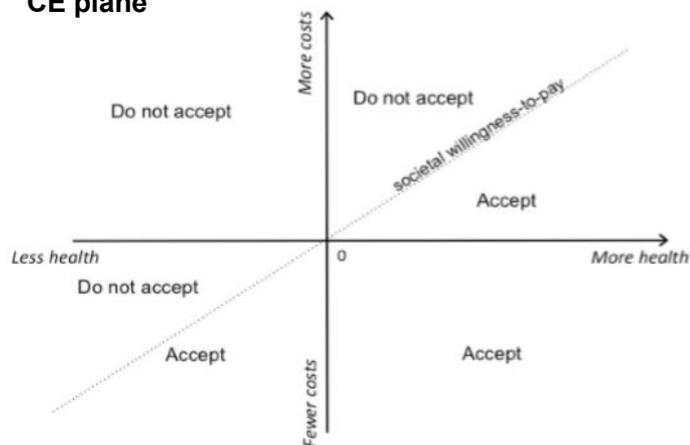


- Incremental CEA compares to the existing package of
- Implicit assumption is that current practice is the most efficient use of resources
- Used regularly in HTA programmes to support decision making at the margin of the benefits package
- Generalized CEA compares everything to the “null” or “do nothing” scenario
- Constraints and baked-in inefficiencies are modelled out
- The allocatively efficient mix of services from all possibilities is established
- Results can then be considered alongside other goals (affordability, financial risk protection)

Interpretation of CEA results

- Selected analyses should suit the policy question and be communicated in an effective manner
- Information on resource use implications - Qs (staff type, staff time, transport etc) as well as Ps
- CE plane for whether interventions result in net cost savings and/or health losses
 - Incremental CERs problematic when ICERs is negative
- Single league table to rank interventions and discuss choice of CE cut-offs
- Expansion path shows packages of services

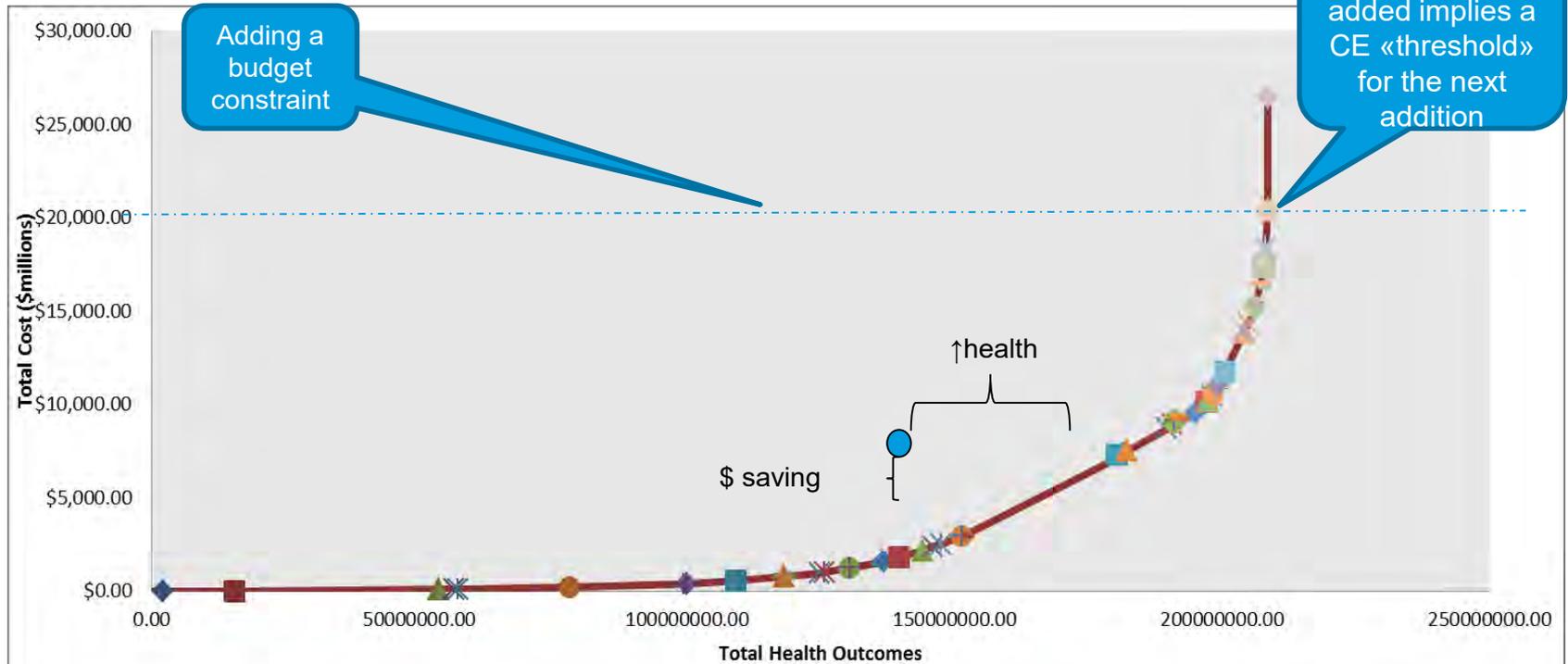
CE plane



League table

Intervention	Total costs	Total effects	ACER	MCER	ICER
X	100	10	=10 (100/10)	-	-
X1	180	12	=15 (180/12)	=40 compared to X, i.e. (180-100)/(12-10)	-
X2	63	7	=9 (63/7)	=12.3 compared to X1, i.e. (100-63)/(10-7)	-
Y	250	20	=12.5 (250/20)	-	=15 compared to X, i.e. (250-100)/(20-10)
Z	125	20	=6.25	-	=2.5 compared to X, i.e. (125-100)/(20/10)
Z2	100	16	=6.25	=6.25 compared to Z (assumes that intervention Z is perfectly divisible and exhibits constant returns to scale)	Z2 weakly dominates X because it has the same cost but is more effective

Example expansion path



- | | | | | | | | | |
|---------|--------|--------|-----------|--------|--------|--------|--------|--------|
| Optimum | UD-2 | TOB-5 | RMNCH-122 | UD-5 | UD-6 | HIV-18 | MAL-2 | TOB-7 |
| TOB-6 | HIV-24 | CVD-32 | CVD-1 | CVD-6 | COP-21 | CVD-19 | TOB-8 | TB-17 |
| CVD-32 | TB-19 | CVC-10 | CVD-40 | EPI-3 | CVD-45 | CVC-16 | AST-14 | HIV-13 |
| COP-30 | CVD-42 | MAL-3 | CVD-46 | CRC-6 | CVC-11 | PA-1 | BRC-6 | AST-13 |
| TB-22 | DEP-5 | CVC-12 | COP-28 | AST-15 | MAL-4 | COP-29 | DM-22 | CVC-18 |
| TOB-9 | CVD-47 | HIV-30 | MAL-5 | PSY-6 | CVD-48 | ANX-1 | BRC-9 | RTI-13 |
| BIP-9 | RTI-10 | CVD-49 | HIV-15 | UD-7 | TB-28 | DM-25 | RTI-11 | TB-7 |
| MAL-8 | | | | | | | | |

Session 6:

Vaccine delivery costing consensus statement

Consensus Statement on Vaccine Delivery Costs

1. Background

This consensus statement is being developed in response to a request from the World Health Organization (WHO) Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC). They requested that ‘guidance be developed for standardization of micro-costing and planning tools on new vaccine introduction on where to obtain data, at what level it should be collected, how to conduct sampling, and methods used in vaccine delivery costing.’ (Weekly Epidemiological Record, No. 24, 15 June 2018). In response to this request, an adhoc advisory group was created to oversee the development of this guidance for WHO.

The advisory group identified that multiple efforts, either in process or completed, addressed the original IVIR-AC request on data collection, sampling, and methods to be used in vaccine delivery costing. Each of these works has different purposes. In addition, they noted that there are some differences in terminology and principles being used by different groups working in this field. As a result, this consensus statement is being developed to harmonize the terminology and methods among the groups. The target audience for the consensus statement is the developers of costing tools or guidance, vaccine delivery cost researchers, and funders of costing tools and guidance. This will be useful for them so that they can apply the same terminology and methods whether developing new tools or guidance, interpreting findings on vaccine delivery, or reviewing studies/research/tools.

This consensus statement seeks to harmonize terminology and methods for future work on vaccine delivery costs, recognizing that retroactive changes to published costing tools and guidance documents that differ from the recommended terminology and methods may not be feasible. Differences in data collection and sampling methods among different costing approaches is summarized as part of the statement.

2. Objectives of the Consensus Statement for the Immunization Costing Community

The objectives of the consensus statement are the following:

- To highlight and explain commonalities and differences across different costing approaches, tools, and guidelines;
- To affirm the existence of different types and objectives of costing;
- To promote continued improvement and innovation in methods and tools that are fit for purpose;
- To advance the immunization economics community of practice by committing to follow certain principles and common definitions (as detailed in Annex) that will make the collective costing work more easily interpretable and useful ¹.

¹ However, we do acknowledge that there are limits to standardization and some deviations will occur.

To achieve these objectives, the advisory group reviewed guidance documents and costing tools for vaccination delivery and the terminology, definitions, and principles. Recommendations for costing principles and terminology for the workstreams were developed.

3. Vaccination Delivery Cost Analyses

Efforts to cost immunization programs, strategies, and new vaccine introductions have utilized various methodological approaches which are described below. The approach selected is usually based on the purpose of the analysis and type of information that decision-makers need. The advisory group qualitatively characterized workstreams based on their knowledge of groups currently working in the field following a 2019 International Health Economics Association pre-congress session on vaccine economics in Basel, Switzerland. These characterizations were intended to help elucidate where and why differences in definitions and methods were occurring, and were not derived from any prior framework.

Major current workstreams on costing of vaccine delivery and immunization program costing identified by the advisory group are the following:

- i. **Retrospective routine immunization cross-sectional costs:** The first workstream is focused on estimating retrospective (i.e., already incurred) routine immunization cross-sectional costs, typically using a full costing approach. This method provide a range of unit costs (cost/dose, cost/child, cost/fully immunized child [FIC]) by facility, district, and higher level in the health system for total routine immunization delivery costs. Costs are economic or financial costs. It includes, for example, the work conducted in the EPIC studies and other work by groups such as the Harvard School of Public Health, Witts University, Curatio Foundation, PAHO, ThinkWell, UNICEF, Johns Hopkins University and PATH. The purpose is to determine delivery costs of the entire routine immunization program as it currently operates for benchmarking or to explain variation in facility costs and unit costs (e.g., cost determinants, efficiency).
- ii. **Retrospective single-vaccine costs:** The second approach is to estimate retrospective ² costs at a given point of time for a specific vaccine, typically using incremental costing. Examples of such studies are being applied by groups such as ThinkWell, International Vaccine Institute (IVI), WHO, and Centers for Disease Control and Prevention (CDC). Costing tools used to estimate retrospective costs include, but are not limited to (see Annexes for websites for these tools):
 - the IVI/WHO CHOLTOOL
 - the WHO Cervical Cancer Prevention and Control Costing Tool (C4P)
 - the WHO Seasonal Influenza Immunization Costing Tool (SIICT)

² Retrospective estimation of incremental vaccine-specific campaign and new vaccine introduction costs differs from full costing of routine immunization in requiring some implicit or explicit estimation of counterfactual resource use in the absence of that campaign or vaccine introduction. This is often done through data collection at a single point in time (post-campaign or post-introduction) with reference to documents and recall by key informants to estimate which resource use was specifically incremental.

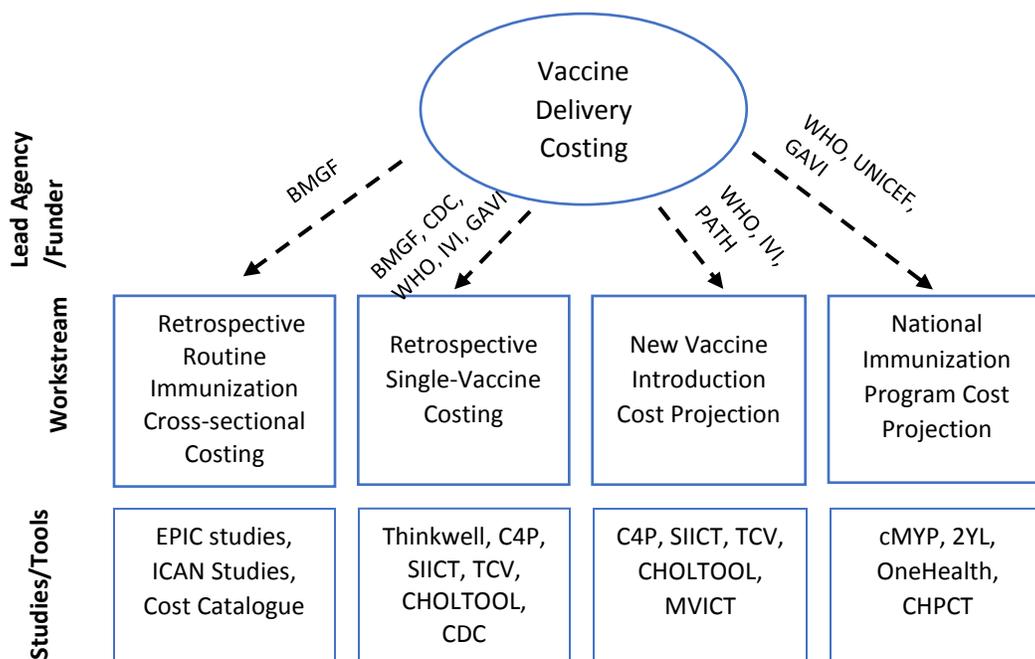
- the WHO/IVI Typhoid Vaccine Costing Tool (TCVC)
- the PATH Malaria Vaccine Immunization Costing Tool (MVICT)

Incremental costing of a specific vaccine, whether delivered through campaign or routine, differs substantially from full costing of routine immunization because it involves not only estimating the proportion of shared health system resources used for immunization but also the extra step of allocation by vaccine. In particular, campaign delivery may differ in frequency, administrative levels (sometimes sub-national rather than national), whether these are preventive or response to outbreaks (e.g., oral cholera vaccine [OCV] provision), for catchup, and whether these involve populations other than young children and pregnant women such as health workers, adolescent girls, or all ages over 1 for OCV. When conducted for a campaign approach, the purpose of these cost analyses may be for retrospective evaluation of campaign costs (including as an input to cost-effectiveness analyses), explaining variation in costs by strategy and venue, and cost projections for planning and decision-making on conducting campaigns. When estimating retrospective costs of new vaccine introduction, whether via campaign or routine immunization, the purpose of these analyses may be to inform country planners and decision makers and global funders on the costs of introduction and recurrent costs over time. Both financial and economic costs are estimated.

- iii. **Projection of new vaccine introduction costs:** The third approach is estimation of new vaccine introduction costs through projection of the price and quantity of ingredients (e.g., time, equipment, vaccines, etc.) needed for vaccine introduction typically using incremental costing for a specific period, e.g., one or five years. The prices and quantities of ingredients are obtained through interviews with program managers and facility visits to obtain current information on these (e.g., personnel time, supplies, and equipment). The projections are conducted with the following costing tools (often the same costing tools as found in the second workstream) - e.g., C4P, SIICT, TCVC, CHOLTOOL, and MVICT. Examples of such studies have been conducted by BMGF (Zambia study), WHO, IVI, CDC, and PATH. The purpose of these cost projections is for planning and decision-making on new vaccines during the introduction period. Costs are shown for both financial and economic costs and include cost per dose and FIC as well as total annual costs.
- iv. **Projection of national immunization program cost:** The fourth workstream is immunization program cost projection (e.g., comprehensive multi-year plan [cMYP], 2nd Year of Life (2YL), OneHealth) where the total cost of a national program is estimated for a baseline year and then the costs of the next five years are projected. This is a type of costing for strategic planning to assist in budgeting, resource planning and mobilization over a five-year period. These projections estimate fiscal costs; also, both annual and five-year costs are estimated.

Figure 1 shows the four workstreams, their lead agencies/funders, and associated studies/tools.

Figure 1. Major Current Workstreams in Vaccine Delivery Costing identified by Advisory Group



4. Review of existing Guidance Documents and Costing Tools

Annex Tables A1a and A1b show the twelve existing guidance documents and ten tools for costing vaccine delivery and immunization programs. These were identified by the advisory group as of July 2020. Note that this list is based on advisory group members’ personal knowledge and prior reference to them in conducting immunization delivery costing and may not be exhaustive. A few of these guidance documents and tools are for costing health services more generally, such as the OneHealth Tool and the Community Health Planning and Costing Tool (CHPCT).

The review showed that some gaps in costing guidance for the workstreams exist, particularly for the cost projections for vaccine introduction.

Terminology and definitions of costs in workstreams

Annex Table A2 shows definitions of costing terminology found in the guidance documents. The guidance documents have similar definitions of financial and economic costs, and recurrent and capital costs, but vary in the level of details of the definitions. Most guidance documents do not describe in detail issues of interactions³ between terminology, perspective, financial vs. economic costs⁴, and how incremental costing affects financial vs. economic costing⁵. For example, incremental costs for financial costs will differ depending on the perspective of the analysis; if the

³ An Interaction is the action or influence of things on one another (Merriam-Webster.com).

⁴ For example, financial costs only include resources paid for by the ‘buyer’ or ‘provider’ and will therefore be affected by the perspective chosen for the analysis.

⁵ The definitions are not clear about what resources that already exist before the intervention (e.g. cold chain equipment) should be included in economic costs and how excess capacity should affect these (e.g., whether the costs should only be included if there is no slack capacity to absorb the new intervention resource requirements).

perspective is of the public health provider, resources donated by external entities will not be included.

Annex Table A3 compares the costing principles in the guidance documents with the Global Health Cost Consortium (GHCC) Principles and Methods Reporting Checklist (GHCC 2017). Guidance documents vary in the extent to which costing principles are discussed. Most guidance documents refer to study purpose, classification of costs, time horizon of data collection, presentation of costing methods, and depreciation of capital costs. Other principles such as describing timing of data collection and listing sources for price data are only discussed by one or two of the guidance documents (see discussion in annex).

Annex Table A4 compares the level of data collection, activities/cost categories, perspective, and definitions of cost terms and perspective among the workstreams and shows the variations among these. Annex Table A5 shows differences in data sources, sampling, and characterization of uncertainty by workstream.

Areas for clarification and harmonization

Based on the review, some specific areas that need further clarification and harmonization have been identified by the advisory group in terms of data collection, sampling, and characterization of uncertainty, and are shown in Annex 5.

5. Recommendations for Costing Principles for the Methodological Approaches

Annex 6 shows the recommended costing terms and principles for the workstreams to adhere to in their guidance documents and costing tools in their future work. The recommended costing principles are shown below as well as in Annex 6.

1. The study scope in terms of its purpose, audience, target population, time horizon, and service/output should be clearly stated. It should also state whether data collection will be prospective or retrospective, and whether the analysis will be retrospective or a cost projection.
2. The perspective of the cost estimation should be stated and justified.
3. Types of costs to be generated should be clearly defined in terms of startup/introduction or non-startup/introduction, recurrent and capital, fiscal, financial or economic, and incremental or full. Capital costs should be appropriately annuitized and depreciated for financial and economic costs, the discount rate justified.
4. The scope of the inputs to be estimated should be defined, justified and if needed referenced. For example, do the costs include national and sub-national costs or only facility service delivery costs? Are non-immunization costs included?
5. The 'units' in the unit costs for strategies, services and interventions should be defined – e.g., cost per dose administered or cost per FIC.
6. If incremental costing is conducted, any assumptions made regarding existing health system capacity should be described. (See GHCC reference case, pg. 64).
7. The selection of the data sources, including for any adjustments to price data (e.g., inflation or currency conversion) should be described and referenced.

8. The methods for estimating the quantity of inputs should be described – whether top-down or bottom-up, methods of allocation, use of shadow prices and opportunity cost of time, and, if relevant, methods for excluding research and evaluation costs.
9. Costs should be mapped and reported as either inputs or activities:
 - i. Resource inputs include, for example, personnel time, vaccines, injection and safety supplies, vehicles, fuel, per diem and travel allowances, cold chain equipment, stationery, laboratory equipment, and buildings;
 - ii. Program activities include, for example, vaccine procurement, service delivery, training, micro-planning, social mobilization and information, education and communication (IEC), monitoring and evaluation, surveillance, non-research evaluations, AEFI monitoring, and supervision.
10. Some boundaries around costs included in the analysis may be employed to keep the costing scope feasible, with the rationale for any exclusions provided (e.g., unless otherwise specified and justified, research costs should not be included; use discretion about including one-time costs that are unique or unlikely to be replicated or transferable across settings such as new vaccine launches with the President; clarify definition and threshold for small costs that have expected small (e.g. <\$25) contribution to total costs in aggregate across all sampled units, such as use of existing office supplies by health facility staff).
11. The sampling strategy employed should aim for internal and external validity of the data. Sampling strategy should be stated, described, and justified, depending on the workstream and costing objectives. Sampling of different service delivery units is desirable as it provides a more representative picture of costs and highlights cost variation and cost drivers for a strategy or vaccine.
12. The uncertainty around the cost estimates should be appropriately characterized (e.g., . sensitivity analyses; ranges of results for different input parameter scenarios for cost projections; mean and standard deviation for non-representative samples with multiple units; and confidence intervals or credible intervals for retrospective analyses).
13. Inclusion and exclusion criteria: ‘stopping rules’ should be defined, explaining which costs are included and the respective rationale.
14. Cost estimates should be communicated clearly and transparently to enable decision-makers to interpret and use the results.

Annex 1. List of Existing Guidance and Costing Tools for Vaccination Delivery Costing

Table A1a presents the list of guidance documents with their year of publication, target interventions, and purpose as identified by the advisory group. One document is a training manual for costing primary health care services, one document is a reference case for costing global health care interventions, and the rest are specifically about costing of vaccine delivery. Note that some publications such as the methodology for costing campaigns and a textbook on vaccine economics are forthcoming.

Table A1a. List of guidelines by publication year, target interventions, and purposes

Developer	Guidelines	Publication years	Target Interventions	Purposes	Link
WHO	Cost analysis in primary health care: A training manual for program managers	1994	Primary health care	Assist health program managers to cost their services for planning and evaluating efficiency	https://apps.who.int/iris/handle/10665/40030
WHO	Guidelines for estimating costs of introducing new vaccines into the national immunization system	2002	New vaccine programs	Assist countries in planning for introduction of new vaccines	https://apps.who.int/iris/handle/10665/67342
	WHO guide for standardization of economic evaluations of immunization programs	2008 (edition I), 2019 (edition II)	Existing and new vaccine programs	Methodology for cost and cost-effectiveness analyses of vaccines	https://apps.who.int/iris/bitstream/handle/10665/69981/WHO_IVB_08.14_eng.pdf;jsessionid=1066569981?sequence=1 https://apps.who.int/iris/rest/bitstreams/retrieve
EPIC	Common Approach for the costing and financing analyses of routine immunization and new vaccine introduction costs	2013	Existing and new vaccine programs	Methods for data collection for routine programs and new vaccine introduction (including delivery costs) and financial flows	http://static1.squarespace.com/static/556deb8ee4b08a534b8360e7/t/55970258e4b03cf942da51ac/1435959896232/WEBSITE_Common+Approach.pdf
	How to Cost Immunization Programs - A practical guide on primary data collection and analysis	2020		Practical guidance on how to conduct a facility-based exercise on immunization program costs, including sampling and analytical techniques	http://immunizationeconomics.org/recent-activity/2019howtocost
Global Health Cost Consortium (GHCC)	GHCC Reference Case	2017	Health interventions in general	Improve quality of cost estimates	https://ghcosting.org/pages/standards/reference_case

Developer	Guidelines	Publication years	Target Interventions	Purposes	Link
WHO	C4P User Guide, Vaccination Module	2012-2019	HPV vaccination programs	Instructions for users of costing tool	TBD
IVI/WHO	CHOLTOOL User Guide	2015	Cholera-specific vaccination programs, including campaigns	Instructions for users of costing tools	https://www.tandfonline.com/doi/full/10.1080/21645515.2020.1747930
WHO	Flutool plus (SIICT): introduction planning and costing	2017	Seasonal influenza vaccination, including campaigns	Instructions for users of costing tool	https://www.who.int/immunization/research/development/Influenza_economics/en/
WHO/IVI	Typhoid Conjugate Vaccine Costing Tool User Guide	2019	Typhoid Congugatesp ecific vaccination programs, including routine and campaigns	Instructions for users of costing tools	TBD
PATH Costing Tool User Guide	Malaria Vaccine mmunization Costing Tool	2019	Vaccine-specific vaccination programs	Instructions for users of costing tools	https://www.path.org
ICAN	Methodology note for systematic review, cost catalogue, and analytics How to conduct the cost of a campaign: methodological guidance” to be completed in 2020	2019	Immunization delivery costs	Designed for users of data, including national and sub-national planners and policymakers, researchers, and international partners supporting country immunization and health system policy, planning, and financing	http://immunizationeconomics.org/ican-idcc-methodology

Table A1b shows the characteristics of costing tools ¹ that have been developed for costing vaccine delivery or immunization programs that were identified by the advisory group. It includes six tools for costing the introduction of single antigens, two to estimate immunization program costs, one for estimating costs of vaccination in the second year of life, and one for estimating the cost-effectiveness of introducing a new vaccine or vaccine technology. Characteristics were self-reported by the tool developers on the advisory group.

Table A1b. List of Costing Tools for Vaccine Delivery or Immunization Program

	Delivery Modality	Antigens included	Retrospective vs. prospective data collection	Retrospective vs. projection analysis	Full or incremental costs	Economic vs. financial (or fiscal)	Intended Perspective	Intended Data Sources	Sampling	Intended User of Results
WHO C4P	Health facility; School; Multiple	HPV	Retrospective	Retrospective; Projection	Incremental	Economic; Financial; Initial Investment	Government; Provider; or Payer	Interviews; Financial records; Expert opinion	No guidance	Planning; RM; CEA
IVI CHOLTOOL	SIA/ campaign	Oral Cholera Vaccine	Retrospective	Retrospective; Projection	Incremental	Economic; Financial	Government; or Payer	Interviews; Financial records; Expert opinion	No guidance	Planning; RM; CEA
WHO SIICT	Health facility; SIA/ Campaign ; Outreach; Multiple	Influenza	Retrospective	Retrospective Projection	Incremental	Economic; Financial	Government; Provider; or Payer	Interviews; Financial records; Expert opinion	No guidance	Planning; RM; CEA
WHO/IVI TCV	Health facility; SIA/ Campaign ; Outreach; Multiple	Typhoid Congulgate	Retrospective	Retrospective; Projection	Incremental	Economic; Financial	Government; Provider; or Payer	Interviews; Financial records; Expert opinion	No guidance	Planning; RM; CEA
PATH MVICT	Health Facility; Outreach	RTS,S	Retrospective	Retrospective Projection	Incremental	Economic; Financial; Initial Investment	Government; or Provider	Interviews; Financial records;	No guidance	Planning; RM; CEA

¹ Costing tools perform analysis and some have accompanying data forms such as the IVI CHOLTOOL

	Delivery Modality	Antigens included	Retrospective vs. prospective data collection	Retrospective vs. projection analysis	Full or incremental costs	Economic vs. financial (or fiscal)	Intended Perspective	Intended Data Sources	Sampling	Intended User of Results
								Expert opinion		
WHO cMYP	Health facility; SIA/ Campaign ; Outreach; Multiple	All	Retrospective	Retrospective Projection	Full	Fiscal	Government	Interviews; Financial records; Expert opinion	No guidance	Planning; RM
UN OneHealth Tool	Health Facility; Outreach; Multiple	All	Retrospective Prospective	Projection	Incremental	Financial	Government	Interviews; Financial records; Expert opinion	No guidance	Planning; Budgeting; RM; CEA
PAHO ProVac/ Costvac	Health Facility; Outreach	All	Retrospective	Retrospective	Full	TBD	Government Provider Payer	Interviews; Financial records; Expert opinion	Random selection; Convenience	Budgeting; Efficiency
UNICEF second year of life (2YL)	Health Facility	All	Retrospective	Projection	Incremental	Economic; Financial	Health sector Government	Interviews; Financial records; Expert opinion	No guidance	Planning
PATH VTIA	Health Facility; Outreach	All	Retrospective	Projection	Incremental	Economic	N/A	Interviews; Financial records; Expert opinion	Convenience	Planning; Decision-making

Abbreviations: C4P = Cervical Cancer Prevention and Control Costing (https://www.who.int/immunization/diseases/hpv/cervical_cancer_costing_tool/en/); CHOLTool = Oral Cholera Vaccine Costing Tool; SIICT = Seasonal Influenza Immunization Costing Tool; TCV = Typhoid Conjugate Vaccine; MVICT = Malaria Vaccine Immunization Costing Tool; cMYP = Comprehensive Multi-Year Plan; 2YL = Second Year of Life; VTIA = Vaccine Technology Immunization Assessment; RM = Resource Mobilization; CEA = Cost-Effectiveness Analysis

Annex 2. Definition of Costing Terminology

Table A2 shows the definition of costing terms presented in the various guidance documents. Most of the guidance documents have similar definitions of financial and economic costs, capital costs, and incremental costs but differ in the level of detail in their explanations. Fewer documents (less than three) have definitions of cost projections, prospective and retrospective costing, perspective, and bottom-up and top-down costing. The GHCC guidance document has the most definitions while other guidance documents focused on methods.

Other differences among the guidance documents are variations in definitions of vaccine delivery cost and prospective costing. The EPIC and ICAN definition of vaccine delivery are that it includes costs of delivering vaccines, exclusive of vaccines. The costing tools, however, use the term service delivery for operational costs of delivering vaccines, exclusive of vaccines, while ‘vaccine delivery cost’ includes all the value of all resources involved in the immunizations. Prospective costing is defined as ‘direct observation’ in EPIC and as projection of costs in the costing tools.

Table A2. Definitions of Costing Terms in Guidance Documents

	WHO 1994	WHO 2002	ICAN & EPIC (including How to Cost Immunization Programs)	GHCC	Costing Tools’ User Manuals	cMYP Guideline	Recommend ation
Vaccine delivery cost	NA	NA	Costs associated with delivering immunizations to target populations, exclusive of vaccine costs (pg.31)	NA	Vaccine delivery includes startup costs, service delivery (personnel time, supplies and transport/allowance), vaccine procurement, monitoring and supervision, and other costs (C4P guide, pg. 262)	NA	Use ICAN/EPIC definition, specify whether is inclusive or exclusive of vaccines and that includes startup, recurrent and capital.

	WHO 1994	WHO 2002	ICAN & EPIC (including How to Cost Immunization Programs)	GHCC	Costing Tools' User Manuals	cMYP Guideline	Recommend ation
Financial cost	NA	Actual expenditure for resources used for goods or services purchased. Does not include cost of existing health personnel time or donated goods (pg. 2)	Financial outlays, usually with straight-line depreciation of capital items (pg. 31)	Capture the resources that are 'paid' for (pg. A-8)	Actual monetary flows of the buyer such as the Ministry of Health. Does not include the value of resources already paid for, such as personnel time. (SIICT guide, pg. 21)	NA	Composite of three definitions, noting that perspective affects the specification of the ingredients.
Economic cost	Value of resources used to produce something, including a specific health service or a set of services (pg. 13)	Resources that have been foregone for alternative uses, or opportunity costs (pg. 2)	Financial outlays plus opportunity costs such as health worker time and any donated items such as vaccines (pg. 31)	The value of the highest value alternative health intervention opportunity forgone; captures the full value forgone of all resources used. (pg. A-8)	Estimates all costs of an intervention, regardless of the source of funding, so that the opportunity cost of all resources is accounted for in the analysis, includes in-kind and donor contributions. (SIICT guide, pg. 21)	NA	ICAN/EPIC definition, with clarification that includes resources from all payers/ resource providers.
Fiscal Costs (called initial investment in costing tool guides)	NA	NA	Financial outlays, usually without depreciation of capital items (pg. 31)	NA	Initial upfront resource requirements (C4P guide, pg. 268)	NA	ICAN/EPIC definition
Start-up or introduction costs	NA	NA	NA	NA	Initial one-time programmatic activities and include micro-planning, initial training activities, and initial sensitization/ social mobilization/ IEC (SIICT guide, pg.21)	NA	Costing tool User Manual definition, with clarification on difference between initial and continuing activities.
Recurrent cost	NA	Items that are used up during a year (pg. 3)	NA	Value of resources/inputs with useful lives of less than one year (pg. 61)	Goods or items used in the delivery of a service or intervention that last less than a year, e.g.	Costs of resources consumed within one year (CMYP)	Composite definition.

	WHO 1994	WHO 2002	ICAN & EPIC (including How to Cost Immunization Programs)	GHCC	Costing Tools' User Manuals	cMYP Guideline	Recommend ation
					personnel salaries. (SIICT guide, pg. 21)	guide, pg. 19)	
Capital cost (sometimes called investment cost)	Inputs that last for more than one year (pg. 6)	Items that last longer than one year and are therefore incurred only every few years rather than annually (pg. 3)	NA	One-time costs for items that have a useful life of over one year (pg. B-23)	Goods that last for longer than one year, such as equipment (SIICT guide, pg. 21)	An input that has a useful life of more than one year. (cMYP guide, pg. 19)	Composite definition.
Incremental cost	NA	Only looks at the cost of an addition, e.g. a new vaccine, to existing services (pg. 2)	Additional costs associated with introducing new vaccines or making changes in delivery (pg. 32)	Cost of adding a new or a batch of services or intervention over and above an existing program (pg. 59)	Additional resources required to add an intervention to an existing immunization program (CHOLTOOL guide, pg. 6)	NA	Composite of definitions, with clarification that if resources are not slack, then have to account of opportunity cost
Full costs	NA	NA	The sum of all costs associated with vaccination delivery (pg. 31)	NA	NA	NA	ICAN/EPIC definition, with clarification that includes vaccines and basic infrastructure.
Prospective	NA	NA	(Direct observation pg. 21)	Direct observation of resource use (pg. 31)		NA	Composite of definitions, with clarification that costs are collected concurrently with interventions implementation

	WHO 1994	WHO 2002	ICAN & EPIC (including How to Cost Immunization Programs)	GHCC	Costing Tools' User Manuals	cMYP Guideline	Recommend ation
Retrospective	NA	NA	NA	Data collection takes place after resource use		NA	GHCC definition
Cost projections		NA	NA	NA	NA	Total future costs of both recurrent and capital inputs to the NIP (cMYP guide, pg. 108)	cMYP definition with clarification that is for intervention or program
Cost budgeting	NA	NA	NA	Estimation of costs over period of time of interventions for the purpose of budgeting	NA	NA	
Micro-costing/Ingredients	NA	NA	(Approach in which prices and quantities of resources are measured, pg. 4)	Focuses on granular accounting of inputs; Disaggregates costs of particular output into specific items consumed (pg. A-13)	NA	NA	GHCC definition
Bottom-up Costing vs Top-down Costing	NA	NA	NA	Bottom-up measures input quantities at the client or activity level; Top-down divides overall program cost or expenditures, often including those above service level, by number of outputs to calculate unit cost (pg. A-13)	NA	NA	GHCC definition
Top-down Costing	NA	NA	NA	Divides overall program cost or expenditures, often including those above service level, by number of outputs	NA	NA	GHCC definition

	WHO 1994	WHO 2002	ICAN & EPIC (including How to Cost Immunization Programs)	GHCC	Costing Tools' User Manuals	cMYP Guideline	Recommend ation
				to calculate unit cost (pg. A-13)			
Perspective	NA	NA	The point of view considered for costs (and benefits, if included), in a costing study; to whom the costs were incurred. Common perspectives include provider, government, healthcare, insurer and societal. (pg. 32)	Describes which payers' costs are included in the estimate. For example, a provider perspective may include costs incurred by health service providers, non-health service providers, and be limited to specific payers. (pg. B-2)	NA	NA	Composite definition

Sources: WHO 1994 Training Manual (<https://apps.who.int/iris/handle/10665/400300>); WHO Cervical Cancer screening and treatment module user manual (https://www.who.int/immunization/diseases/hpv/cervical_cancer_costing_tool/en/); ICAN (<http://immunizationeconomics.org/ican-idcc-methodology>); GHCC (https://ghcosting.org/pages/standards/reference_case); WHO 2013 cMYP Guidelines (https://www.who.int/immunization/programmes_systems/financing/tools/cmyp/en/#:~:text=cMYP%20Guidelines&text=Better%20alignment%20of%20immunization%20and,than%20by%20disease%20or%20initiative)

In addition, most guides define incremental costing but not full costing. Only one of the documents (EPIC) had nuanced discussions of how perspective affects financial costs, incremental costing affects economic costs, and how the purpose of the analysis affects what cost ingredients should be included. Specifically, the perspective of the costing affects the designation of which inputs/resources are donated – e.g. vaccines in GAVI-eligible countries are donated if the perspective is the government and therefore would appear only as an economic cost, whereas if the study were conducted from a health sector perspective these might be included as financial costs. It is critical to clarify if the perspective is defined in terms of the payer (i.e., the organization outlaying the funds directly to the provider of goods or services) or the funding source; for example, when donor funds are channeled to the government and the government conducts the monetary outlay, this would be considered both an economic cost if the government perspective is used but a financial and economic cost if defined in terms of the payer (donor). Thus, the perspective will affect which resources are included in financial costs. For incremental costs, the guides define these as additional costs incurred with the introduction of a new vaccine or other technology but don't indicate what inputs/resources should be included in economic costs – i.e., which recurrent and existing capital costs should be included.

Annex 3. Costing Principles

Table A3 compares the costing principles in the guidance documents with the GHCC Principles and Methods Reporting Checklist. The guidance documents focus on five of the principles: 1) defining the purpose of the study (GHCC principle 1); 2) classifying the costs as recurrent/capital and financial/economic (GHCC principle 3) ; 3) specifying the time horizon of data collection (GHCC principle 5) ; 4) presenting costing methods (GHCC principle 7); and 5) depreciating the capital costs (GHCC principle 12).

Other GHCC principles were only discussed in one or two of the other guidance documents: 1) importance of stating the perspective; 2) scope of costing; 3) sampling strategy; 4) timing of data collection; 5) sources for price data; 6) selection of discount rate; 7) use of shadow prices; and 8) characterization of uncertainty.

Table A3. Comparison of Costing Principles among Guidance

GHCC Principle #	WHO 1994	EPIC/Common Approach/Reference Guide	Costing Tools	cMYP	Recommendation
1 The purpose, the population, and the intervention and/or service/output of the cost estimation should be clearly defined.	NA	At the earliest stage of planning a costing exercise, one should consider objectives and rationale.	User should assess whether financial or economic costs are most appropriate based on the objective (C4P, SIICT, CHOLTOOL, SIICT, TCV, MVICT)	The objectives are to analyze program costs, financing and financing gaps and these should be linked to the program objectives.	Combine GHCC principles 1 and 5 (Principle # 1)
2 The perspective of the cost estimation should be stated and justified.	NA	Perspective is an important concept that is somewhat unique to economic studies, as compared to other types of health service research.	NA	NA	GHCC principle (Principle # 2)
3 The type of cost should be clearly defined, in terms of economic vs. financial, incremental vs full cost, and whether the cost is 'net of future cost.'	Costs should be classified by inputs: recurrent and capital; Can also be classified by function/activity, level, source, and type of currency; Economic costing should be used for cost-effectiveness analyses.	It is important to make the distinction between financial and economic costs.	Costs are classified as financial and economic as well as recurrent and capital in the costing tools. (C4P, SIICT, CHOLTOOL, TCV, MVICT)	Costs are defined as recurrent and capital.	Composite of definitions.(Principle # 3)
4 The 'units' in the unit costs for strategies, services and interventions should be defined.	Explains general nature of unit costs and gives examples of unit costs.	All resources used in an intervention divided by number vaccination	Unit costs are measured as cost per dose administered, child	NA	Composite of definitions (Principle # 5)

GHCC Principle #	WHO 1994	EPIC/Common Approach/Reference Guide	Costing Tools	cMYP	Recommendation
			or girl fully vaccinated		
5 The time horizon of data collection should be explicit and of sufficient length to capture costs relevant to the purpose, and consideration should be given to disaggregating costs into separate time periods where they vary over time.	Should choose the most recent year for which cost data are available for one full year.	When collecting primary data retrospectively, one must set boundaries of the time horizon in which resource use occurred.	The user should specify whether the estimates are cost projection or retrospective analyses. (C4P, CHOLTOOL, MVICT)	Planning horizon is five years or less.	Included in Principle # 1).
6 The scope of the inputs to include in the cost estimation should be defined and justified relevant to purpose.	Need to be clear about scope of the costing.	The decisions about scope should be made when planning the exercise, before data is collected.	NA	NA	Included in Principle # 4
7 The methods for estimating the quantity of inputs should be described, including methods, data sources and criteria for allocating resources.	NA	Presents methods for recurrent and capital costs.	Presents methods of calculation and suggests data sources. (C4P, SIICT, CHOLTOOL, TCV, MVICT)	Ingredients approach is used to estimate costs – quantities x price x % used in immunization.	Included in Principle # 8
8 The sampling strategy used should be specified and designed to minimize bias.	It is necessary to choose a sample and use one of four types: either random, cluster, systematic, or stratified.	Published guidance for sampling health facilities that was developed for health facility data collection alongside DHS household surveys can be applied to immunization costing studies.	NA	NA	Combined definitions and edits by advisory group.that is dependent on workstream and costing objective. (Principle # 11)
9 The selection of the data source(s) and methods for estimating service use should be described, and potential biases reported in the study limitations.	Methods are described.	Recommend being aware of the quality of available data sources and reporting systems and comparing data sources.	Data sources and methods for estimating service use are described. (C4P, SIICT, CHOLTOOL, TCV, MVICT)	NA	Composite definition (Principle # 7)
10 Consideration should be given to the timing of data collection to minimize recall bias and, where relevant, the impact of seasonality and other differences.	NA	Notes that the major advantage of direct observation methods is lack of recall bias.	NA	NA	

GHCC Principle #	WHO 1994	EPIC/Common Approach/Reference Guide	Costing Tools	cMYP	Recommendation
11 The sources for price data should be listed by input, and clear delineation should be made between local and international price data sources, and tradeable, non-tradeable goods.	NA	NA	Sources for price data should be noted in the designated worksheets. (C4P, SIICT, CHOLTOOL, TCV, MVICT)	NA	Included in Principle # 6
12 Capital costs should be appropriately annuitized or depreciated to reflect the expected life of capital inputs	Recommends straight line depreciation.	For economic cost evaluation, all capital costs need to be annualized based on a discount rate and estimates of useful life.	Straight line depreciation is calculated for financial costs, and annualization and discounting for economic costs. (C4P, SIICT, TCV, MVICT)	NA	Included in Principle # 3
13 Where relevant, an appropriate discount rate, inflation and exchange rates should be used, and clearly stated.	NA	Recommends using a 3% discount rate unless there is another justification.	NA	NA	Include in Principle # 3
14 The use and source of shadow prices for goods and the opportunity cost of time should be reported.	NA	NA	NA	NA	Include in Principle # 8
15 Variation in the cost of the intervention by site/organization, sub-populations, or by other drivers of heterogeneity should be explored and reported.	NA	NA	NA	NA	Not included
16 The uncertainty associated with cost estimates should be appropriately characterized.	NA	Standard statistical approaches can be used to calculate an unbiased measure of mean, and the uncertainty in this mean estimated.	NA	Recommends scenario-building to take in account uncertainty; also risk assessment.	Combined definition in Principle 11
17 Cost estimates should be communicated clearly and transparently to enable	NA	Section in the Common Approach focuses on writing up results	NA	It is essential to communicate the results clearly.	Combined definition in Principle # 14.

GHCC Principle #	WHO 1994	EPIC/Common Approach/Reference Guide	Costing Tools	cMYP	Recommendation
decision-maker(s) to interpret and use the results.					

Annex 4. Characteristics of Costing Workstreams

Table A4 shows characteristics of the four costing workstreams identified based on recent work known to the advisory group. It shows that the activities/cost categories used in costing are largely similar within the guidance documents for immunization costing. However, in a few cases, the terminology differs – e.g. vaccines/injection supplies for program costing, vaccine procurement for cost projections and retrospective campaign costing, and vaccine, collection, distribution and storage for retrospective routine immunization costing. In addition, some workstreams use the term service delivery to encompass health personnel time, supplies, and transport while other workstreams separate these into individual components. Also, two of the workstreams, program costing and retrospective routine costing, explicitly mention surveillance as an activity while the other workstreams include surveillance under the monitoring activity/cost category. Similarly, two of the workstreams include micro-planning, cost projections and retrospective campaign costing, while this activity is not included in the other workstreams.

Table A4. Characteristics of Costing Workstreams

	Level of Data Collection	Activities/Cost categories	Perspective	Incremental or full	Similarities and Differences in workstream guidance in definitions of terms and perspective
Retrospective routine immunization cross-sectional costs	Facility with some data collection at higher levels	Vaccine, collection, distribution, storage Facility-based service delivery (personnel, time and resources) Monitoring and evaluation Supervision Training Social mobilization Surveillance Program management Cold chain maintenance Other capital	Health sector, i.e., ignored costs accruing to patients	Full or Incremental	- Similar definitions of financial and economic costs and recurrent and capital costs - Uses health sector perspective
Retrospective single-vaccine costs	Program and facility with sampling or interviews with program managers	Vaccine procurement Service Delivery (personnel and transport) Distribution Supervision Micro-planning Training	Payer or health system/government	Incremental	- Similar definitions of financial and economic costs and recurrent and capital costs - Uses government and payer perspectives - Costing tools assume incremental economic costs do not include existing

	Level of Data Collection	Activities/Cost categories	Perspective	Incremental or full	Similarities and Differences in workstream guidance in definitions of terms and perspective
		Other Recurrent Cold Chain AEFI Surveillance Other capital			equipment since these have available capacity (excess capacity)
Projection of new vaccine introduction costs	Program and facility	Vaccine procurement Service Delivery (personnel and transport) Distribution Supervision Micro-planning Training Other Recurrent Cold Chain AEFI Surveillance Other capital	Government or payer perspective	Incremental	<ul style="list-style-type: none"> - Similar definitions of financial and economic costs and recurrent and capital costs - Uses government and payer perspectives - Assumes incremental economic costs do not include existing equipment since these have available capacity (excess capacity)
Projection of immunization program costs	Program	Vaccines/injection supplies Personnel Transport Social Mobilization/IEC Training Supervision Monitoring (includes surveillance Cold chain equipment Other capital	Provider (could include external funding)	Full or Incremental	<ul style="list-style-type: none"> - Similar definitions of recurrent and capital costs except for US\$100 requirement for capital costs per item; uses straight line depreciation - Cost projections also similar to other definitions - Perspective is government but includes value of donated goods and personnel time

Variation among Workstreams

The workstreams shows the different approaches on data sources, sampling, and characterization of uncertainty, as shown in Table A5. This makes sense given the different recommended uses of the different workstreams. For example, cost projections of new vaccine introduction or an five-year immunization program are by definition an exercise in assumptions about an unknown future program with hypothetical information on costs and quantities; therefore, larger or more representative sampling of sites may not reduce uncertainty about this future program, whereas exploration of a range of scenario input parameters can help identify influential programmatic and cost elements and the range of possible cost results.

Table A5. Data sources, sampling and characterization of uncertainty, and terminology by Workstreams

	Recommended Use	Perspective	Data Sources	Sampling	Characterizing Uncertainty
Retrospective routine immunization cross-sectional costs	Compare costs of vaccine delivery for benchmarking and to explain variation in facility costs and unit costs and evaluate efficiency and equity	Provider or Payer	Health facility records; interviews with national and sub-national program managers	Representative sampling of health facilities (stratified, random)	Characterized based on number of sites in sample, stratification of units, and basis of probability of selection; one-way sensitivity testing or scenario analysis
Retrospective single-vaccine costs	Estimate costs of campaigns or routine health facility delivery for benchmarking and to explain variations by strategy and venue	Provider or payer	Interviews with national and sub-national program managers	Representative sampling of health facilities or campaign sites; Convenience samples	Characterized based on number of sites in sample, stratification of units, and basis of probability of selection
Projection of new vaccine introduction costs	Estimate costs to assist program managers in planning and decision-making on vaccine introduction	Provider or payer	Expert opinion; visits to selected health facilities; workshops with stakeholders	Does not use representative sampling but includes visits to selected facilities – urban and rural, etc.	Results based on estimated parameters; conduct scenario analysis to have a range of estimates
Projection of Immunization program costs	Estimate costs to assist in budgeting, planning and resource mobilization over a five-year period	Provider	Interviews with national and sub-national program managers; visits to selected health facilities sometimes	Can collect data at the sub-national as well as national levels	Results based on estimated parameters and necessarily have uncertainty; conduct scenario analysis to have a range of estimates

Annex 5. Areas for clarification and harmonization

Areas for clarification and harmonization are defined as problem areas or areas without a consensus. The following are the areas that have been identified from the review of guides and costing tool manuals.

1. Definitions on terminology among and within workstreams differ and need to be harmonized, where appropriate, acknowledging the different workstream purposes. See Annex 6 for recommended terms
2. The options for study perspective should be agreed upon by advisory group, including use of perspective in financial vs. economic costing.
3. Definition of “vaccine delivery costs” differs among workstreams.
4. Inconsistent labeling of program activities vs. resource inputs as cost categories, inconsistent nesting of resource inputs inside program activities and vice versa without regard for the perspective of the analysis.
5. Definition of incremental and full costing is not consistent.
6. Sampling and uncertainty: What are the appropriate sampling approaches (random, purposive) for different costing objectives (assuming time and money are not the limitations)? What level of uncertainty is appropriate?
7. Gaps in practical guidance on aggregating costs across levels of the health system and clarity on level of activity vs. level of payer.

Annex 6: Recommended Terms and Principles by Advisory Group

Consensus costing terms

The following definitions of costing terms are recommended by the advisory group:

1. Vaccine delivery costs: All costs associated with delivering immunizations to target populations (should note whether is inclusive or exclusive of vaccines); Includes startup, recurrent and capital.
2. Financial: Monetary outlays, with straight-line depreciation for capital goods; does not include opportunity costs for use of resources such as existing health personnel costs or donated goods. Definition is dependent on perspective since monetary outlays are specific to the payer defined in the analysis.
3. Economic: The value of all resources, regardless of the source of financing. Includes opportunity costs such as health worker time and any donated items such as vaccines and volunteer staff.
4. Fiscal (or initial investment): Monetary outlays, without depreciation of capital items.
5. Recurrent: Value of resources that last less than one year.
6. Capital: Value of resources lasting more than one year such as equipment and buildings
7. Incremental: Cost of adding a new or a batch of services or intervention over and above an existing program; inclusion of existing resources will depend on assumptions made about excess capacity (i.e. resources are underemployed; if there are no slack resources, e.g. personnel time, then their use for the new service or intervention incurs an opportunity cost that should be included – either by measurement or assumption).
8. Full: The sum of all costs associated with vaccination delivery, including vaccines and basic infrastructure.
9. Cost projection: Estimation of future costs of both recurrent and capital inputs.
10. Cost forecast:
11. Cost prediction:
12. Prospective data collection: Direct observation of resource use during data collection, i.e. data are collected concurrently with intervention implementation.
13. Retrospective data collection: Data collection after resource use completed.
14. Cost budgeting: Estimation of costs over a period of time of interventions for the period of budgeting.
15. Startup costs: Initial one-time programmatic activities and include micro-planning, initial training activities, and initial sensitization/ social mobilization/ IEC; Does not include routine programmatic activities such as refresher training.
16. Micro-costing: Focuses on granular accounting of inputs; disaggregates costs of particular output into specific items consumed.
17. Bottom-up: Measures input quantities at the client or activity level.

18. Top-down: Divides overall program cost or expenditures, often including those above service level, by number of outputs to calculate unit cost.
19. Perspective: Describes which payers' costs are included in the estimate. A provider perspective includes costs incurred by health service providers (can be limited to the government), a payer perspective includes costs to the payer(s), such as an external partner, while the societal perspective includes all costs incurred by providers as well as clients.

IVIR-AC meeting report (6-8 March 2018)
Session 9: Standardization of delivery costing

Introduction

In the past, IVIR-AC reviewed the micro-costing and planning tools supported by WHO to assist countries in estimating the cost of introducing and delivering new vaccines that often target populations who are not among the standard age groups of the Expanded Programme on Immunization, such as adolescents, adults, health workers and people with chronic diseases. The tools for costing vaccine delivery and introduction supported by WHO include C4P, the RTS,S malaria vaccines introduction costing tool and introduction costing tools for influenza vaccine, oral cholera vaccines and, recently, typhoid vaccines. As these delivery costing tools are based on different methods and sometimes different terminology, a plan to standardize delivery costs has been prepared.

Review and discussion

Costing tools can help in standardization of costs and to include economic costs that are often left out of analysis (e.g. in-kind costs, personnel time costs, etc). Furthermore tools ensure that users list their assumptions and sources of information and tools can be used to calculate costs of different scenarios so that these can be compared.

Challenges with using different tools include lack of standardization of cost categorization (e.g. omissions, misclassifications), availability of economic costs, inclusion of capital costs, differentiation between fixed and variable costs, and variable cost perspective.

Questions to be addressed

1. Is the suggested framework for cholera vaccine delivery costs appropriate and useful?
2. What is the guidance from IVIR-AC around addressing different perspectives and capital costs in delivery costing tools and methods?
3. Is it always necessary to include both economic and financial costs?
4. To what extent should vaccine delivery costing methodologies be standardised across vaccines?

Summary and Recommendations

In the past, IVIR-AC reviewed the micro-costing and planning tools supported by WHO to assist countries in estimating the cost of introducing and delivering new vaccines that often target populations who are not among the standard age groups of the Expanded Programme on Immunization, such as adolescents, adults, health workers and people with chronic diseases. The tools for costing vaccine delivery and introduction supported by WHO include C4P, the RTS,S malaria vaccines introduction costing tool and introduction costing tools for influenza vaccine, oral cholera vaccines and, recently, typhoid vaccines. As these delivery costing tools are based on different methods and sometimes different terminology, a plan to standardize delivery costs has been prepared.

- IVIR-AC concluded that standardization of the costing tools would be useful and necessary for comparing the costs of delivery within and across countries and by product or delivery strategy.
- Economic costs should be included for economic evaluations. Modelling may be required if economic costs are projected over long periods.
- IVIR-AC suggested that the standardization methods also include uncertainty analysis; most of the tools provide no means for including uncertainty or sensitivity analyses.
- The Committee suggested that guidance would be useful on where to obtain data, at what level (national, subnational or district level) and how to conduct sampling. In addition, the data collection tools and forms should be validated.
- Finally, the Committee suggested that the costing guide for standardization of delivery costs be linked with the Global Health Costing Consortium. Reference costs should be used as a checklist to ensure quality, and definitions and terminology should be aligned.

IVIR-AC meeting report (12-14 March 2019)
Session 6: WHO guide on vaccine delivery costs

Introduction

WHO, in collaboration with Levin and Morgan Global Health Consultants, has developed several costing tools including the WHO Cervical Cancer Prevention and Control Costing Tool (C4P), the Seasonal Influenza Vaccine Costing Tool, and the Malaria Vaccination Introduction and Costing Tool. Other tools are currently under development or piloted, including the Typhoid delivery costing tool, and the Cholera vaccine costing tool. Other actors are also developing costing tools; the Bill and Melinda Gates Foundation (BMGF) has published a working paper on a common approach for the costing and financing analyses of routine immunization and new vaccine introduction costs. Because these tools use different definitions and apply different methodological approaches, there is a need for standardization. In March 2018 IVIR-AC concluded that standardization of costing tools is required to compare delivery costs within and across countries and to compare delivery costs by product or by delivery strategy.

An overview of existing methods and guidance costing tools, with an explanation of the different purposes they serve, were presented to IVIR-AC. Furthermore, the Immunization Costing Action Network (ICAN) and EPIC3 (immunization costing) programme of work in the area of standardization of vaccine delivery costs was presented.

Review

A systematic review has highlight the strong need for standardization of definitions and data collected for vaccine delivery costing studies. Moreover, it is clear that there is also a need to standardize the way cost of delivery data is reported in publications. The reporting should be done in such a way that individual cost components can be broken down so that both financial and economics costs, and (ideally) costs from societal versus healthcare provider prospective can be determined for future studies. The Immunization Delivery Cost Catalogue (IDCC) might provide a useful template for this. Systematic and standardized data collection and reporting would make extraction and comparison of data across different studies more manageable.

It is important to ensure that the cost of delivery for campaign doses is collected in a way that these can be directly compared to costs for routine doses.

WHO should consider whether it is possible to develop a cost of delivery tool that can be easily adapted to new vaccines, e.g. by offering different options for oral vs

injectable vaccines, delivery strategies, etc. rather than developing new tool for each vaccine.

EPIC's proposed meta-regression analysis of delivery costs across different countries is potentially very useful in understanding uncertainty in delivery costs both for existing studies and extrapolation to new countries.

It is important to understand how different the needs are for cost of delivery tools for retrospective vs prospective (new vaccine) analyses.

It might be useful to have a workshop to explore the existing guidelines (being developed by EPIC/ICAN) and tools in more detail, standardize definitions and cost categories collected/reported, provide an overview of modelling approach(s), and obtain input from country-level users (target audience).

Discussion

It was discussed whether there is a need for the WHO guide to be developed, or whether the existing tools and those that are already being developed are enough. It was proposed that this requires a critical review from WHO with participation from EPI programme managers (possibly through the International Organisation of Immunization Managers). If the current tools are promising, then perhaps a third effort is not needed.

The ICAN guidelines seem very developed but it was unclear whether they meet the need for retrospective and prospective data collection.

There seems to be some divergence between the ICAN (BMGF tools) and those developed by WHO because partly they have the different aims (prospective or retrospective). The possibility was discussed to have a workshop with all partners to come up with joint guidelines.

Questions to be answered

- Does IVIR-AC have any feedback on the plan of work for the development of the WHO guide?
- How should the WHO guide build on existing guidance documents and/or provide additional guidance where there are gaps?

Summary and Recommendations

WHO is considering the development of a Guide on Vaccine Delivery Costs. Costing tools for vaccine delivery have been developed for a variety of disease. ICAN is also in the process of developing costing guidance and tools. An overview of activities on vaccine delivery costing was presented, and IVIR-AC was asked to comment on how the WHO guide should build on existing guidance documents and/or provide additional guidance where there are gaps.

Recommendations

- A systematic review has highlighted the need for standardization of data collection and reporting, to allow extraction of costing data for example so that both financial and economic costs¹ can be calculated.
- It is important to identify the target group for the guide and tools. IVIR-AC recommends that members of the target group (e.g. National Immunization Programme Managers) are included in the development of the guide.
- IVIR-AC noted that there is a lot of activity going on with different tools being developed, but also that there seems to be some potential divergence between the ICAN (BMGF/funder focused tools) and those developed by WHO (EPI manager focus), partly because they have different aims (prospective costing for vaccine introduction versus retrospective costing of existing programmes). Some of this apparent divergence may be simply due to different terminology.
- IVIR-AC feels that the need for a WHO guide to be developed requires some careful consideration, given the availability of existing guides and tools. This requires a critical review from WHO, with participation from EPI programme managers.
- IVIR-AC recommends a workshop with all partners involved in vaccine costing methodology to have detailed discussions and potentially develop joint guidelines; WHO should develop a guide on its own only if this is not possible.

¹ Financial costs are actual monetary costs that appear in budgets, whereas economics costs are opportunity costs that include the value of alternative uses of resources such as staff or cold chain capacity.

IVIR-AC meeting report (18-20 September 2019)
Session 7: Standardization of vaccine delivery costs

Summary

Different methodologies and terminologies have been employed by micro-costing and planning tools for immunization programs. Standardization of vaccine delivery costing was first raised in the March 2018 IVIR-AC meeting. In that meeting, IVIR-AC concluded that standardization of costing tools is vital for comparing delivery costs across countries, across products and across delivery strategies. In the March 2019 IVIR-AC meeting, a literature review on three existing guidelines and three WHO costing tools was presented. The need for a standardization guideline was reinforced. However, given the availability of existing related guidelines from BMGF and other costing tools which were not included in the literature review, IVIR-AC recommended more detailed discussions and proposed to develop joint guidelines. In July 2019, eleven experts from different organizations and institutions in immunization economics gathered in Basel. They redefined the scope of review, adding more guidelines and tools for consideration, so that a total of three guidelines and ten tools (some of which are vaccine specific, e.g. for HPV vaccination, oral cholera vaccines, typhoid vaccine, etc.) are included.

A matrix of selected guidelines and tools was drafted to facilitate a comparison. A preliminary analysis of these guidelines and tools on vaccine delivery costs was conducted based on this matrix and was presented in this IVIR-AC meeting. The three guidelines were compared on three aspects: target intervention, focus and purpose, while the ten tools were compared on eighteen perspectives, including purpose, intended use, perspective, etc. Commonalities and differences were identified, including the absence of uncertainty analysis as a built-in function in most costing tools, and differences in cost categories used in the tools.

The conclusion is that both commonalities and gaps exist among current guidelines and tools in various perspectives. Further efforts will be made in harmonizing the differences and fill-in the gaps in the standardization of vaccine delivery costs guideline. A future workshop on further steps might be planned.

Session 6: Vaccine Delivery Costing Consensus Statement

Karene Yeung

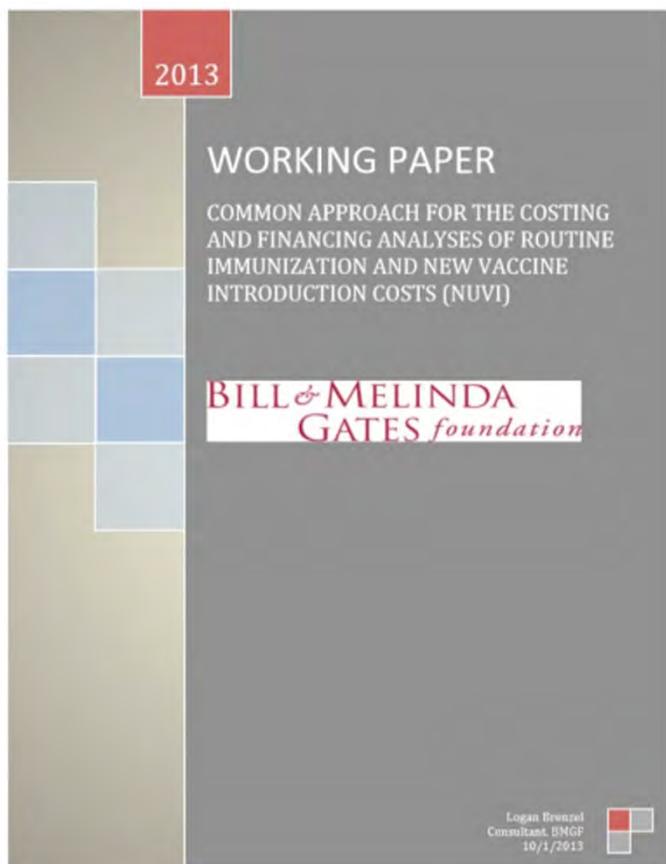
Value of Vaccines, Modeling and Economics,
Immunization Analysis & Insights, IVB



World Health
Organization

Guidelines

GHCC



Reference Case for Estimating the Costs of Global Health Services and Interventions

Anna Vassall, Sedona Sweeney, James G. Kahn, Gabriela Gomez, Lori Bollinger, Elliot Marseille, Ben Herzel, Willyanne DeCormier Plosky, Lucy Cunnam, Edina Sinanovic, Sergio Bautista, GHCC Technical Advisory Group, GHCC Stakeholder Group, Kate Harris, Carol Levin

Guidelines for estimating costs of introducing new vaccines into the national immunization system



DEPARTMENT OF VACCINES AND BIOLOGICALS



World Health Organization
Geneva
2002



Costing tools

C4P Vaccination Module

Master File (Zeros)

Cervical Cancer Prevention and Control Costing (C4P) Tool (Cost Projection)

[Go to Table of Contents](#)



Primary Developer: Winthrop Morgan, MPH (win@levinmorgan.com)

Cover Notes:
 This is version 4 (July, 2020)
 Vaccination Module
 Please use Table of Contents for navigation.
 Please save often to avoid accidental loss of data.
 Password to unprotect worksheets: MYC4P



Tools use different definitions and apply different methodological approaches

- Need for standardization



Recommendations IVIR-AC March 2018

- **Standardization of costing tool** is useful and needed to **compare delivery costs within and across countries** and to compare delivery costs **by product** or **by delivery strategy**.
- The standardization methods also deal with **uncertainty analysis** as most of the tools lack any means for factoring in uncertainty or sensitivity analyses.
- Guidance would be useful on **where to get the data**, **at what level** (national, sub-national versus district level) and how to deal with the **sampling**.
- **Data collection tools and forms** should be **validated**.
- **Economic costs should be included** for economic evaluations. Modeling may be required if economic costs are projected over long time horizons.
- Linking the costing guide for standardization of delivery costs with the **Global Health Costing Consortium (GHCS)** was suggested. Reference costs should be used as a checklist to ensure quality and also that definitions and terminology are in line with the GHCS.



Literature review on 3 existing guidelines and 3 WHO costing tools

- The need for standardization guideline was reinforced.



Recommendations IVIR-AC March 2019

- It is important to identify the target group for the guide and tools. Members of the target group (e.g. National Immunization Programme Managers) are recommended to be included in the development of the guide.
- There is a lot of activity going on with different tools being developed, but there seems to be some potential divergence between the ICAN (BMGF/funder focused tools) and those developed by WHO (EPI manager focus), partly because they have different aims (prospective costing for vaccine introduction versus retrospective costing of existing programmes). Some of this apparent divergence may be simply due to different terminology.
- The need for a WHO guide to be developed requires some careful consideration, given the availability of existing guides and tools. This requires a critical review from WHO, with participation from EPI programme managers.
- A workshop with all partners involved in vaccine costing methodology was recommended to have detailed discussions and potentially develop joint guidelines; WHO should develop a guide on its own only if this is not possible.



Summary of updates IVIR-AC Sep 2019

- In July 2019, eleven experts from different organizations and institutions in immunization economics gathered in Basel and redefined the scope of review and added more guidelines and costing tools for consideration.
- A matrix of selected guidelines and tools was drafted to facilitate a comparison.
- Both commonalities and gaps exist among current guidelines and tools in various perspectives.
- Further efforts will be made in harmonizing the differences and fill-in the gaps in the standardization of vaccine delivery costs guideline.



Final draft of Consensus Statement of Vaccine Delivery Costs

- 12 guidelines
- 10 costing tools



Advisory group members

- Ann Levin, Levin and Morgan LLC
- Logan Brenzel, Bill & Melinda Gates Foundation
- Sarah Pallas, Centers for Disease Control and Prevention
- Ulla Griffiths, UNICEF
- Laura Boonstoppel, ThinkWell
- Vittal Mogasale, International Vaccine Institute
- David Bishai, Johns Hopkins University
- Stephen Resch, Harvard T.H. Chan School of Public Health
- Christian Suharlim, Harvard T.H. Chan School of Public Health
- Stephane Verguet, Harvard T.H. Chan School of Public Health (IVIR-AC member)
- Mark Jit, London School of Hygiene & Tropical Medicine (IVIR-AC member)
- Xiao Xian Huang, World Health Organization
- Raymond Hutubessy, World Health Organization



Questions to IVIR-AC

- Review the process leading to the final draft of the consensus statement
- Any clarifications of content and issues?
- What are the next steps?
- What are the lessons learnt from the process?



PROCESS OF DEVELOPING A CONSENSUS STATEMENT ON IMMUNIZATION COSTING

ANN LEVIN, MPH, PHD

IVIR-AC MEETING, SEPTEMBER 24, 2020

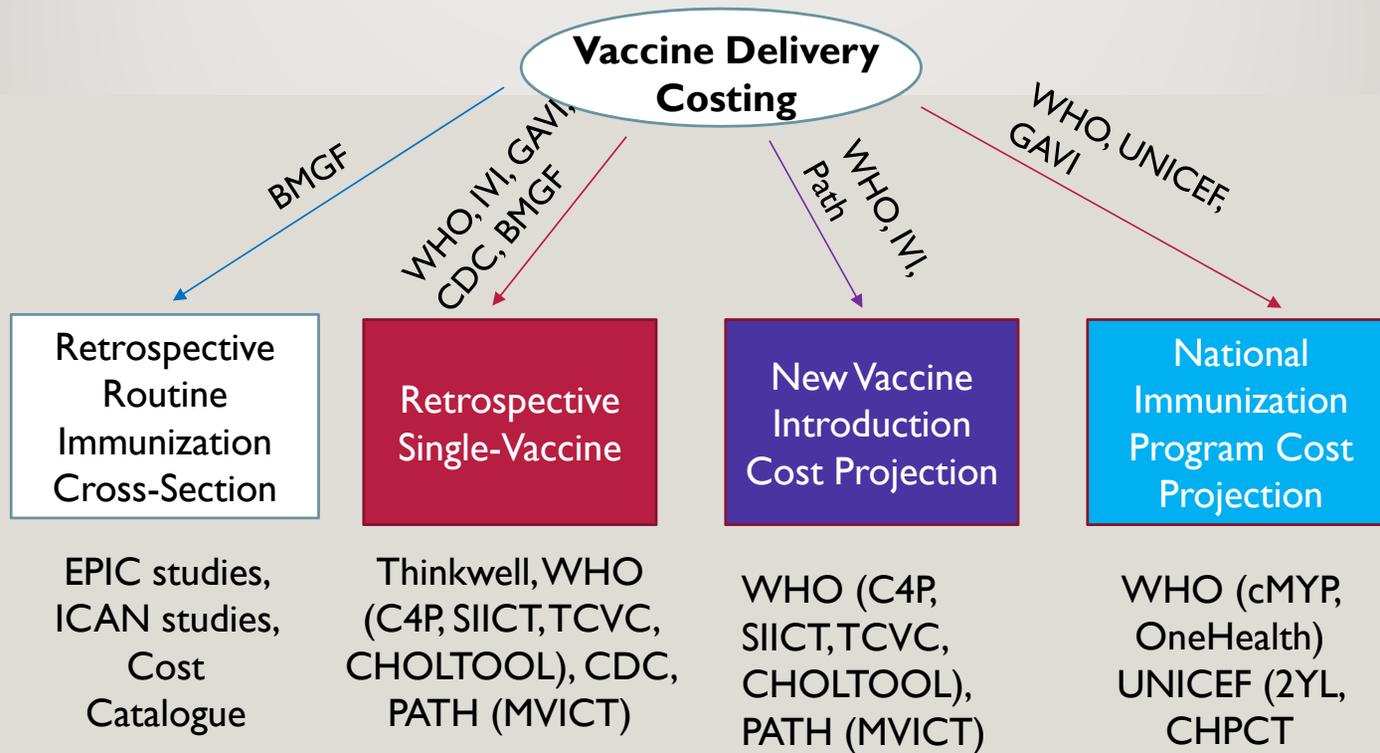
BACKGROUND

- IVIR-AC Recommendation to Update Guidance for Estimation of Costs for New Vaccines, particularly Costing Tools March 2018
- Initial Advisory Group formed (BMGF, WHO, UNICEF, IVI, UW, Mahidol University, IVIR-AC) – Sept 2018
 - Decided many workstreams on immunization costing are taking place and should present to IVIR-AC on findings

BACKGROUND

- Presented to IVIR-AC March on varying workstreams (WHO and Thinkwell) March 2019
 - Recommendation to compare similarities and differences to decide whether guidance document is needed
 - Conduct a workshop with all partners to have detailed discussions and potentially develop joint guidelines
- Meeting/workshop during International Health Economic Association to discuss how to move forward with BMGF, WHO, UNICEF, IHI, Harvard SPH, Thinkwell, CDC July 2019
 - Decided to develop a consensus statement to harmonize differences in costing terminology and principles

FOUR WORKSTREAMS IDENTIFIED



GUIDANCE DOCUMENTS/TOOLS

- BMGF/Thinkwell/HSPH
 - Developed/ing guidance on estimating retrospective immunization costs
 - The Common Approach (EPIC studies), How to Cost Immunization (Harvard School of Public Health), ICAN Methodology, Forthcoming – guidance on estimating costs of campaigns (Thinkwell)
- WHO
 - Developed guides and costing tools on cost projection of introducing new vaccines and economic evaluation of Immunization Programs
 - (2002 Guidance on Cost of New Vaccine Introduction, 2019 Guide on Economic Evaluation)
- Global Health Costing Consortium Reference Case on Costing Health Services

Gap: Guidance for Costing Tools on Data Collection, Sampling, and Uncertainty Analysis for Single Vaccine Cost Projections and Retrospective Single Vaccine

OBJECTIVES OF CONSENSUS STATEMENT

- To highlight commonalities and differences across different costing approaches, tools, and guidelines;
- To affirm the existence of different types and objectives of costing;
- To promote continued improvement and innovation in methods and tools that are fit for purpose;
- To advance the immunization economics community of practice by committing to follow certain principles and common definitions that will make the collective costing work more easily interpretable and useful

CONSENSUS STATEMENT

- Summarizes different types and objectives of Vaccination Delivery costing of Workstreams
- Reviewed terminology, definitions, and costing principles in guidance documents
 - Summarized similarities and differences in Costing Terms
 - Compared Costing Principles of guidance documents with GHCC's
- Presented recommendations for Costing Definitions and Principles

FINDINGS ON COSTING TERMINOLOGY

- Similar definitions
 - Financial and economic costs
 - Recurrent and capital costs
 - Incremental cost
- Differences
 - Vaccine delivery cost – whether inclusive or exclusive of vaccines
 - Prospective costing
 - No definition of full costing
- No discussion
 - Interaction between perspective, financial and economic, and incremental costing
 - Is critical to specify whether the perspective is in terms of payers or funding source
- Few documents (<3) define terminology
 - Timing of costing i.e. projections, prospective, and retrospective
 - Perspective
 - Bottom-up or top-down costing
- GHCC reference case has the most definitions

FINDINGS ON COSTING PRINCIPLES

- Similarities
 - Defining purpose of the study
 - Classifying costs as recurrent/capital and financial/economic
 - Specifying the time horizon of data collection
 - Presenting costing methods
 - Depreciating capital costs
- Only specified in one or two guides:
 - Specifying perspective, scope of costing, sampling strategy, sources for price data, selection of discount rate, use of shadow prices, and characterization of uncertainty

CHARACTERISTICS OF COSTING WORKSTREAMS

	Recommended Use	Data sources	Sampling	Characterizing Uncertainty	Perspective
Retrospective routine immunization	For benchmarking/ explain variation	Health facilities; interviews	Representative sampling	Based on # of sites in sample, stratification	Provider or payer
Retrospective single-vaccine	For benchmarking/ explain variation; planning	Interviews; records	Representative or convenience	Based on # of sites in sample, stratification; in others, not characterized	Provider or payer
Projection of new vaccine	Planning and decision-making	Interviews; facility visits	Not representative	Conduct scenario analysis	Provider or payer
Projection of immunization program costs	Assist in budgeting, planning, and resource mobilization	Interview; facility visits	Not representative; facility visits	Conduct scenario analysis	Provider

RECOMMENDED TERMS

- Vaccine delivery costs
- Financial, economic and fiscal
- Recurrent and capital
- Incremental and full
- Projection, prospective, retrospective
- Startup costs
- Micro-costing
- Bottom-up and Top-down
- Perspective

Justification for these recommendations is provided in Annexes.

RECOMMENDED PRINCIPLES

- Study scope – purpose, audience
- Perspective – stated and justified
- Types of costs defined
- Units defined
- Assumptions regarding full or slack capacity
- Selection of data sources
- Methods described
- Costing boundaries
- Sampling strategy described
- Uncertainty described
- Cost estimates should be communicated clearly

Justification for these recommendations is provided in Annexes.

NEXT STEPS

- Develop WHO web page with a road map and primer with links to all guidelines and tools, explaining which is best to use for different purposes, and presenting how guidelines and tools relate to each other
- Develop a guideline with greater specificity to specific vaccines that explains underlying costing principles for costing of specific vaccines, including more detail on incremental costing assumptions, glossary of terms, how to use the tools retrospectively as well as for cost projections, and provide guidance on data collection.

ACKNOWLEDGEMENTS

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- Ulla Griffiths, UNICEF
- Laura Boonstoppel, Thinkwell
- Stephen Resch, EPIC Project, Harvard Center for Health Decision Science
- Chris Suharlim, EPIC Project, Harvard Center for Health Decision Science
- Vittal Mogasale, International Vaccine Institute
- David Bishai, John Hopkins SPH
- Xiaoxian Huang, WHO
- Raymond Hutubessy, WHO
- Karene Hoi Ting Yeung, WHO
- Mark Jit, IVIR-AC
- Stephane Verguet, IVIR-AC

Session 7:

IA 2030 Modelling

Vaccine Impact Estimates for IA2030

Analysis Framework

William Msemburi*

August 4, 2020

Background

Reduction in child mortality continues to be a major goal for global health investment and strategies. Decisions regarding specific global priority investments are increasingly based on quantitative analysis of benefits. Advocacy and public health communication around full value of vaccines rest on credible, evidence-based analysis of the impact of vaccines. There is an urgent need for advancing quantitative global analyses on vaccine benefits for monitoring and for advocacy purposes, not the least for the Immunization Agenda 2030 (IA2030) and the 13th General Programme of Work (GPW13).

It has been frequently cited that 2.5 million lives are saved every year due to vaccination. This figure has been used to describe the impact of vaccines in WHO documents, media, on UN and other organization's websites and even in scientific literature. However, limited documentation of the methodology and scope of analysis requires us to revisit the figure. It is critical to update the modelled health impact estimate and document the methodology in a transparent manner for the coming decade to inform strategic priorities for IA2030 and the Triple Billion targets for GPW13.

To this end, WHO IVB and DDI will collaborate with the Bill and Melinda Gates Foundation (BMGF), Gavi, the Vaccine Alliance (Gavi), Vaccine Impact Modelling Consortium (VIMC), Institute for Health Metrics and Evaluation (IHME) and other partner institutions to generate global and regional estimates of lives saved due to vaccination based on transparent methodologies.

*World Health Organization: Data analytics and Delivery for Impact (DDI)

1 Vaccine Impact Estimates for Immunization Action 2030

1.1 Goal

WHO IVB and DDI aim to update the modelled health impact estimate and document the methodology in a transparent manner for the coming decade to inform strategic priorities for IA2030 and the Triple Billion targets for GPW13.

1.2 Objectives

WHO IVB and DDI aim to generate global and regional estimates of lives saved due to vaccination for 194 Member States to be available for the 74th World Health Assembly 2021. The scope of work includes:

- **Pathogens/diseases:**
 - 17 pathogens (diseases): Hepatitis B, Haemophilus influenzae type b (Hib), Human papillomavirus (HPV), Measles, Pneumococcal disease, Rotavirus, Rubella, Japanese encephalitis (JE), Neisseria Meningitidis type A (MenA), Yellow fever (YF), BCG (tuberculosis), Diphtheria, Tetanus, Pertussis, Polio, Cholera and Typhoid.
- **Target countries:**
 - 194 WHO Member States
- **Time frame:**
 - First year with available data – 2019/2020: deaths averted due to vaccination in a given year
 - 2021- 2030: future deaths averted due to vaccination in a given year
 - Cross-sectional deaths averted (total deaths that would have occurred in a given year which was averted due to vaccination in any year)
 - Cohort deaths averted (total deaths averted due to vaccination for a given birth cohort)

2 Methods

2.1 Mathematical model

Projection of deaths for the counterfactual scenarios and calibration of impact parameters will use the cohort component method of population projection (CCMPP)¹. Based on the demographic balancing equation, the CCMPP assumes that the population size at time $t + \delta$ is equal to the size at time t plus births and immigrants, minus deaths and emigrants, over the time interval δ . Projection proceeds in discrete steps and can be represented as:

$$\mathbf{n}_{t+1} = \begin{bmatrix} n_{0,t+1} \\ n_{1,t+1} \\ \vdots \\ n_{\omega-1,t+1} \\ n_{\omega,t+1} \end{bmatrix} = \begin{bmatrix} \bar{f}_{0,t} & \bar{f}_{1,t} & \cdots & \bar{f}_{\omega-1,t} & \bar{f}_{\omega,t} \\ s_{1,t} & 0 & & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & \cdots & s_{\omega,t} & s_{\omega+1,t} \end{bmatrix} \times \begin{bmatrix} n_{0,t} + g_{0,t}n_{0,t}/2 \\ n_{1,t} + g_{1,t}n_{1,t}/2 \\ \vdots \\ n_{\omega-1,t} + g_{\omega-1,t}n_{\omega-1,t}/2 \\ n_{\omega,t} + g_{\omega,t}n_{\omega,t}/2 \end{bmatrix} + \begin{bmatrix} g_{0,t}n_{0,t}/2 \\ g_{1,t}n_{1,t}/2 \\ \vdots \\ g_{\omega-1,t}n_{\omega-1,t}/2 \\ g_{\omega,t}n_{\omega,t}/2 \end{bmatrix}$$

where ω is the beginning of the open-interval age and the \mathbf{n}_t , \mathbf{s}_t , \mathbf{g}_t and \mathbf{f}_t , denote vectors of age- and year-specific population counts, survival rates, net migration rates, and fertility rates. We use,

$$\bar{f}_{a,t} = s_{0,t}(1 + SRB)^{-1}(f_{a,t} + f_{a+1,t} \cdot s_{a+1,t})(1/2)$$

to determine the sex-specific births for the corresponding sex-ratio-at-birth (SRB). The analysis focuses on determining counterfactual estimates for the surviving fraction s_t , assuming the survival vector is a function of the mortality vector:

$$\mathbf{s}_t = 1 - \boldsymbol{\mu}_t$$

where the mortality vector itself is the sum of deaths attributable to vaccine-preventable causes and deaths attributable to other causes-of-death i.e.

$$\boldsymbol{\mu}_t = \boldsymbol{\mu}_t^{VPD} + \boldsymbol{\mu}_t^{Other}$$

Also noting that for the $c \in \{1, \dots, 17\}$ antigens listed above

$$\boldsymbol{\mu}_t^{VPD} = \sum_c \boldsymbol{\mu}_{c,t}$$

¹Preston, S., Heuveline, P., & Guillot, M. (2000). Demography: measuring and modeling population processes. 2001. Malden, MA: Blackwell Publishers.

The major under-taking of this project will be to evaluate, for each relevant vaccine-preventable cause-of-death c , a function that relates the vaccine coverage to prevalence of the fatal condition, an estimate of the case-fatality or proportion dying per prevalent case η_c as well as some reduction factor γ_c that is as a result of the vaccine scale-up in the population i.e.

$$\mu_{c,t} = f_c(t, cov_c, prev_c, \eta_c, \gamma_c)$$

As previously described, the overall mortality attributable to vaccine preventable diseases is

$$\mu_t^{VPD} = \sum_c \mu_{c,t}$$

When considering the aggregate reduction in VPD mortality attributable to the combined impact of the vaccine interventions, the cumulative impact is assumed to be multiplicative rather than additive to reduce the extent of double-counting². This follows a population attributable fraction approach with the vaccination risk reduction for cause c as quantified by γ_c assumed to not act independently of the other reductions $\gamma_{j \neq c}$. The adjusted VPD mortality after accounting for the reduction from the $c \in C$ causes/vaccines is assumed to be:

$$\mu_t^{VPD_{adj}} = \mu_t^{VPD} \prod_c (1 - \gamma_c)$$

2.2 Input data

2.2.1 Vaccine Impact Modelling Consortium (VIMC) country/vaccines

From the VIMC³ we will obtain several inputs which are country and antigen specific⁴ covering a total of 110⁵ countries and 10 vaccines i.e. HepB, Hib, HPV, Measles, PCV, Rotavirus and Rubella as well as the region-specific JE, MenA and YF:

²Theoretically, as there are more combined vaccinations that occur across all vaccines than there are children, a one-to-one assumption on live-saved and vaccinations leads to more children saved than are in the population, however we assume you can only be saved once. Approaching this problem this way, finds the middle ground and assumes that the presence of a single vaccine leads to a quantifiable decreased mortality risk vs it leading to a fully averted death.

³<https://www.vaccineimpact.org/>

⁴<https://www.vaccineimpact.org/resources/VIMC-country-antigen-list.xlsx>

⁵Counting West Bank and Gaza as well as Kosovo, this would be 112 but these two are not included in the WHO 194 member states

(a) 57 countries with 7 core vaccines (no regional vaccine) :

[1] Afghanistan, Albania, Algeria, Armenia, Azerbaijan, Belarus, Belize, Bolivia,
[9] Bosnia and Herzegovina, Cape Verde, Comoros, Cuba, Djibouti, Egypt, El Salvador,
[18] Fiji, Georgia, Guatemala, Guyana, Haiti, Honduras, Islamic Rep Iran, Iraq, Jamaica,
[25] Jordan, Kiribati, Kyrgyzstan, Lesotho, Macedonia, Madagascar, Malawi,
[32] Marshall Islands, Micronesia, Moldova, Mongolia, Morocco, Mozambique, Namibia,
[39] Nicaragua, Paraguay, Samoa, Sao Tome e Principe, Serbia, Solomon Islands,
[45] South Africa, Swaziland, Syria, Tajikistan, Tonga, Tunisia, Turkmenistan,
[52] Tuvalu, Ukraine, Uzbekistan, Vanuatu, Yemen, Zimbabwe.

(b) 17 countries with core vaccines and JE :

[1] Bangladesh, Bhutan, Cambodia, China, India, Indonesia, Korea, DPR, Lao PDR,
[9] Myanmar, Nepal, Pakistan, Papua New Guinea, Philippines, Sri Lanka, Thailand,
[16] Timor-Leste, Vietnam

(c) 10 countries with core vaccines and YF :

[1] Angola, Colombia, Congo Rep, Ecuador, Liberia, Peru, Sierra Leone, Somalia, Venezuela,
[10] Zambia

(d) 26 countries with core vaccines and MenA and YF :

[1] Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad,
[7] Congo DR, Cote d'Ivoire, Eritrea, Ethiopia, Gambia, Ghana, Guinea, Guinea-Bissau,
[15] Kenya, Mali, Mauritania, Niger, Nigeria, Rwanda, Senegal, Sudan: North,
[23] Sudan: South, Tanzania, Togo, Uganda.

2.2.2 VIMC vaccines for non-VIMC countries

The VIMC inputs/outputs will be used to calibrate the effects in the relationship:

$$\mu_{c,t} = f_c(t, cov_c, prev_c, \eta_c, \gamma_c)$$

This is a vaccine-specific function relating the mortality attributable to the corresponding disease to the vaccine coverage, some measure of the number of disease cases per population, the number of deaths expected per case and the reduction in the mortality that is as a result of the level of vaccine coverage. This can be perceived for the point in time (period) or the group of children vaccinated (cohort). The next step will be extending this function to the non-VIMC countries but for the same 10 vaccines assuming the function

can be generalized according to average effects extended out-of-sample. From WUENIC⁶ we will obtain the estimates of coverage⁷.

84 countries not included in VIMC :

- [1] Andorra, Antigua and Barbuda, Argentina, Australia, Austria, Bahamas,
- [7] Bahrain, Barbados, Belgium, Botswana, Brazil, Brunei Darussalam,
- [13] Bulgaria, Canada, Chile, Cook Islands, Costa Rica, Croatia,
- [19] Cyprus, Czechia, Denmark, Dominica, Dominican Republic, Equatorial Guinea,
- [25] Estonia, Finland, France, Gabon, Germany, Greece, Grenada, Hungary, Iceland,
- [34] Ireland, Israel, Italy, Japan, Kazakhstan, Kuwait, Latvia, Lebanon, Libya,
- [43] Lithuania, Luxembourg, Malaysia, Maldives, Malta, Mauritius,
- [49] Mexico, Monaco, Montenegro, Nauru, Netherlands, New Zealand,
- [55] Niue, Norway, Oman, Palau, Panama, Poland, Portugal, Qatar, Republic of Korea,
- [64] Romania, Russian Federation, Saint Kitts and Nevis, Saint Lucia,
- [68] Saint Vincent and the Grenadines, San Marino, Saudi Arabia, Seychelles, Singapore,
- [73] Slovakia, Slovenia, Spain, Suriname, Sweden, Switzerland, Trinidad and Tobago,
- [80] Turkey, United Arab Emirates, United Kingdom, United States of America, Uruguay.

For these 84 we will assume the same average prevalence number per population as for VIMC. In addition the case fatality per prevalent case and mortality reductions estimated by the VIMC for the 110 countries will be used.

The algorithm will work as follows:

1. Determine the births and population by age using the cohort component model.
2. Use the vaccine specific prevalence scaling factor from the VIMC to predict the number of cases.
3. Conditional on the coverage value (0 for counterfactual vs the actual observed value) predict both the adjustment to prevalence as well as the reduced deaths based on the reduction on the case fatality rate. The reduction factor remains the same based on the VIMC input.

In this way, the vaccines included in the VIMC will also be estimated for then non-VIMC countries using comparable assumptions on the impact of vaccine scale-up on the mortality and prevalence of the disease.

⁶https://www.who.int/immunization/monitoring_surveillance/data/en/

⁷We will need to explore if this is the only coverage source, it will be important that the coverage source used here is the same as the one informing the function to remove any coverage source bias

2.2.3 All countries for non-VIMC vaccines

There are seven vaccines that are either not modelled by the VIMC or will not have results within the time-frame of this analysis. These are Typhoid, Cholera, BCG (tuberculosis), Diphtheria, Tetanus, Pertussis and Polio. For Typhoid, Cholera, BCG, Pertussis and Polio, the approach for determining the impact will be similar to that described for the VIMC but with a three notable differences. Firstly, unlike for the VIMC vaccines, impact will not be drawn from models that have explicitly modelled the vaccine for a population. Rather, the no-vaccine level will be the extrapolation of the mortality rate from the last point when the coverage for the relevant vaccine was zero. The second difference follows directly from the first methodological differences. Extrapolation of mortality levels will be country-sex-age specific rather than being estimated indirectly according to the average prevalence scaling factor and case-fatality ratios. The third difference will be on the data sources. Mortality rates for Typhoid, Cholera and Tuberculosis will be taken from the GBD study. Polio numbers will be taken from the repositories stored by the WHO⁸. The numbers for Pertussis will either come from the GBD2017 study where Pertussis is estimated as an intermediate outcome or from the WHO child-mortality estimate. The latter has the disadvantage of being for limited years only and so the two sources can be compared. For Diphtheria and Tetanus, a models by the IDM will be explored for inclusion; with the same base assumptions as used for the vaccines described above. Table 1 summarizes the current framework:

⁸The WHO looks like it has links to some Polio numbers. Following the 1988 resolution by the World Health Assembly the Global Polio Eradication Initiative (GPEI) has seen most Polio eradicated <http://polioeradication.org/>. I will just need to get country specific source data for this to get a country-specific counter-factual that can be extrapolated to 2030, assumed constant.

Table 1. Summary of analytical assumptions

<p>1 VIMC countries and vaccines</p>	<p>For the 110 VIMC countries and 10 vaccines i.e. HepB, Hib, HPV, Measles, PCV, Rotavirus and Rubella as well as the region-specific JE, MenA and YF. Determine</p> $\mu_{c,t} = f_c(t, cov_c, prev_c, \eta_c, \gamma_c)$ <p>from output but use the impact estimates from VIMC as data to be reproduced by the model</p>
<p>2 VIMC vaccines and remaining countries</p>	<p>For the 84 non-VIMC countries and for the same 10 vaccines i.e. HepB, Hib, HPV, Measles, PCV, Rotavirus, Typhoid, Cholera and Rubella as well as where relevant, the region-specific JE, MenA and YF. Apply the vaccines specific function from VIMC countries</p> $(\mu_{c,t} = f_c(t, cov_c, prev_c, \eta_c, \gamma_c)$ <p>taking average effects applied to the population in the cohort component model.</p>
<p>3 All countries Diphtheria and Tetanus</p>	<p>Use the outputs from the IDM model</p>
<p>4 All countries Typhoid, Cholera, BCG, Pertussis and Polio</p>	<p>Use the GBD, WHO and GPEI results in conjunction with coverage estimates to determine parameters for the function. In this case, extrapolate from last zero coverage year to get counterfactual trends in mortality.</p>

2.3 Expected outputs

The demographic model will output for each year, country, age and sex combination the numbers in the population projected to 2030 as well as the number of vaccine-specific deaths occurring under the observed scenario vs alternative scenarios. Of main interest is the alternative scenario in which no vaccines are introduced. However this can be changed to be some fixed coverage number e.g. the last observed number for 2019 and also an accelerated scale-up. The two main outputs will be dis-aggregated by sex and country and will be conditional on the assumptions of vaccine coverage in the scenario used for projection:

- Number of deaths attributable to each vaccine-preventable cause by period
- Number of deaths attributable to each vaccine-preventable cause by cohort

Ultimately, the impact of vaccination will be the difference between these numbers, estimated for each country and aggregated to give a global number. The outputs are largely in the mortality space.

2.4 Anticipated challenges

This framework assumes certain data availability, anticipated challenges are:

- Plausible assumptions on age-specific migration, fertility and age-specific non-VPD mortality for each country and year combination,
- Obtaining the cause-specific mortality and corresponding vaccine coverage for each country-cause combination,
- Averages from calibration of function may give implausible default values for the prevalence scaling factor, mortality reduction of vaccine scale-up impact,
- Correctly accounting for campaign/SIA vs routine coverage,
- Incorporating uncertainty,
- Determining non-fatal outputs e.g. YLDs to estimate DALYs. We could consider a crude approximation that assumes a constant relationship between YLLs and YLDs for each cause,
- Time-constraints - there is a tight-deadline to produce the preliminary estimates. These means some constraints on obtaining all the data, calibrating the models and running models for each country.

Vaccine Impact Estimates for Immunization Agenda 2030: For IVIR-AC recommendation

WHO IVB&DDI Project Team

23 September 2020

Agenda

1. Background & context
2. Project
3. Analytical framework
4. Questions for IVIR-AC

Background & Context

Why update the vaccine impact estimates?

An updated set of estimates based on latest information and robust methodology is required both for advocacy and measuring the impact of the Immunization Agenda 2030

1

Internal requests to update the estimates of lives saved by vaccines annually for **advocacy** purposes

- It has been frequently cited that 2.5 million lives are saved every year due to vaccination.
- This figure has been used to describe the impact of vaccines in WHO documents, media, on UN and other organization's websites and even in scientific literature.
- However, limited documentation of the methodology and scope of analysis requires us to revisit the figure.

2

IA2030: searching for robust ways to **measure impact** of the Immunization Agenda 2030

- There is an urgent need for advancing quantitative global analyses on vaccine benefits for monitoring and as well as for advocacy purposes
- Measures such as deaths averted by vaccines are core measures of impact

IA2030 M&E



- IA 2030 is putting together a joint framework Monitoring, Evaluation and Accountability for which a draft will be presented at SAGE
- A measurement approach (including indicators) is being developed in parallel
 - A key area is how to measure the impact goals?

IA2030 Three Impact Goals



Vision



Impact goals

1

A world where everyone,
everywhere, at every age...



Reduce mortality and morbidity from vaccine-preventable diseases for all across the life course.

2

...fully benefits
from vaccines...



Leave no one behind, by increasing equitable access and use of new and existing vaccines.

3

...for good health
and well-being



Ensure good health and well-being for everyone by strengthening immunization within primary health care and contributing to universal health coverage and sustainable development.

Project objectives

WHO IVB and DDI aim to:

- Update the modeled **vaccine impact estimates**
- Document the **methodology** in a transparent manner
- Inform **strategic priorities** for:
 - Immunization Agenda 2030
 - Triple Billion target for the Thirteenth General Programme of Work (GPW 13),
- Provide **baseline estimates** for IA2030 Impact Goal 1.

Project

Stakeholder Committee & Project team

Stakeholder Committee

- **BMGF:** Emily Dansereau/Brittany Hagedorn
- **CDC:** Mike Lynch
- **Gavi:** Dan Hogan
- **IHME:** Jon Mosser
- **VIMC*:** Katy Gaythorpe
- **VIMC* Scientific Advisory Board:**
 - Cherry Kang (**Christian Medical College, Vellore, India**)
 - Ulla Griffiths (**UNICEF**)
 - Raymond Hutubessy (**WHO IVB**)
- **WHO IVIR-AC:** Walt Orenstein
- **WHO DDI:** Somnath Chatterji
- **WHO IVB:** Ann Lindstrand

VIMC: Vaccine Impact Modelling Consortium

Project team

- **Supervision:** Raymond Hutubessy
- **Analytics:** William Msemburi, Austin Carter
- **Project management:** Yoonie Sim
- **IVB focal point:** Olivia Bullock
- **ME&A focal point:** Jan Grevendonk
- **VIMC focal point:** Katy Gaythorpe (VIMC)

Timeline & Deliverables

Project timeline

IA2030 ME&A timeline

2020	July	Work plan, scoping exercises and selection of the Stakeholder Committee (SC) members
	August	Analytical framework presented to IA2030 ME&A taskforce
	September	Kick-off meeting with SC
	October	Analytical framework & methodologies presented to IVIR-AC
	November	Project updates presented to SC
	December	Preliminary results presented to SC
2021	January	A slide deck, draft manuscript and database for the final estimates*
	February	Final results presented to SC
	March	
	April	Publication of the manuscript in a peer-reviewed journal*
	May	Close-out meeting with SC

■ Project deliverables*

Finalization of IA2030 strategic priority and impact goal indicators & outline of the framework presented to SAGE

IA2030 Draft ME&A framework to be reviewed by SAGE, regions, SB, EB and core partners

IA2030 final ME&A framework submitted to the World Health Assembly

Scope of Analysis

- **Timeframe:**
 - 2021-2030
- **Vaccine impact estimates:**
 - Primary indicator: future deaths averted due to vaccination
 - Additional indicators (TBD)
 - Future DALYs averted due to vaccination
 - Economic impact
 - <5 yr mortality rate prevented by vaccines/ (<5 yr mortality rate+<5 yr mortality rate prevented by vaccines)
 - Mortality rate prevented by HepB and HPV vaccines/ (mortality rate prevented by HepB and HPV vaccines+ mortality rate attributed to cardiovascular disease, cancer, diabetes or chronic respiratory disease)
- **Countries:**
 - 194 WHO Member States
 - Global, regional and country estimates

Scope of Analysis

- 17 pathogens/diseases and vaccines (TBD)

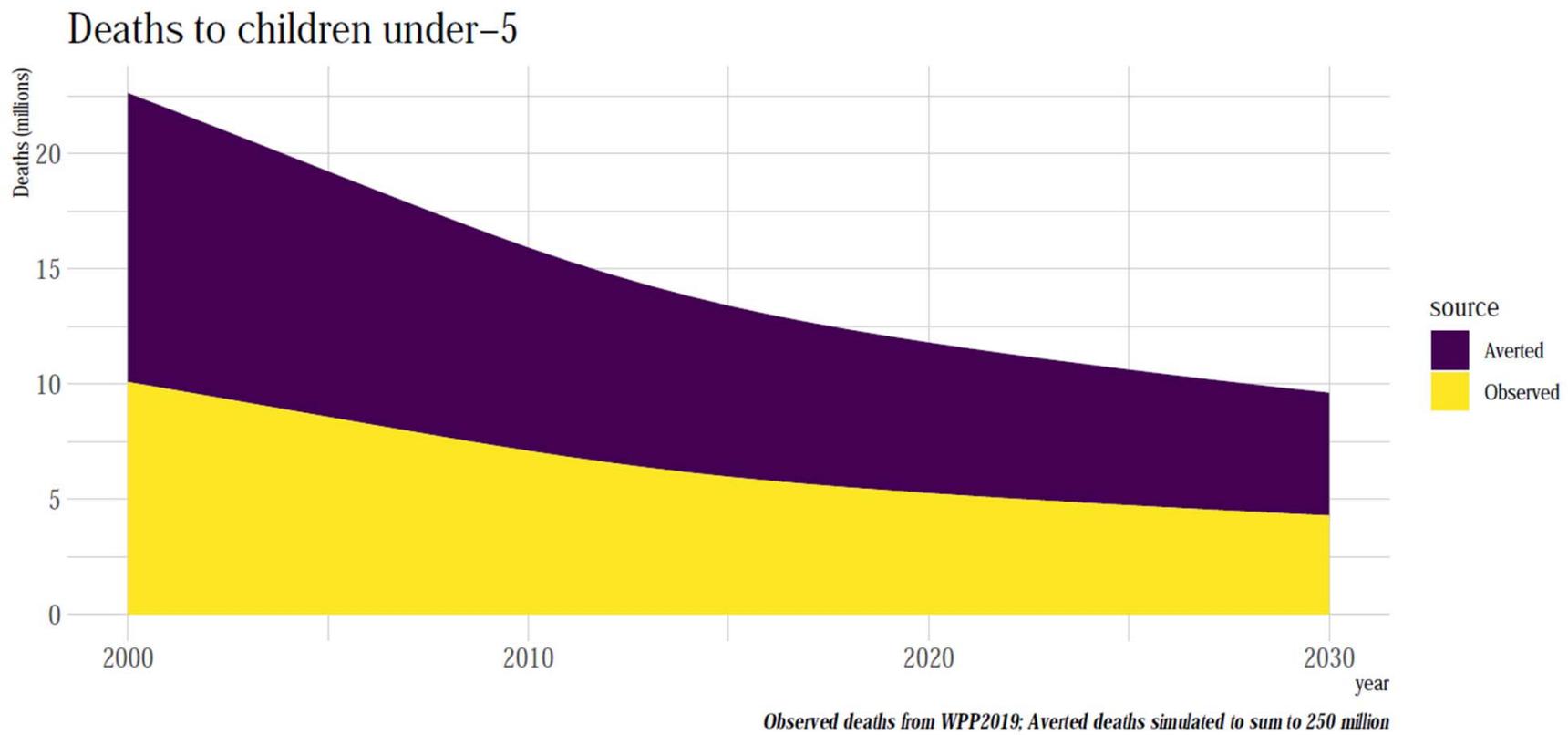
	Pathogens	Vaccines (WHO VPD monitoring system)
1	Cholera	Cholera
2	Diphtheria	Diphtheria-containing combination
3	Hepatitis B	Hep B birth dose, Hep B-containing combination
4	Hib	Hib-containing combination
5	HPV	HPV
6	Japanese encephalitis	JE inactivated, JE live
7	Measles	Measles, MM, MR, MMR, MMRV
8	Meningitis A	Men A, Men A conjugate
9	Pertussis	Acellular or whole cell pertussis-containing combination
10	Pneumococcal	Pneumococcal PS, Pneumococcal conjugate
11	Polio	OPV, IPV
12	Rotavirus	Rotavirus
13	Rubella	Rubella, MR, MMR, MMRV
14	Tetanus	Tetanus toxoid-containing combination
15	Typhoid	Typhoid PS, Typhoid conjugate
16	Yellow Fever	YF
17	TB (BCG)	BCG

 Included in VIMC portfolio*

Inclusion criteria for target pathogens to be refined based on available data and feasibility assessment

Analytical framework

Goal: determining number of deaths averted



How? Counterfactual demographic change

- Project population forward using cohort component projection model (CCPM)

$$P_{t+1} = L(P_t + 0.5M_t) + 0.5M_t$$

where $P[i]$ is vector of age- and sex-specific population numbers at time $[i]$, L is Leslie matrix comprising of fertility and survival factors and $M[i]$ gives relative number of net-migrants.

- Assume migration and fertility according to WPP2019
- Survival indirectly proportional to mortality
 - Mortality comprises of "VPD" component and "Non-VPD" component

Vaccination CCPM model: calibration

$$\mu_{c,t} = f_c(\text{cov}_t, \text{prev}_t, \eta_t, \gamma_t)$$

- Assume VPD mortality for some antigen related cause-of-death c is a function of coverage, the prevalence of the condition, case-fatality and mortality reduction due to vaccination
- Calibrate CCPM model to estimate these elements using
 - VIMC deaths averted estimates vs vaccine coverage (110 countries & 10 vaccines)
 - GBD cause-specific mortality estimates vs vaccine coverage (all countries, remaining vaccines)
- Project coverage to 2030, estimating VPD deaths for each year
- Based on estimated function, infer deaths when coverage is 0 (assume fertility, migration and non-VPD mortality remain unchanged) and project "no vaccination" mortality to 2030

Vaccination CCPM model: outputs

- Total and VPD deaths by age-sex-year-country under business as usual scenario
- Total and VPD deaths by age-sex-year-country under no-vaccines scenario
 - Estimates of deaths averted
- Cohort and period estimates of VPD deaths and deaths averted
- Country quintiles of performance between 2000 and 2020 (mortality reduction)
- Use highest performing to inform feasibility and target setting

Questions for IVIR-AC

Questions for IVIR-AC

- How to best include a structure of competing risk (to avoid double counting)?
- How to best compare health outcomes with a short-term impact vs long term impact (Measles vs HPV vaccine)?
- How to include different sources of uncertainty?

Session 8:

CAPACITI

CAPACITI | Country-led Assessment for Prioritisation on Immunisation

A systematic approach to support decision-making



Background

Birgitte Giersing (WHO/IVB)

IVIR-AC, 24 September 2020

What is the goal of CAPACITI?

To strengthen the ability of LMICs to **evaluate immunisation products, services and/or strategies** according to their priorities and programme context, both for national immunisation programme decisions and to inform vaccine supply, research and development

What is the goal of CAPACITI?

To strengthen the ability of LMICs to **evaluate immunisation products, services and/or strategies** according to their priorities and programme context, both for **national immunisation programme decisions** and to inform vaccine supply, research and development

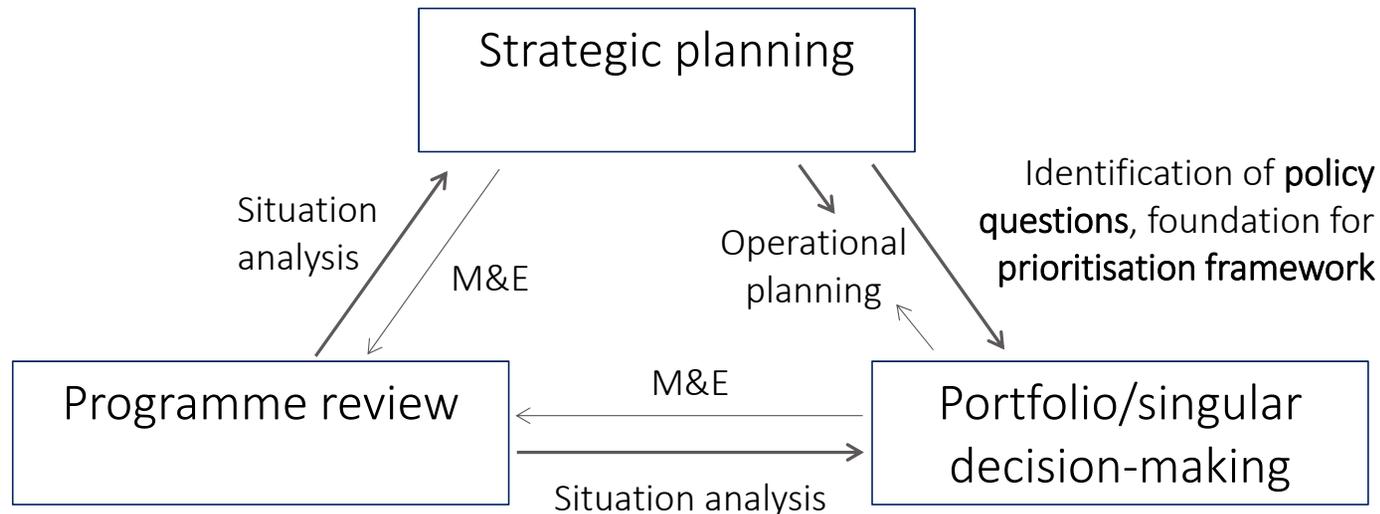
Strong country-led priority-setting is essential for national immunisation programmes to achieve IA2030 goals



➤ Especially in the COVID-19 context:

- anticipated **budget constraints** with economic contraction due to COVID-19
- comparing options to **continue vaccination activities** given COVID-19 response
- prioritising populations and delivery strategies for a **COVID-19 vaccine**

Priority-setting at the country level ideally incorporates programme review, strategic planning, and individual decisions

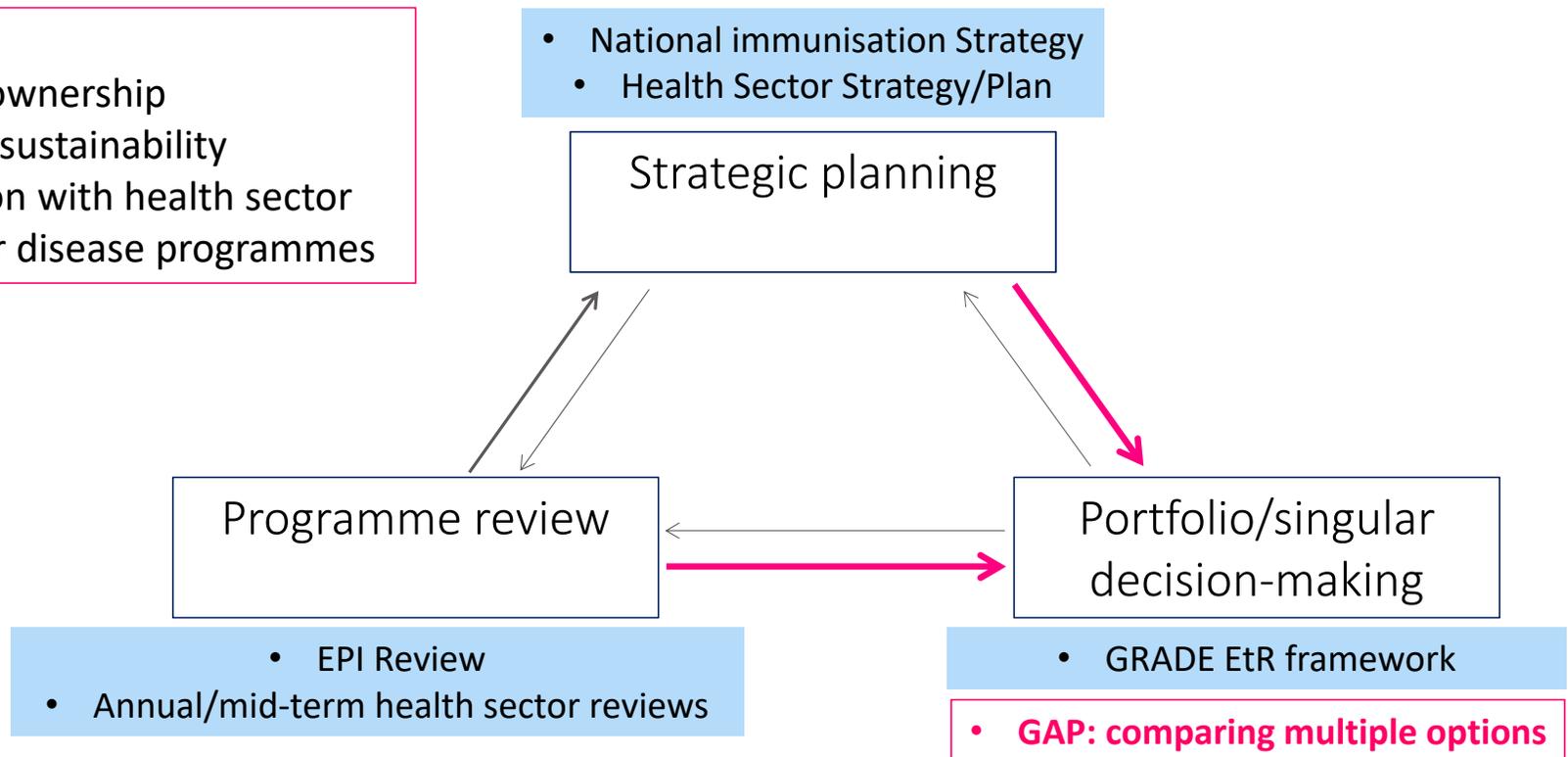


Source: Lauer J, Rajan D, Bertram M. Priority Setting for Universal Health Coverage: We Need to Focus Both on Substance and on Process Comment on "Priority Setting for Universal Health Coverage: We Need Evidence-Informed Deliberative Processes, not Just More Evidence on Cost-Effectiveness". International Journal of Health Policy and Management. 2017;6(10):601-603. 562

There are gaps in WHO guidance for national immunisation programme priority-setting processes

Key issues:

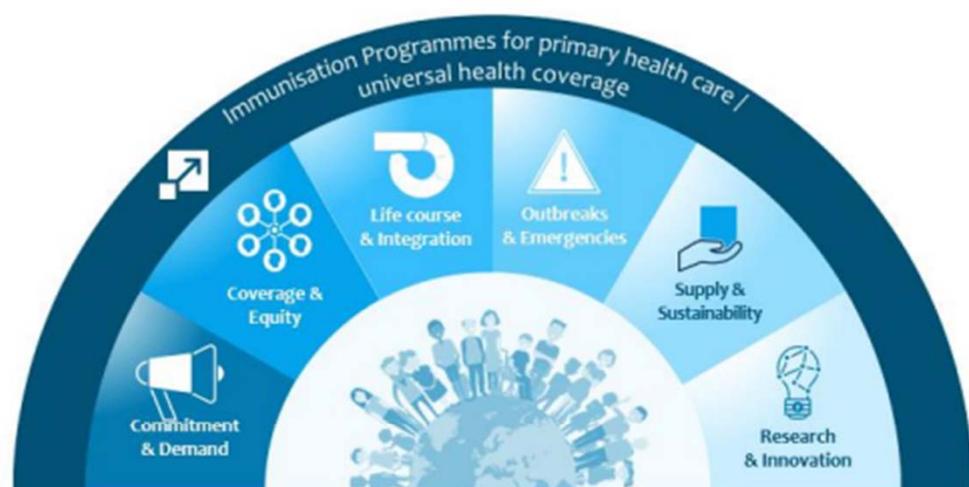
- Country ownership
- Financial sustainability
- Integration with health sector and other disease programmes



What is the goal of CAPACITI?

To strengthen the ability of LMICs to **evaluate immunisation products, services and/or strategies** according to their priorities and programme context, both for national immunisation programme decisions and **to inform vaccine supply, research and development**

Strong country-led priority-setting is also essential for SP7: Research & innovation

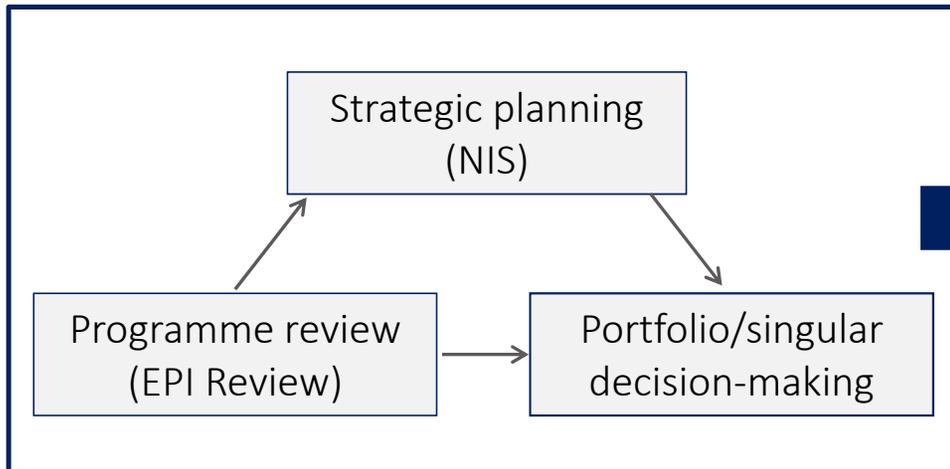


➤ Country and regional engagement is needed to ensure that **R&D is tailored to the needs of LMICs**:

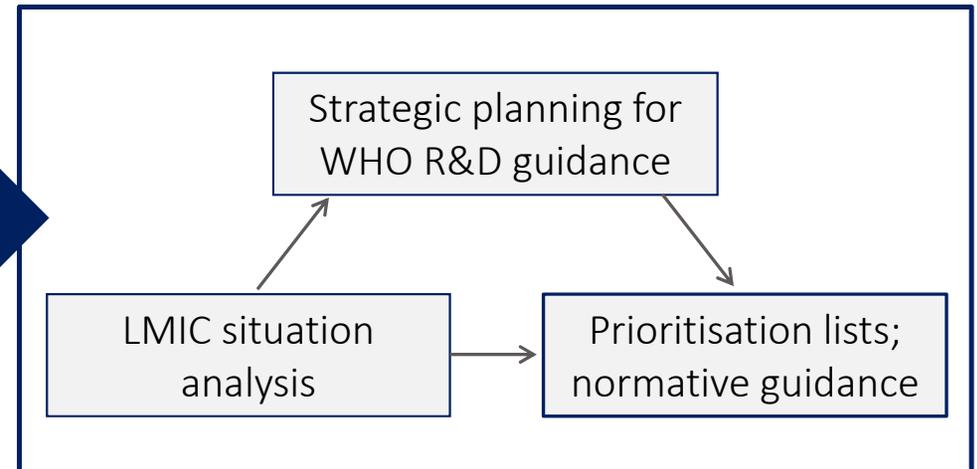
- what are global and regional **strategic priorities** for immunisation R&D?
- which **product areas or manufacturing platforms** should be prioritised?
- which **product characteristics** are desirable to countries?
- what **data** is needed to inform national policy and uptake?

R&D prioritisation should be aligned with immunisation programme prioritisation

WHO support for NIP priority-setting processes

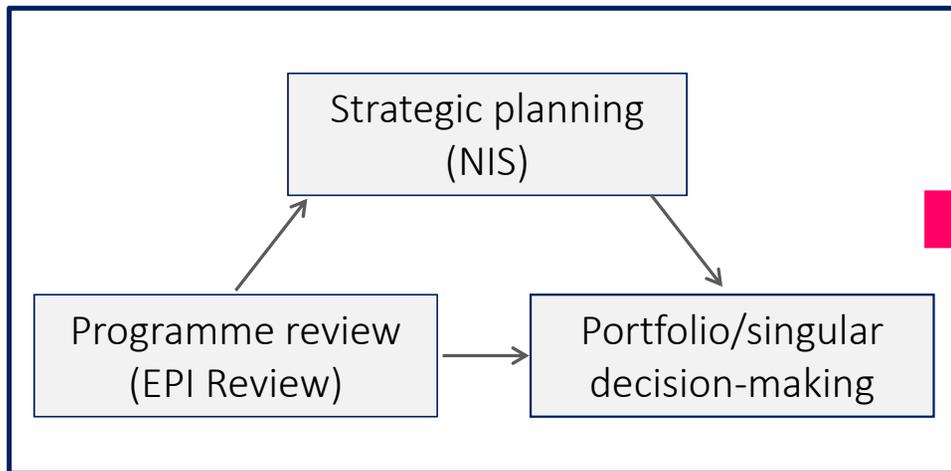


WHO R&D priority-setting processes

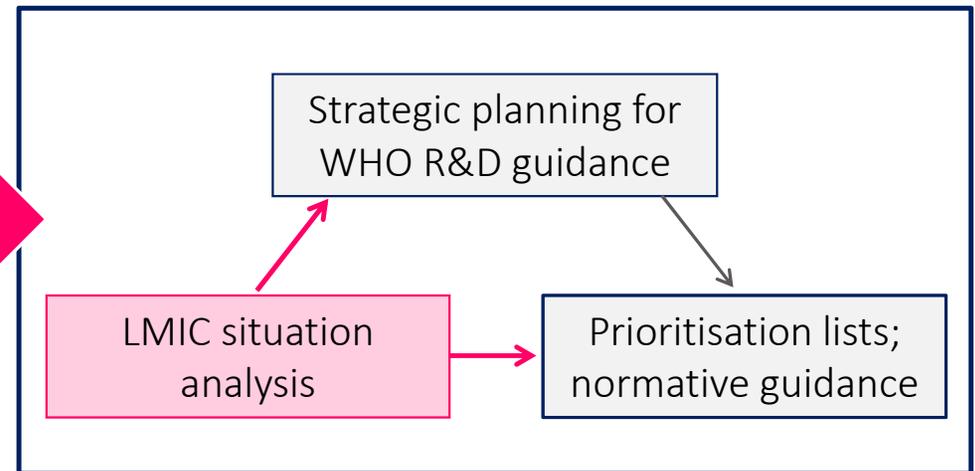


But we have no established mechanism or platform to systematically link NIP and R&D priority-setting

WHO support for NIP priority-setting processes



WHO R&D priority-setting processes

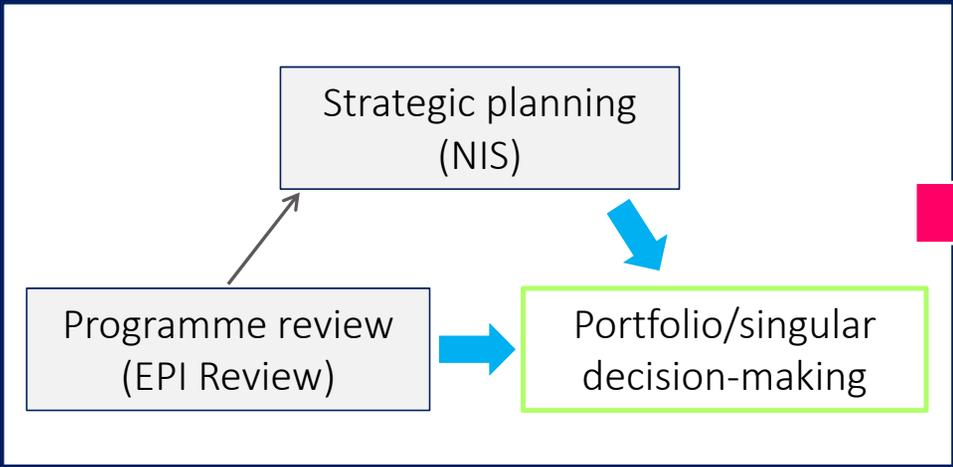


Key issues:

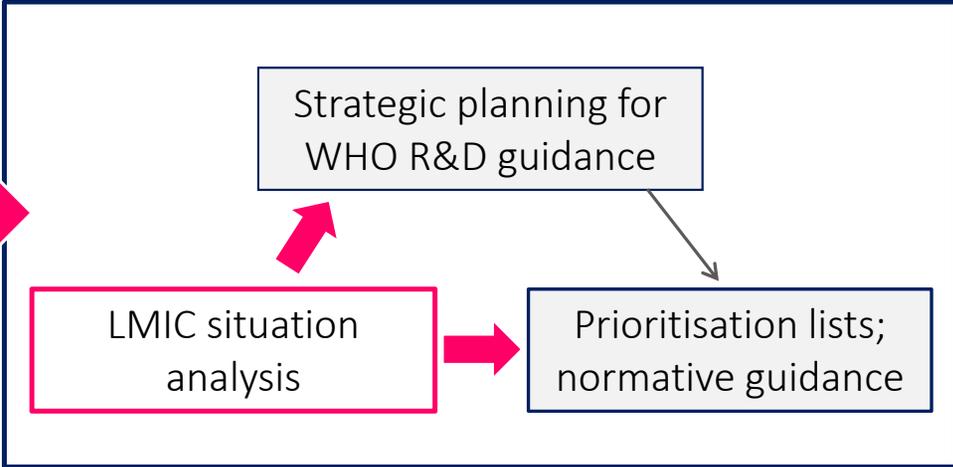
- Uncertain demand => **no incentive to invest** in products with potential public health impact
- No LMIC validation of target profiles => **slow or poor LMIC uptake** of products coming to market

CAPACITI aims to address gaps in WHO guidance for NIP and R&D priority-setting processes

WHO support for NIP priority-setting processes



WHO R&D priority-setting processes



Country context framework

Decision-support framework

Innovation framework

Concurrently strengthening and linking NIP and R&D priority-setting would be mutually beneficial

Benefit for R&D stakeholders:

- Stronger NIP processes improves consistency of country decision-making (and **predictability of uptake**)
- Better understanding of **product profiles** and **evidence required** for country uptake
- Better understanding of **use case** and **potential demand**

Benefit for NIP stakeholders:

- Better insight into future decisions:
 - **Decision-making and regulatory processes** are equipped for the future
 - Greater foresight for **programme planning** to facilitate rapid uptake
- Stronger **negotiation power**
 - Countries have defined “value” and/or willingness to pay for local context
 - Procurement agencies (e.g. PAHO Revolving Fund, Gavi) have better demand forecasting

Structure of this session

1. Review of the CAPACITI **decision-support** framework and Excel tool
 - Pilot involved 12 countries across Africa, Asia, the Americas
 - Presented to IVIRAC in Sep 2019
 - **Is the decision-support tool ready to be made available online Dec 2020?**
2. Review of the CAPACITI **country context** and **innovation** frameworks
 - Overview of piloting experience, framework iterations, and learnings
 - Brainstorming with the committee
 - **Does the committee have advice on the structure and development of the country context and innovation frameworks?**

CAPACITI | Country-led Assessment for Prioritisation on Immunisation

A systematic approach to support decision-making



Decision-support framework and Excel tool

Praveen Thokala (University of Sheffield)

IVIR-AC, 24 September 2020

Purpose of the decision-support framework

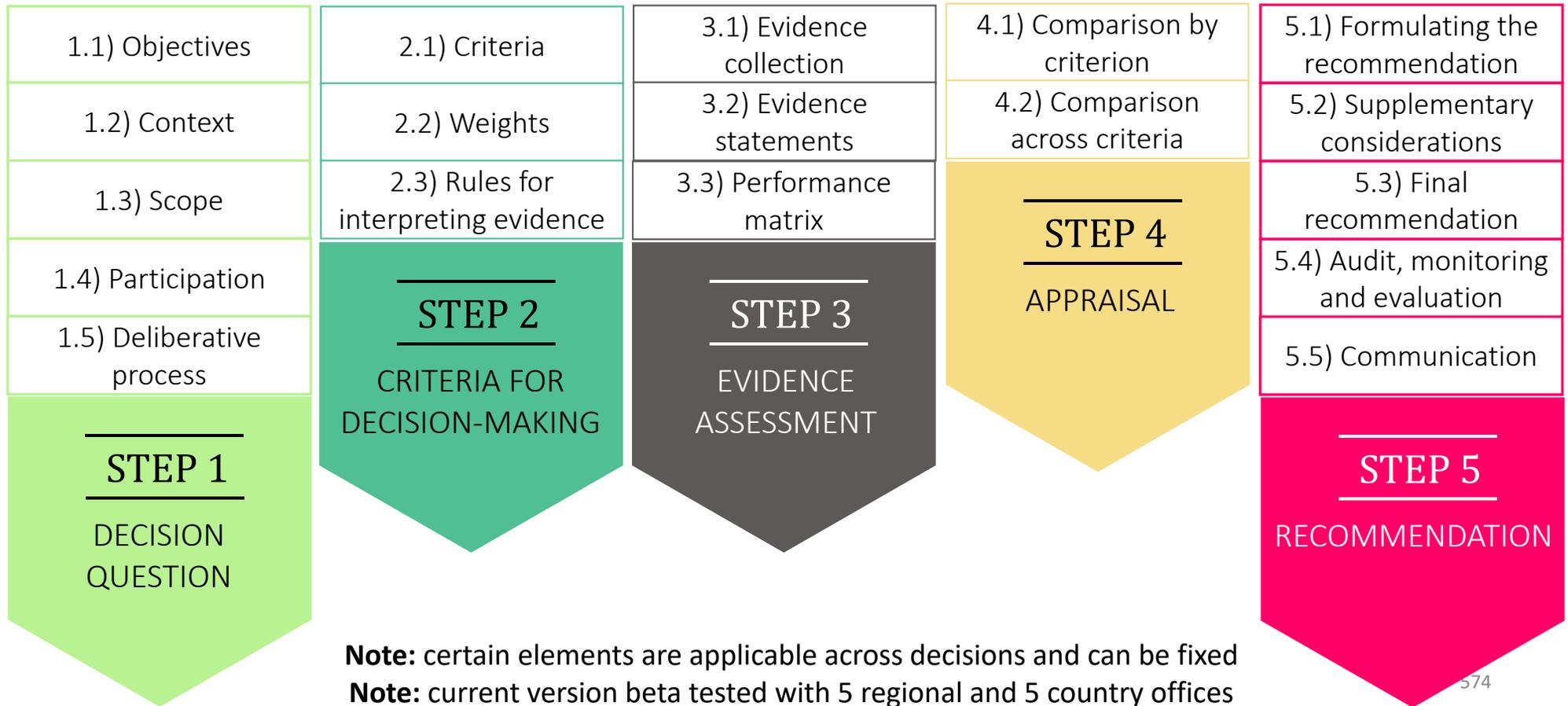
For comparison between **two or more options** when there is:

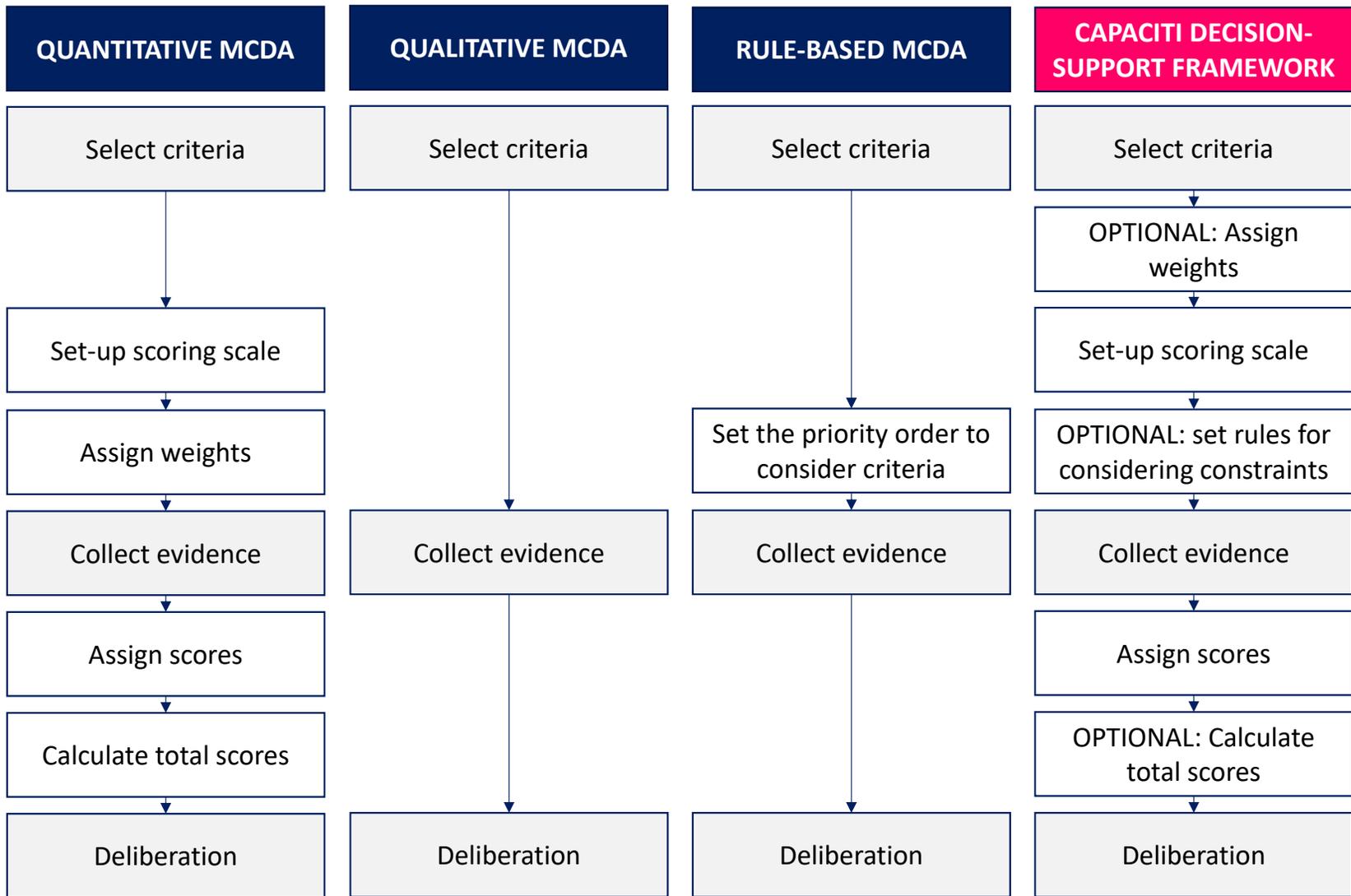
- input from **multiple stakeholders**
- use and contextualisation of **evidence across disciplines**
- incorporate **social values** and/or implementation feasibility
- significant data **uncertainty**

IVIR-AC recommendations (Sep 2019)

1. The framework should be flexible to discussion-based or threshold-based approaches
2. Quantitative MCDA should not be recommended without the expertise to select and weight criteria
3. Separation of cost criteria should be left to countries
4. The tool should be piloted for strategy choice (e.g. improving coverage)
5. The tool should incorporate perspective of vaccination providers, communities and individuals

Overview of the framework





Modification 1: flexibility to different types of MCDA or a hybrid approach

Guidance on the pros/cons of each approach

Recommended approach:

- Weighting (so that committee members understand each others' perspective)
- Scoring scale (increased transparency and consistency in interpreting the evidence)
- Total scores (quantitative MCDA) **may or may not** be used to interpret the evidence
- Focus is on **deliberation**

		MCDA methods			CAPACITI decision-support framework
		Quantitative	Qualitative	Rule-based	
1) Objectives					
2) Decision criteria	Select criteria (2.1)	✓	✓	✓	Mandatory The committee may use an existing criteria list or select criteria de novo
	Assign weights to criteria (2.2)	✓	✗	✗	Recommended Discussing weights can promote a shared understanding of which criteria are most important across the committee.
	Set a scoring scale (2.3.1)	✓	✗	May use threshold	Recommended Agreeing the scale by which to assess the options can remove bias and enhance consistency in interpreting the evidence.
	Define rules (2.3.2)	✗	✗	✓	Optional It is possible to state whether certain criteria will be considered before/after the total scores in <u>quantitative</u> MCDA (for example, cost-effectiveness).
3) Evidence assessment					
4) Appraisal	Assign scores (4.1)	✓	✗	✗	Recommended Facilitates reporting of the recommendation and aligns with the GRADE ETR framework.
	Calculate total scores (4.2)	✓	✗	✗	Optional (for quantitative MCDA only)
	Sensitivity analysis (4.2)	✓	✗	✗	Optional (for quantitative MCDA only)
	Deliberation across criteria (4.2)	From total score	From summary matrix	In order stated by rules	For all approaches, it is strongly recommended to refer to the evidence statements (3.2) during appraisal.
5) Recommendation					

Modification 2: incorporation of constraints for quantitative MCDA

It is recommended that constraints are considered separately to the total scores:

- Fixed budget
- Cost-effectiveness threshold
- Fixed cold chain capacity
- Human resources limitations
- Etc

It is recommended to **set the weight to zero** and to consider constraints

- either **before** to shortlist options
- or **after** to consider feasibility



Modification 3: greater guidance on stakeholder engagement

The tool includes the following steps:

1. Which stakeholders should be engaged for **information, legitimacy, or ownership?** (based on Fung's principles)
2. Where does the decision question sit? (for example, NITAG mandate, ICC, requires ad-hoc committee) and **are there TORs/SOPs determining stakeholder selection and/or interaction?**
3. Based on 1 and 2, identify **who is on the recommendation committee** and **how will other stakeholders be engaged?**

CAPACITI | Country-led Assessment for Prioritisation on Immunisation

A systematic approach to support decision-making



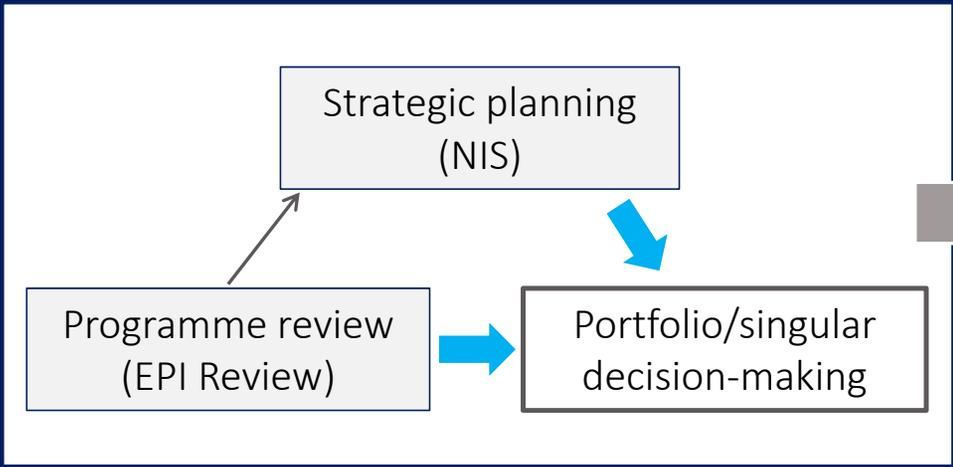
Country context & innovation frameworks

Siobhan Botwright (WHO/IVB)

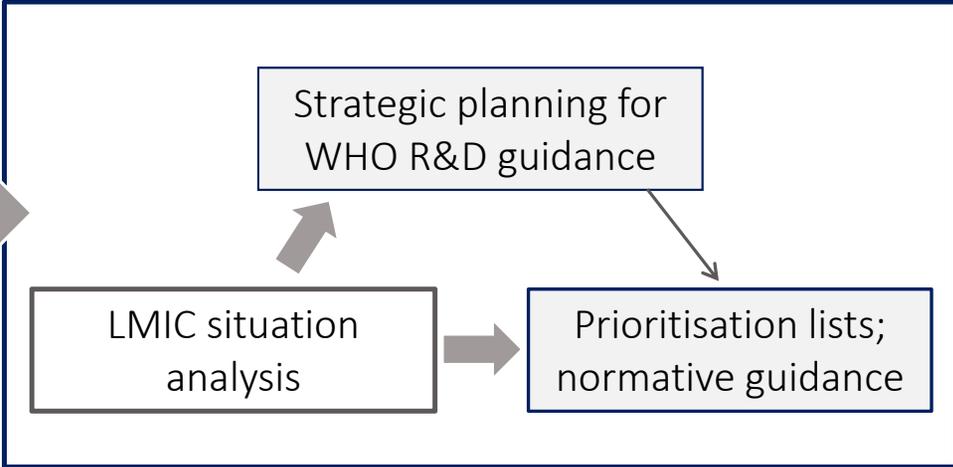
IVIR-AC, 24 September 2020

Current progress on the country context framework

WHO support for NIP priority-setting processes

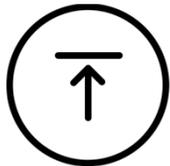


WHO R&D priority-setting processes



— Country context framework — Decision-support framework — Innovation framework

Rationale – why is this part of CAPACITI?



MALI

The decision-support tool could better incorporate **programme constraints**



INDONESIA

Identifying **bottlenecks to immunisation** would strengthen the decision-support process



CUBA

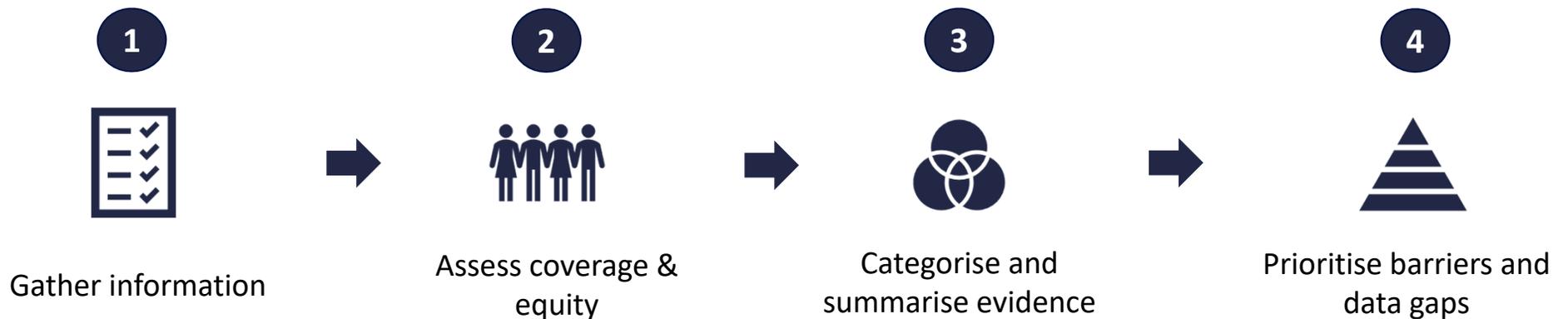
Review of programme pre/post PCV introduction will inform **rotavirus decisions** and **R&D for PCV-penta** combination vaccine

Initially conceptualised as an **algorithm/flowchart to select criteria** according to **coverage and equity bottlenecks**. But:

- Not flexible to country context or question
- No **comprehensive source** to holistically summarise and document country programme +/-
- **Beyond criteria**: decision question, stakeholders, options, fixed constraints, scoring scales, ...

Country-context framework: Version 1

Synthesises evidence on barriers to immunisation **before** using the decision-support tool



- The review does not involve primary data collection
- It can be conducted in workshop format or as a desk review
- The review is country-led and uses country-specific data

1 Information sources

Suggested keywords for search in document: *funding, national policy, vial*

Program management & financing	Comprehensive multi-year plan (cMYP)	EPI review	Missed opportunities for Vaccination (MOV) Assessments
	1	1	N/A

2

Date when the table was completed	25/08/2020
-----------------------------------	------------

3

Policy & guidance: Adequate national immunization laws and policies regarding immunization practices (e.g. opening multi-dose vials, catch-up vaccination, discarding vaccine wastage)	Did you identify information about the barrier?	Is there a reason to believe there is a barrier? (YES/NO)	Which findings suggest there is/isn't a barrier?	Source (Document name, page, etc.)	Potential data limitations	Any other (e.g. does disproportion affect)
<p><i>Guiding questions</i></p> <ul style="list-style-type: none"> • Are there national policies regarding immunization practices? • Are they clearly stated? • Are health workers aware of the policies? • Do health workers have clear understanding of policy? • Are health workers aware of the policy, but concerned about wastage criticisms? 	YES	yes	<ol style="list-style-type: none"> 1. Some findings are that the national policy is not yet aligned to global recommendation to expand age range as per global recommendation (e.g. Rota, MR) 2. Based on the PIE/EPI Review (2014) findings, coverage for antigens provided at same age/visit not consistent 3. Very few adverse events following immunisation (AEFI) have been reported. 4. Incorrect technique of administration of injectable vaccines 5. Some Health Workers not aware of the national policy or misinterpret the national policy on vaccinations (e.g. age limit on Rota vaccination as per national guideline) 6. Staff reluctance to open multi-dose vials for small vaccination sessions 	<ol style="list-style-type: none"> 1. PIE/EPI Review (2014) Page 30 2. PIE/EPI Review (2014) Page 30 3. PIE/EPI Review (2014) Page 30 4. PIE/EPI Review (2014) Page 30 5. PIE/EPI Review (2014) Page 30 6a. PIE/EPI Review (2014) Page 30 6b. 10-dose versus 5-dose MR Study, pageX 		

Prioritize the barriers that were identified in the previous step (the list below is self-generated based on previous answers) based on the guiding questions that are given in Table 1. In the field below briefly comment on the prioritisation process. What were your main considerations?

Note that the prioritization of barriers should be based on relative importance of the barrier compared to the other barriers. The shaded area in Table 1 is automatically populated based on your previous answers in Step 3.

<i>Automatically generated list including all the barriers that were identified</i>	Priority	<i>Comments</i>
Policy & guidance: Adequate national immunization laws and policies regarding immunization practices (e.g. opening multi-dose vials, catch-up vaccination, discarding vaccine wastage)		
Policy & guidance: Missed opportunities resulting from regulation/policy restrictions prevent some health worker cadres or non-health workers from administering vaccines		
Governance & accountability: Level of functioning of the NITAG and related national-level immunization committees		
Governance & accountability: Poor communication and information flow between different levels of the health sector		
Planning & procurement: Efficient planning processes, aligned with other planning processes and linked to financial planning		
Budgeting & financing: Insufficient national financial resources for allocations to immunization		

Country context framework – version 1



Positive feedback

West Africa, Cuba, Zambia,
Indonesia



Requires **significant time**
and effort to complete



Broader applicability
at the country level

The workbook will be incorporated to **support the initial stages of the EPI review**

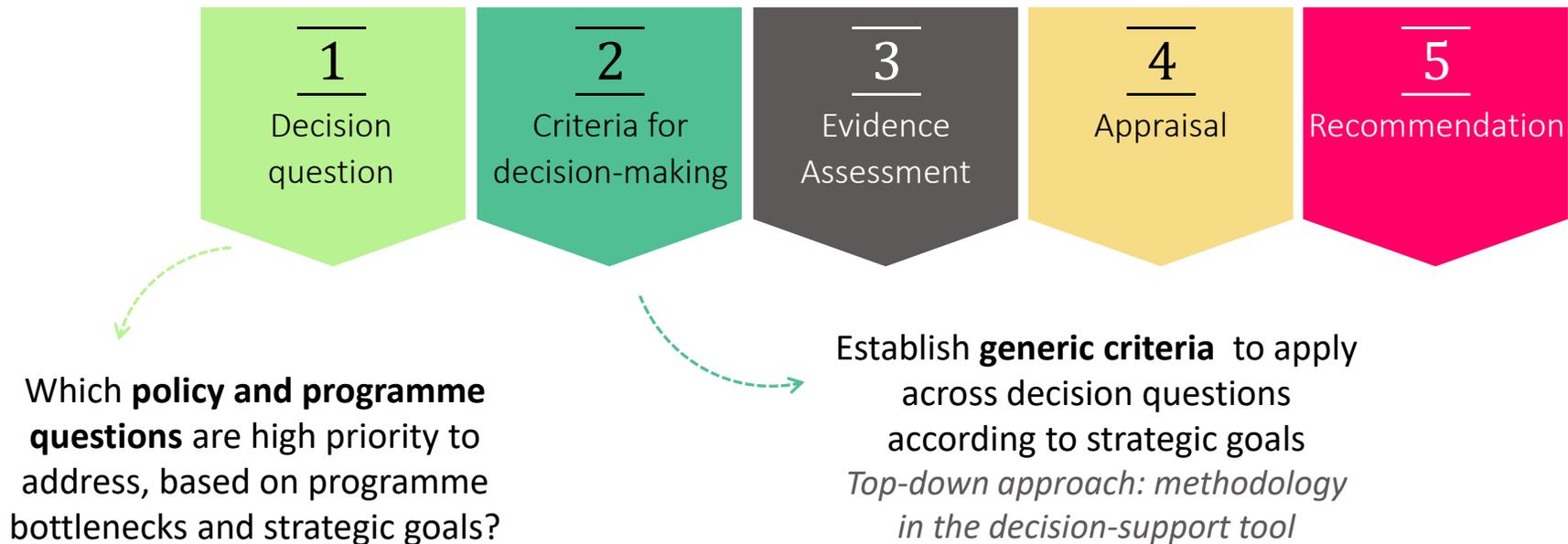
The focus of CAPACITI is instead:

- How do the outputs **link to the decision-support tool?** (not obvious in Indonesia)
 - Also link to **national immunisation strategy** and **health sector alignment**

Country context framework – current thinking

APPLICATION 1: institutionalising the decision-support framework

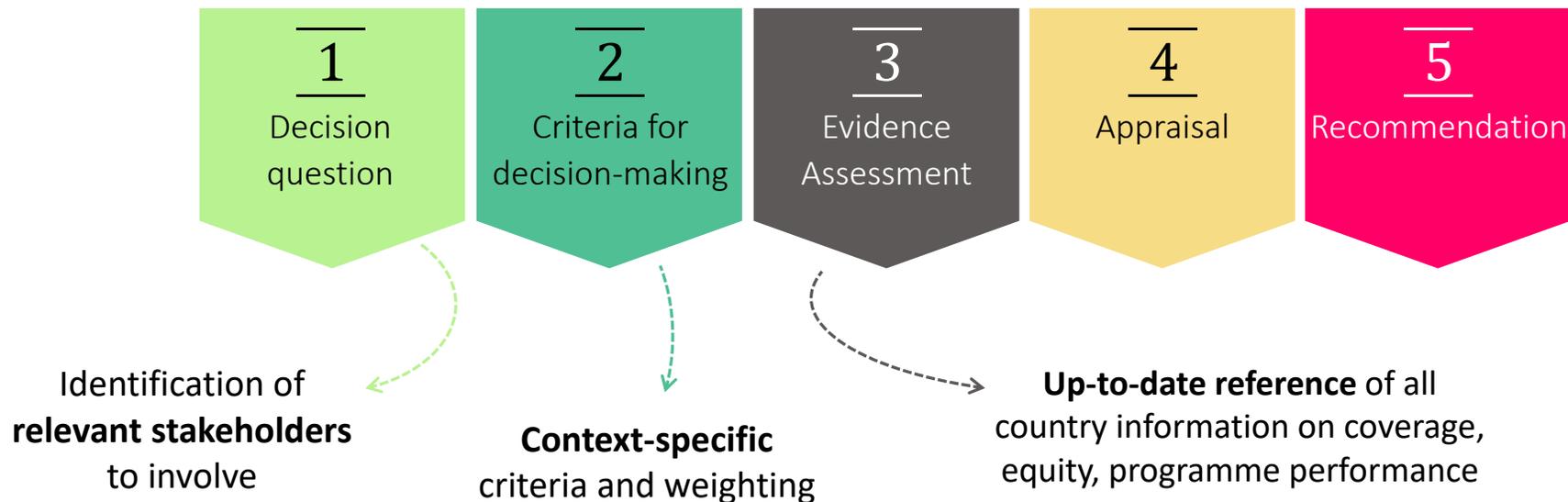
Using EPI Review workbook, NIS, health sector strategy and reviews



Country context framework – current thinking

APPLICATION 2: specific questions for decision-support framework

EPI workbook, perhaps with further reference to individual data sources (e.g. BeSD, TIP, PIE)



Country context framework – current thinking

What is the best format?

- Guidance accompanying the decision-support tool?
- Information sheets at relevant points within the tool?
- ...?

Important considerations:

- Country flexibility
- DIALOGUE

INFORMATION SHEET

Selecting or reviewing the set of decision criteria (2.1)

◀ Return to sheet
2.1 Criteria list

[1\) Using standardised or question-specific criteria](#)

[2\) Using an existing set of criteria](#)

[3\) Developing a set of criteria specific to the decision question \(one-off approach\)](#)

[4\) Establishing a set of criteria for use across recommendations \(institutionalised approach\)](#)

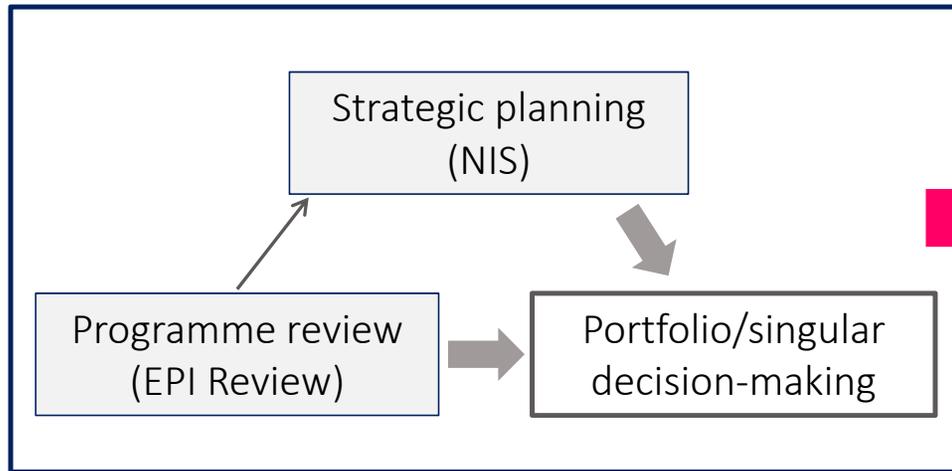
1) Using standardised or question-specific criteria

Refer to manual: 2. Criteria for decision-making, pages 37-38

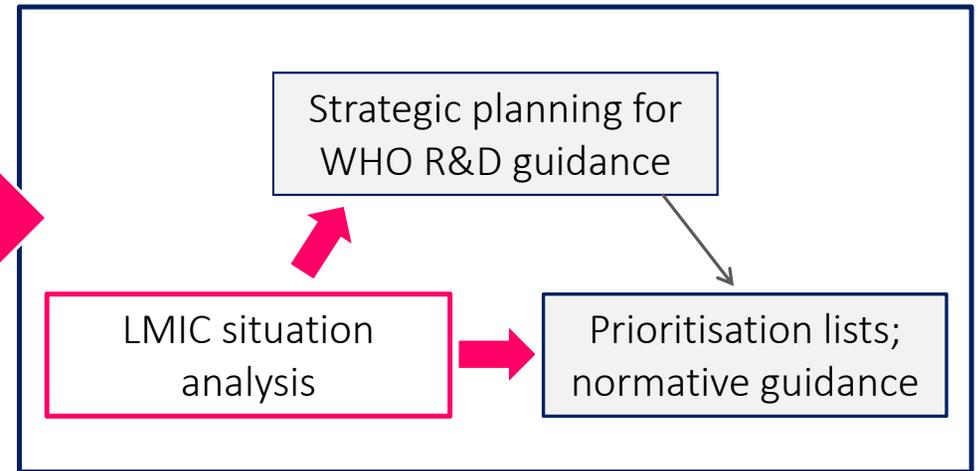
In most situations, it is recommended to establish a standard set of criteria to apply across decision questions, since this can streamline the criteria selection process and enhance consistency of decision-making. This is referred to in the table below as an "institutionalised approach".

Innovation framework: initial testing and iterations

WHO support for NIP priority-setting processes



WHO R&D priority-setting processes



— Country context framework

— Decision-support framework

— Innovation framework

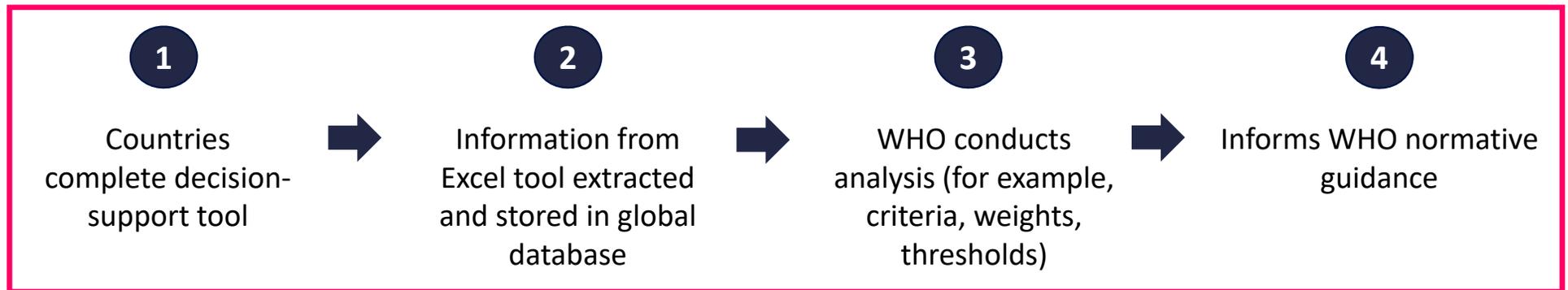
Archer R, Kapoor R, Isaranuwatthai W, Teerawattananon Y, Giersing B, Botwright S et al. 'It takes two to tango': Bridging the gap between country need and vaccine product innovation.

Innovation framework – version 1

Countries enter data; product-specific characteristics can be modified to identify thresholds to out-perform current options; **standardised criteria and scoring scales across countries for simplified analysis**

			RV-Vaccine 1		RV-Vaccine 2		RV-Vaccine 3		RV-Vaccine 4	
		Weights	Score		Score		Score			
Health impact	Vaccine efficacy	10	78	7.8	65	6.5	52	5.2	65	6.5
	Product attributes impacting vaccine effectiveness:	2	8	0.16	4	0.08	4	0.08	5.333333	0.106667
	Duration of protection	8	25	2	10	0.8	8	0.64	14.333333	1.146667
Financial Impact	Financial Risk protection	26	90	23.4	40	10.4	75	19.5	68.333333	17.766667
Coverage	Increase coverage	14	3	0.42	5	0.7	7	0.98	5	0.7
	Product attributes impacting reach and timeliness:	8	2	0.16	8	0.64	8	0.64	6	0.48
Safety	Adverse events following Immunization	0	32	0	54	0	31	0	39	0
	Product attributes impacting safety:	0	23	0	15	0	26	0	21.333333	0
Commodity cost	Vaccine product costs including wastage	2	12	0.24	44	0.88	11	0.22	22.333333	0.446667
	Delivery technology costs	10	24	2.4	21	2.1	13	1.3	19.333333	1.933333
	Safety box costs	0	25	0	88	0	46	0	53	0
Delivery cost	Storage costs	20	56	11.2	15	3	13	2.6	28	5.6
	Transport costs	0	44	0	45	0	55	0	48	0
	Administration costs	0	23	0	21	0	22	0	22	0
	Waste disposal costs	0	10	0	21	0	32	0	21	0
	Introduction costs	0	12	0	12	0	21	0	15	0
		100								
				47.78		25.1		31.16		34.68

Innovation framework – version 2



Innovation framework – version 2

Category	Criteria	Weight	Score		
			Vaccine A	Vaccine B	Product X
Health impact	Effectiveness	25	3	3	
Cold chain impact	Thermostability	10	3	1	
	Cold chain volume per course	5	3	4	
Equity	Ability to reach unvaccinated populations	40	4	2	
Economic impact	Cost per full course including wastage	20	3	3	
TOTAL SCORE			340	245	0
RANK ORDER			1	2	3

Product X data
Efficacy: 85%
Thermostability: 24 months at 2-8°C

Reference: scoring scales

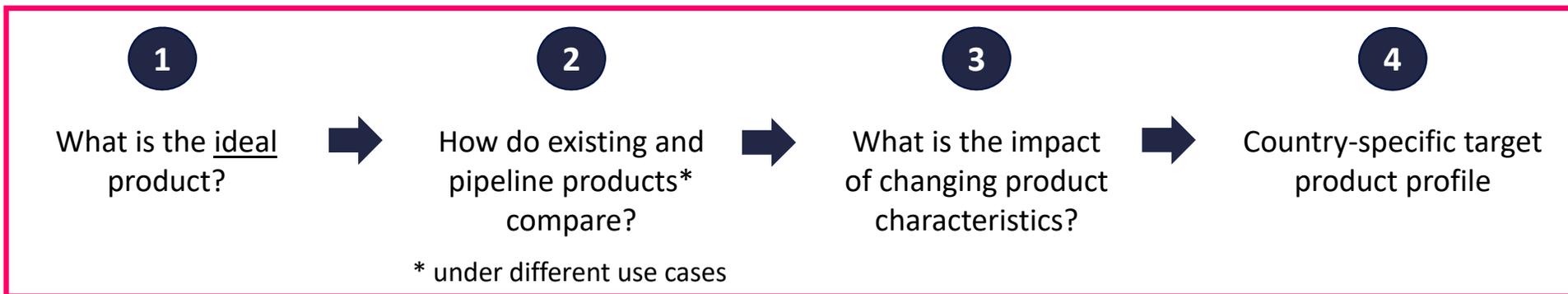
Category	Criteria	1	2	3	4	5
Health impact	Effectiveness	0-40%	40-50%	50-60%	60-80%	80-100%
Cold chain impact	Thermostability	Requires storage below 0°C or less than 12 months storage	12 months at 2-8°C	24 months at 2-8°C	24 months at 2-8°C and CTC (3 days at 40°C)	24 months at 2-8°C and over 30 days at 40°C
	Cold chain volume per course	Greater than 100cm ³	30-100cm ³	20-30cm ³	10-20cm ³	Less than 10cm ³
Equity	Ability to facilitate outreach	Outreach significantly more difficult	Outreach slightly more difficult	Baseline - DTP3 vaccination	1-2 characteristics facilitating outreach	3+ characteristics facilitating outreach
Economic impact	Cost per full course	Over \$10	\$6-\$10	\$4-\$6	\$1.50-\$4	Less than \$1.50

Innovation framework – version 2

Issues:

- Granularity – difficult to extract specific thresholds
- Representativeness – current decisions may not reflect decisions around innovative technologies
- Variation – countries will be using the tool for varied decision questions, a large number of data points is required
- Access to country data – ethical issues, reluctance to share, resourcing for follow-up
- No country ownership – analysis at global level without active country voice

Innovation framework – version 3 – COUNTRY WORKSHOPS



CAPACITY		EVALUACIÓN DE PRODUCTOS			
Herramienta de innovación		Puntuación			
ANÁLISIS DE LA SITUACIÓN					
Características deseadas					
Recopilación de datos					
EVALUACIÓN DE PRODUCTOS					
Características invalidentes					
Puntuación					
Comparación					
INCERTIDUMBRE					
Característica	Ponderación (de 1 a 5)	Puntuación			
		Injectavax	Neovac		
1 que se pueda producir en el país o estrategia de negocio exitosa	5	0	5		
2 que incluya cepas predominantes, inmunidad prolongada	10	10	5		
3 evidencia solida de proteccion cruzada contra otras cepas	4	no informacion		no informacion	
4 que minimize los ESAVIS graves + riesgo de invaginacion intestinal	5	10	10		
5 menor numero de dosis para mayor proteccion	3	10	10		
6 primer semestre de vida para administracion	3	5	10		

Innovation framework – version 3

Considerations:

- Survey to product developers (Caramori et al, 2020, in progress) identified that:
 - i. **consensus across countries** is most needed
 - ii. outputs must be seen as credible
 - separate review of established **preference methods** identified that a mixture of methods is needed, dependent on the question
- Countries have greatest interest in **pipeline products close to market** or being **manufactured locally**
- Feasibility of the approach (resourcing, country interest)
- **How are priority product areas identified? This must be country led**

Innovation framework – current thinking

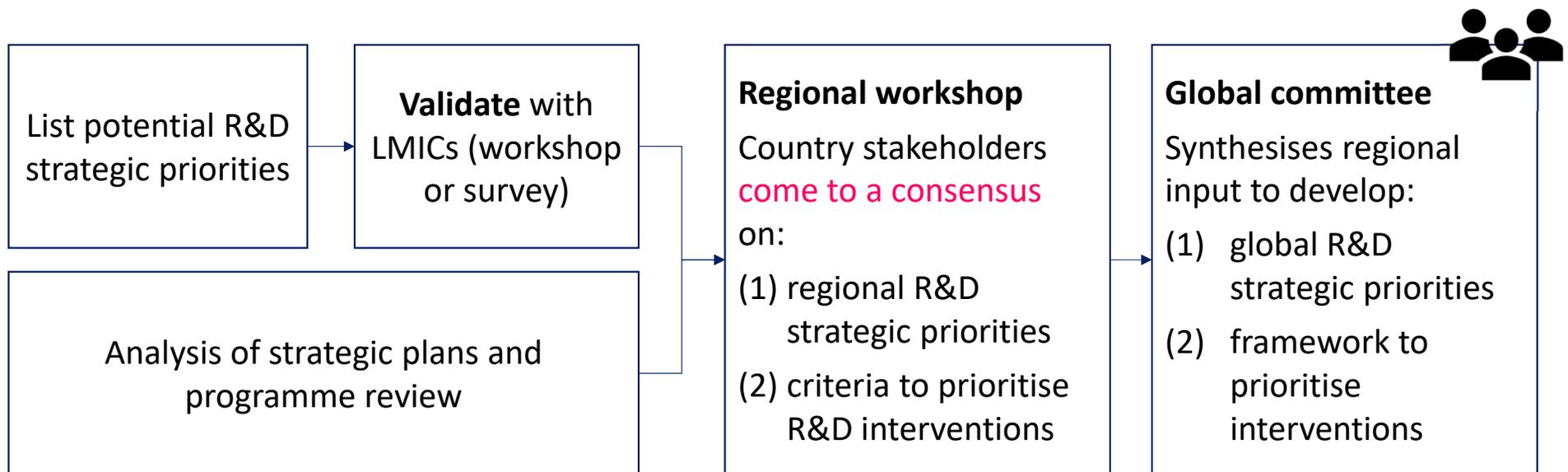
APPLICATION 1: setting WHO R&D strategic priorities and focus areas

For example (**ILLUSTRATIVE**):

- Country focus on C&E => innovative delivery technologies
- Country focus on outbreak response => innovative manufacturing platforms
- Country focus on supply security => strengthen local manufacturing

Innovation framework – current thinking

APPLICATION 1: setting WHO R&D strategic priorities and focus areas



Can leverage methodology in decision-support tool for stakeholder dialogue

Innovation framework – current thinking

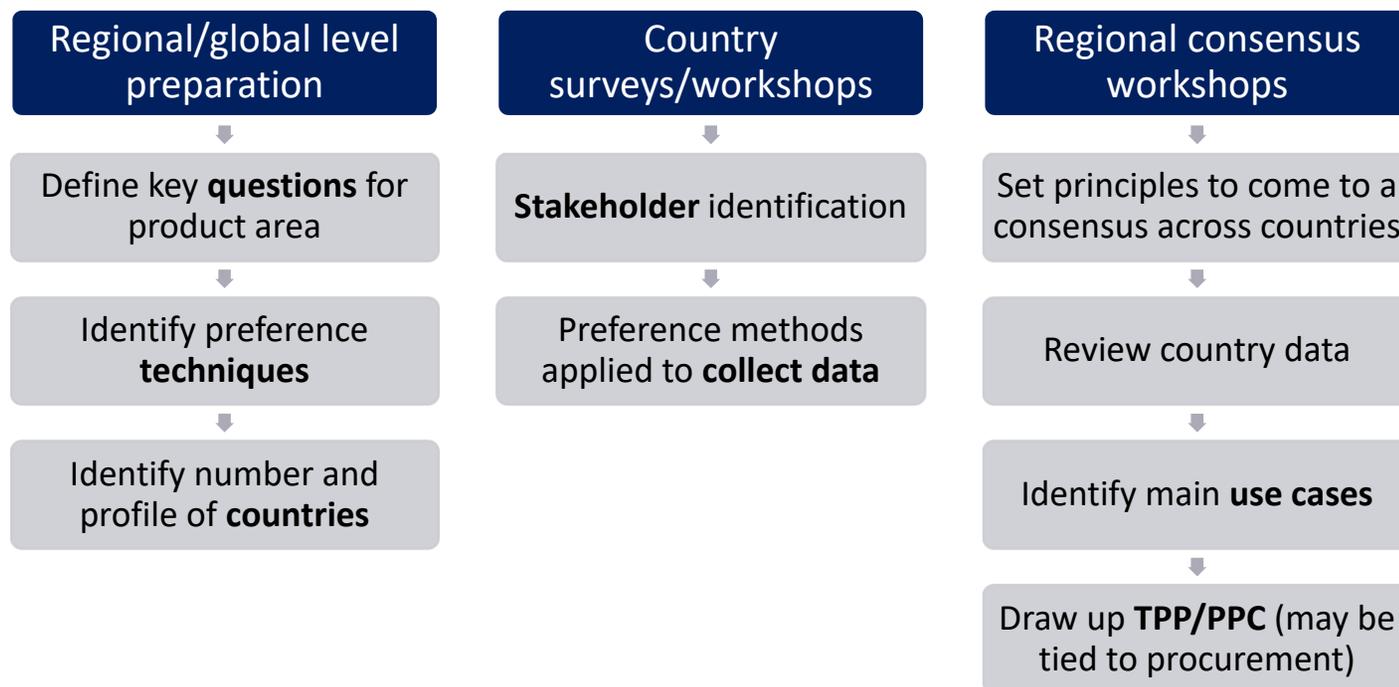
APPLICATION 2: defining **normative guidance** for prioritised interventions

For example:

- Target product profiles (TPPs) and preferred product characteristics (PPCs)
 - linked to use case
- Full Value of Vaccines Assessment (FVVA)

Innovation framework – current thinking

APPLICATION 2: defining **normative guidance** for prioritised interventions



THANK YOU!

ACKNOWLEDGEMENTS:

Country teams in Cuba, Indonesia, Mali, Thailand, Zambia
WHO AFRO, IST WA, PAHO, WPRO
CAPACITI steering committee
Barriers workbook: Dijana Spasenoska, Anna-Lea Kahn

|CAPACITY|

Questions to the committee

1. Is the decision-support tool ready to be made available online in December 2020?
2. Does the committee have advice on the structure and development of the country context and innovation frameworks?

The CAPACITI Decision Support Tool will soon become available at:

<https://decidehealth.world/en/capaciti>

CAPACITI (formerly TSE): summary of previous IVIR-AC recommendations

	IVIR-AC recommendation	How the comment was addressed
March 2018	<ul style="list-style-type: none"> The Committee welcomed the ambitious TSE project but asked for a clearer definition of TSE and the specific goals of the project. 	Objectives of the pilot defined: To assess the relevance of TSE for product selection decisions in LMICs and to determine country requirements for applying TSE to country product selection decisions
	<ul style="list-style-type: none"> It will be difficult to differentiate among vaccine products with regard to the many population outcomes (health benefits, equity, financial risk protection), especially in view of the uncertainties in input, structure and model. A simple MS Excel®-based static model may not be sufficient to capture such differences and uncertainties, particularly for vaccine products that differ negligibly in efficacy. TSE could, however, be useful for differentiating among vaccine products with regard to cold chain requirements, schedules and procurement prices. Implementation and modelling require further consideration and should be more systematic. It might be useful to involve anthropologists in finding out why vaccines are not taken up. 	<p>Modelling working group was formed, with expertise in multi-criteria decision analysis and developing analytical tools for LMICs to use in vaccine introduction or product selection decisions.</p> <p>Outcome was shift from an MCDA model requiring set data inputs and giving defined outputs to a process-based tool to guide country users through the steps of a recommendation, using MCDA.</p>
	<ul style="list-style-type: none"> The Committee therefore suggested that key informant interviews be conducted in countries to determine: where and by whom decisions are made; the important factors (rather than pre-designed components) and data gaps; and how and whether TSE will be used. These criteria should be revised before a pilot study is conducted, which should have clearly stated objectives. Formulating the objectives may require changing the timing of the pilot study. 	<p>Country workshops reviewed existing product selection processes before evaluating TSE and its relevance. Findings:</p> <ul style="list-style-type: none"> Criteria should be defined by countries The tool should be flexible to existing country advisory and decision-making processes Data inputs should not be fixed, so that countries can use existing data relevant to the decision question
September 2018	<ul style="list-style-type: none"> The flexibility of the new TSE interface to allow countries to use self-defined criteria is excellent. However, TSE needs to be aligned with, and ideally embedded in, other priority-setting initiatives in countries, such as efforts to strengthen HTA and NITAG mechanisms. 	<p>Collaboration with iDSI and HTA focal points within WHO:</p> <ul style="list-style-type: none"> Scope defined as decisions devolved to EPI Links to identify established national HTA processes <p>Collaboration with NITAG focal points (global, regional, country level):</p> <ul style="list-style-type: none"> Revision of stakeholder selection and criteria selection steps to align with recommended NITAG processes

CAPACITI (formerly TSE): summary of previous IVIR-AC recommendations

		<ul style="list-style-type: none"> Articulated differences between GRADE evidence to recommendation (EtR) framework (commonly used by NITAGs) and CAPACITI; steps of decision-support tool aligned with EtR framework
	<ul style="list-style-type: none"> There is a need to ensure that TSE actually provides useful market signals to vaccine developers, including developers of vaccines targeted to LMICs, considering the long lead time (>10 years) needed to develop a new vaccine. It would be useful to get input from vaccine developers of characteristics of TSE that would be most helpful to them in making decisions about whether to try to develop and market potential vaccines. 	<p>Regular review of the framework with PDVAC (WHO product development for vaccines advisory committee)</p> <p>Survey circulated to IFPMA, DCVMN, WHO delivery technologies working group to understand manufacturer perspective (May 2020)</p>
September 2019	<ul style="list-style-type: none"> A key determinant of the value of TSE is its ability to align with other initiatives to support vaccine decision-making, including health technology assessment and NITAG strengthening. While there have been useful moves on a country level, there needs to be more conceptual thinking to allow national Health Technology Assessment (HTA) frameworks to fit within the TSE framework. These range from deliberative processes to use of a cost-effectiveness threshold. The TSE framework should be flexible enough to adapt to the different ways that vaccine decision making is done. In particular, quantitative MCDA requires technical expertise to choose and weigh criteria to avoid overlap or double counting, so should only be recommended where such expertise is available. Currently the tool has been piloted for choices of vaccines although it has been developed for broader vaccination choices (e.g. a new vaccine introduction or delivery strategies). It has been noted that TSE may be a potential tool for choices of strategies to improve immunization coverage (e.g., checking vaccination records at school entry versus reminder systems in early childhood). However, it was recommended that the tool be first piloted for use in improving immunization coverage before it is promoted as such. This will ensure the process is suitable, such as whether scoring the associated criteria is feasible. 	<p>The tool has been adapted to be flexible to quantitative, qualitative, rules-based MCDA, or to use a hybrid approach. Guidance is given in the tool for selecting which approach to take, but ultimately the choice is left to the country.</p> <p>To note: deliberation and discussion is a key step of the tool and the total scores in MCDA are used to guide, not determine the outputs of, discussions.</p> <p>The tool now provides further guidance on when to use existing lists of criteria and when it is appropriate to align criteria with those used for HTA</p> <p>There was intention to pilot this broader scope, but pilots were put on hold due to COVID-19. We are hoping to test the tool in 2 West African countries by the end of the year, and are discussing applications of the tool that are focussed on strategy.</p> <p>Scoring has been made more flexible in the tool, so that a smaller range of scores and different labels (e.g. “bad”, “average”, “good”) can be used instead.</p>

CAPACITI (formerly TSE): summary of previous IVIR-AC recommendations

<ul style="list-style-type: none"> The decision to separate cost and non-cost criteria in TSE should be considered carefully and left to country stakeholders, because many quantities without explicit prices (such as cold chain and human resources capacity) can be considered costs from an economic perspective, and because financial criteria are often crucial to decisions. 	<p>For quantitative MCDA, the tool advises separating “constraints” (budget, cost-effectiveness, fixed cold chain or HR capacity, etc) from total score in quantitative MCDA. However, this decision, and the order in which constraints are considered relative to the total score, is left to country stakeholders.</p>
<ul style="list-style-type: none"> TSE should allow ways to incorporate views of vaccination providers, communities and individuals (e.g. parents/vaccinees) into the decision tools. Options include having these stakeholders on the prioritization committee, undertaking research, and/or using deliberative methods to elicit criteria that are important to communities in program considerations. 	<p>In line with other steps of the tool, specific stakeholders to include are not mandated in the tool. However, the guidance for stakeholder selection has been expanded in the tool (following Fung’s principles for stakeholder engagement). The participation step considers members of the committee as well as other mechanisms for engagement of relevant stakeholders.</p>

Session 9:

Burden of Enteric Diseases

Burden of Enteric Diseases

Background and problem statement



Mateusz Hasso-Agopsowicz



Overview of the IVIR-AC BoED session

Time	Session Title	Content	Purpose	Speakers
1430-1435 5'	Burden of Enteric Diseases: Background and problem statement	<ul style="list-style-type: none"> U5 mortality estimates for Shigella and ETEC reported by two modelling groups IHME and MCEE have diverged over the years and have impacted investment decisions; BoED WG developed and completed workstreams to address PDVAC's needs. 	For information	G Giersing/M Hasso-Agopsowicz
1435-1500 25'	Efforts to assess the differences in U5 mortality estimates for enteric pathogens.	<ul style="list-style-type: none"> Results from workstreams to assess the mortality estimates Perspectives from IHME and MCEE and suggested approaches to incorporate methods from the analyses 	For information	B Lopman V Pitzer M Hasso-Agopsowicz J Platts-Mills
1500-1520 20'	Q&A and Discussion	<ul style="list-style-type: none"> Do these workstreams potentially impact the assessment of pathogen mortality, and therefore relative value of vaccines against these pathogens? Does IVIR-AC agree that results of the mortality workstreams should be included in future enteric mortality modelling estimates? 	For recommendation	S Verguet, P Luz, X Wang
1520-1535 15'	The impact of enteric pathogens on morbidity: proposed scope of work.	<ul style="list-style-type: none"> WHO proposes workstreams to systematically capture evidence on the impact of enteric pathogens on long-term morbidity; 	For information	I Khalil
1535-1555 20'	Q&A and Discussion	<ul style="list-style-type: none"> Are there other elements/activities that should be included in the proposed scope of work to assess long term morbidity? Is the proposed scope of work considered appropriate <u>next step</u> for further evaluating the full burden, and ultimately the value, of enteric vaccines? 	For recommendation	S Verguet, P Luz, X Wang



Rationale for the work

* Shift in U5 mortality assessment and divergence between MCEE and IHME in 2016

Study	CHERG/MCEE 2011	MCEE 2017 (Interim Unpublished)	GBD 2010	GBD 2013	GBD 2015	GBD 2016
ETEC deaths (uncertainty range)	42,000 (20,000 – 76,000)	44,078 (32,848 – 58,054)	38,700	23,100 (17,000 – 30,400)	23,600 (9,600 – 44,300)	18,669 (9,800-30,659)
Shigella deaths (uncertainty range)	28,000 (12,000 – 53,000)	25,008 (17,148 – 35,878)	42,600	33,400 (24,900 – 43,500)	54,900 (27,000 – 94,700)	63,713 (41,191-93,611)

PDVAC Recommendation 2018:

“To further investigate understanding and credibility of Burden of Disease estimates, through the formation of a joint IVIRAC/PDVAC independent working group to evaluate diarrheal burden models, and particularly to assess the level of uncertainty regarding ETEC mortality estimates.”



Link to the Full Value of Vaccine Assessment (FVVA)



To prioritise vaccine development, introduction and use, we need to articulate the impact of vaccines in its full capacity.

Vaccine impact is dependant on vaccine's ability to address disease burden; related to both mortality and morbidity.

The FVVA for vaccines is a concept that describes the **global value of a vaccine, including from an LMIC perspective**. It aims to articulate the full direct (individual) and **indirect (population) effects** of a vaccine.

The intent of FVAA assessment is to **support decision-making across the continuum of vaccine development and uptake**, with a line-of-sight to **sustainable socio-economic and public health impact**.

We established a WG to begin with assessment of U5 **mortality estimates**

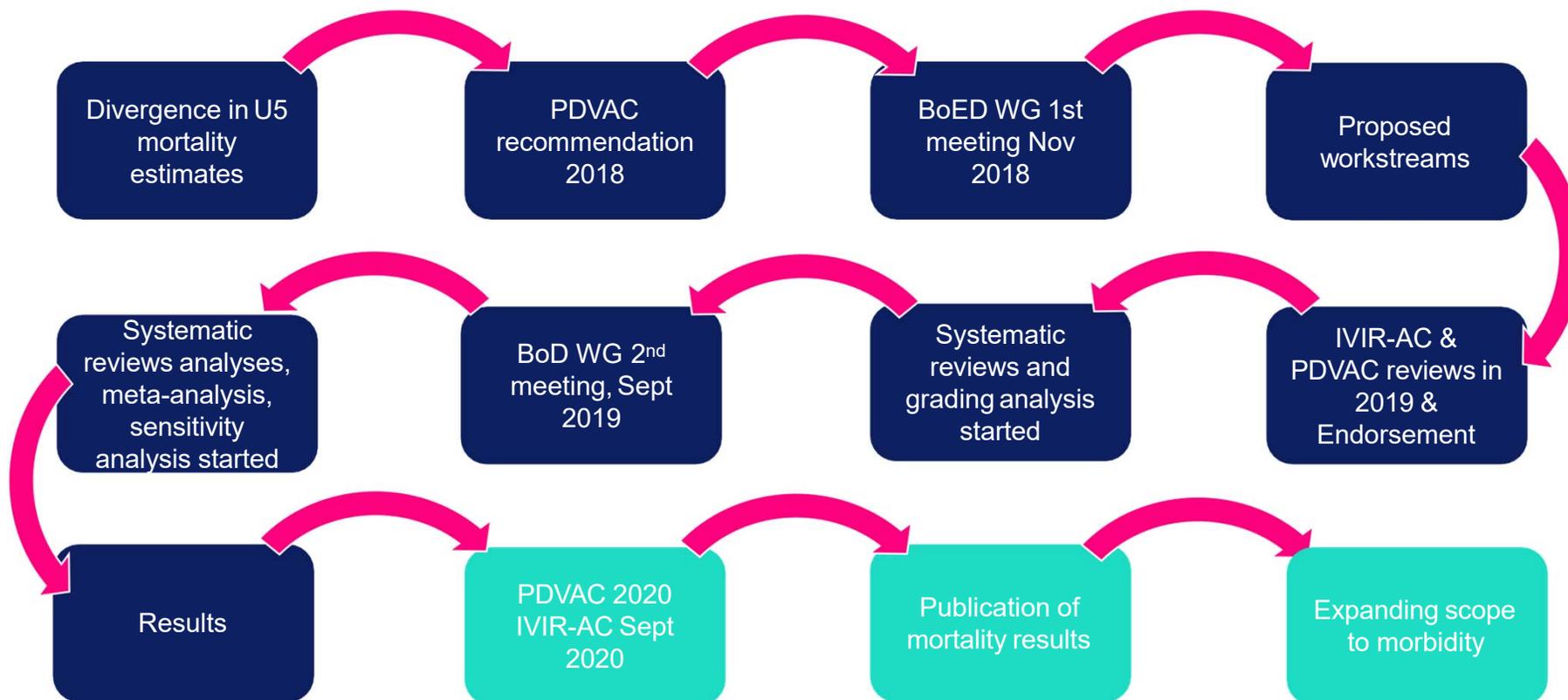
We propose to now expand the scope to address **assessment of morbidity** (long term sequelae) due to infections enteric pathogens.



Participant	Affiliation
Ben Lopman	Emory, USA
Cherry Kang (PDVAC)	Translational Health Science and Technology Institute, India
Claudio Lanata (PDVAC)	Nutritional Research Institute, Peru
Mark Jit (IVIR-AC)	LSHTM, UK
Mark Riddle	Uniformed Services University, USA
Peter Smith (PDVAC)	LSHTM, UK
Robert Breiman (Chair)	Emory, USA
James Platts-Mills	University of Virginia
Virginia (Ginny) Pitzer	Yale University, USA
Wilfred Ndifon (IVIR-AC)	African Institute for Mathematical Sciences, South Africa



Development and progress of Enteric BoED WG workstreams



Summary of workstreams

1. **Data Gaps – to identify and address areas of commonality where additional evidence may improve future estimates. Gaps where new data is needed**
 - A) Systematic review of odds ratios of developing diarrhoea when a pathogen is detected in stool: Ben Lopman, Julia Baker (Emory University)
 - B) Systematic review of pathogen specific case fatality rates: Ginny Pitzer, Ernest Asare (Yale University)



Summary of workstreams

1. **Data Gaps – to identify and address areas of commonality where additional evidence may improve future estimates. Gaps where new data is needed**
2. **Study Quality Exercise – to improve understanding of the studies, and the quality of the studies, included in the modelling process.**
 - A) Grading analysis of input studies: Egle Butkeviciute (LSHTM), finalised
 - B) Sensitivity analysis of low quality studies: IHME



Summary of workstreams

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3. **Data Processing Exercise – a high level assessment of similarities and differences in study data included in the models, how it is processed**
 - A. Meta-analysis of input studies and the impact of model adjustments: James Platts-Mills, Sarah Elwood (University of Virginia)



Previous IVIR-AC meetings

March 2019 Recommendations:

- IVIR-AC agrees with the approach proposed to be taken and highlights the importance of having multiple models and model comparison exercises to better understand methodology involved in estimating disease burden.
- IVIR-AC recommends that we better understand the margin of error in mortality estimates that policy-makers are prepared to accept in prioritizing development of vaccine candidates.
- For the systematic review the inclusion of search terms related to death / CFR might lead to bias towards studies in which deaths occurred. Therefore, it is important to also include other search terms, e.g. related to hospitalization.
- It is critical given the importance of these estimates that adequate resources are available to conduct this comparison exercise.

September 2019:

- High level update on workstreams, no recommendations



Questions to IVIR-AC

Related to mortality workstreams:

- Do these workstreams potentially impact the assessment of pathogen mortality, and therefore relative value of vaccines against these pathogens?
- Does IVIR-AC agree that results of the mortality workstreams should be included in future enteric mortality modelling estimates?

Related to morbidity workstreams:

- Are there other elements/activities that should be included in the proposed scope of work to assess long term morbidity?
- Is the proposed scope of work considered appropriate next step for further evaluating the full burden, and ultimately the value, of enteric vaccines?



Closing slide



World Health
Organization

WHO

20, Avenue Appia
1211 Geneva

Switzerland



Efforts to assess the differences in U5 mortality estimates for enteric pathogens



Julia Baker, Ginny Pitzer, Mateusz Hasso, James Platts-Mills



Summary of workstreams

1. **Data Gaps – to identify and address areas of commonality where additional evidence may improve future estimates. Gaps where new data is needed**
 - A) Systematic review of odds ratios of developing diarrhoea when a pathogen is detected in stool: Ben Lopman, Julia Baker (Emory University)
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Systematic review And Meta-Analysis of diarrhea pathogen odds ratios



**Benjamin Lopman &
Julia Baker**

Emory University

Study rationale, aim, expected outcome

Rationale:

- IHME uses odds ratios of developing diarrhea when a pathogen is detected in stool to estimate population attributable fractions (PAF) ($PAF = \text{proportion} \times (1 - 1/OR)$)
- PAFs are multiplied by the total number of diarrhea deaths to calculate the estimated number of deaths for a given pathogen
- ORs based on molecular diagnostic results from GEMS (<1 yr, 1-5 yrs) are limited to only seven sites, and are extrapolated globally

Aim:

- Examine the relationship between the presence of pathogens and the occurrence of diarrhea through a systematic review of literature and meta-analysis

Outcome:

- Database of ORs of developing diarrhea when a pathogen is detected in stool stratified by pathogens, mortality regions, detection methods, with an aim to incorporate ORs to PAF calculations and improve future mortality estimates

Methodology

- Data on the presence of 15 pathogens in diarrhea & non-diarrhea stool samples
 - Systematic review of literature (1990-2019), University of Washington START Center
 - MAL-ED and GEMS data
 - 145 studies, 1,324 observations, 15 pathogens

- Random effects meta-analysis to model OR for each pathogen
 - Unadjusted/unstratified
 - Stratified by age group & child mortality, adjusted for diagnostic method & study design

- Sensitivity analyses using same model above but excluding:
 - Outliers/influential observations
 - RRs (i.e. only using ORs in the meta-analysis)
 - Coinfections

Factor distributions

Factor	Category	n obs (%) among all pathogens	Notes
Age group	0-5 years	973 (0.73)	
	Mixed	253 (0.19)	
	>5 years	98 (0.07)	
Child mortality status	Very low	158 (0.12)	<ul style="list-style-type: none"> Based on quintiles of under 5 child mortality (UNIGME estimates from 2003) Very low & low combined for analysis
	Low	411 (0.31)	
	High	755 (0.57)	
Pathogen detection method	EIA	229 (0.17)	<ul style="list-style-type: none"> EIA/ELISA, culture/isolation, microscopy (electronic) combined into “conventional” methods for analysis
	Culture	181 (0.14)	
	Microscopy	81 (0.06)	
	PCR	402 (0.30)	
	Other/Unspecified	201 (0.15)	
	Missing	230 (0.17)	
Study design	Cohort	312 (0.24)	<ul style="list-style-type: none"> Cohort: prospective, retrospective, cross-sectional, RCT Case-control: standard or nested
	Case-control	1012 (0.76)	

Unadjusted & final model results by pathogen

	Unadjusted and unstratified OR (95% CI)	0-5 years of age		> 5 years of age
		Very low/low child mortality OR (95% CI)	High child mortality OR (95% CI)	All child mortality levels OR (95% CI)
Adenovirus	2.1 (1.8, 2.6)	3.6 (1.9, 6.8)	1.3 (0.8, 2.1)	
Astrovirus	1.9 (1.6, 2.3)	0.8 (0.3, 2.1)	1.7 (0.9, 3.1)	
Norovirus	1.7 (1.4, 2.0)	7.7 (1.3, 44.8)	2.9 (1.4, 6.0)	3.2 (1.3, 7.6)
Norovirus GI	1.4 (0.7, 3.0)	1.6 (0.5, 5.2)	0.8 (0.5, 1.2)	1.4 (0.4, 4.4)
Norovirus GII	2.1 (1.6, 2.9)	1.8 (0.6, 5.1)	1.7 (1.2, 2.4)	3.4 (1.3, 8.8)
Rotavirus	6.4 (5.6, 7.3)	7.1 (3.7, 13.3)	5.9 (4.1, 8.4)	2.9 (1.3, 6.5)
Sapovirus	1.8 (1.5, 2.1)	3.5 (2.5, 4.8)	1.5 (1.2, 1.9)	
Aeromonas	2.4 (1.7, 3.3)	0.6 (0.1, 6.6)	3.7 (3.2, 4.2)	
Campylobacter	1.7 (1.5, 1.9)	2.4 (1.3, 4.6)	1.7 (1.3, 2.2)	5.1 (2.6, 10.0)
V. cholerae	5.3 (1.6, 17.1)			
EPEC	1.4 (1.2, 1.6)	2.4 (0.5, 10.7)	1.4 (0.9, 2.0)	2.0 (1.2, 3.4)
ETEC	1.8 (1.6, 1.9)	0.5 (0.3, 0.9)	1.5 (1.2, 1.9)	1.4 (0.1, 24.7)
ST ETEC	2.2 (1.9, 2.6)	1.3 (0.9, 1.7)	1.6 (1.1, 2.5)	4.8 (1.7, 14.2)
LT ETEC	1.1 (1, 1.3.0)	0.4 (0.2, 1.0)	1.0 (0.7, 1.4)	1.2 (0.2, 6.3)
Salmonella	1.9 (1.4, 2.5)	1.5 (1.0, 2.2)	1.4 (0.8, 2.5)	0.9 (0.6, 1.3)
Shigella	5.5 (4.3, 7.1)	4.6 (2.2, 9.8)	4.2 (2.4, 7.3)	2.8 (1.5, 5.5)
Cryptosporidium	2.2 (1.9, 2.4)	1.4 (0.8, 2.5)	1.9 (1.7, 2.2)	3.4 (1.2, 9.6)
E. histolytica	1.3 (1.1, 1.6)	0.6 (0.2, 1.9)	1.7 (1.1, 2.7)	1.2 (0.6, 2.3)
Giardia lamblia	1.0 (0.9, 1.1)	2.0 (1.3, 3.1)	0.8 (0.6, 1.1)	1.2 (0.6, 2.3)

Key takeaways

- **Viruses-** lower ORs in high child mortality strata (vs low child mortality strata)
 - Increased force of infection and frequent asymptomatic infections in high child mortality settings.
- **Rotavirus-** lower ORs in >5 years of age
 - Immunity builds over repeated exposures
- **Bacteria-** the trends are less clear
- **Shigella-** lower ORs in high child mortality strata, however, confidence intervals are wide
- **ETEC-** stronger association with diarrhea in high child mortality strata
- **ST ETEC** more associated with diarrhea than **LT ETEC**

Main findings & Conclusions

Key results

- Association between pathogen detection and diarrhea varied substantially by pathogen
- Summary ORs differed by age group, child mortality status, or both (wide CIs for many)
- ORs estimated may relate to epidemiologic/natural history/immunity characteristics of pathogens
- Minimal changes in ORs in sensitivity analyses
- **ORs may be (adapted and) used as inputs in burden models**

Limitations

- Pathogen detection methods vary
- Potential age bias when studies are not age matched
- ORs are only part of the attributable fraction calculations (prevalence is another important factor)

Output

- A publication that summarizes the ORs is in preparation
- Both modelling groups expressed an intent to incorporate these results into their future mortality estimates

Case fatality rate of diarrheal pathogens: a meta-analysis



Ernest O. Asare & Virginia E. Pitzer

Yale School of Public Health

Study rationale, aims, expected outcome

Rationale:

- Burden models assume that deaths from enteric pathogens occur in proportion to the distribution of pathogens in hospitalized cases
- Burden models do not account for potential differences in the case fatality risk (CFR) of various pathogens

Aims:

- To investigate heterogeneity in the CFR of different diarrheal pathogens
- To examine how the CFR varies by age group, setting (hospital or community), and country characteristics

Outcome:

- A model to estimate the CFR overall and for each pathogen, controlling for predictors of heterogeneity

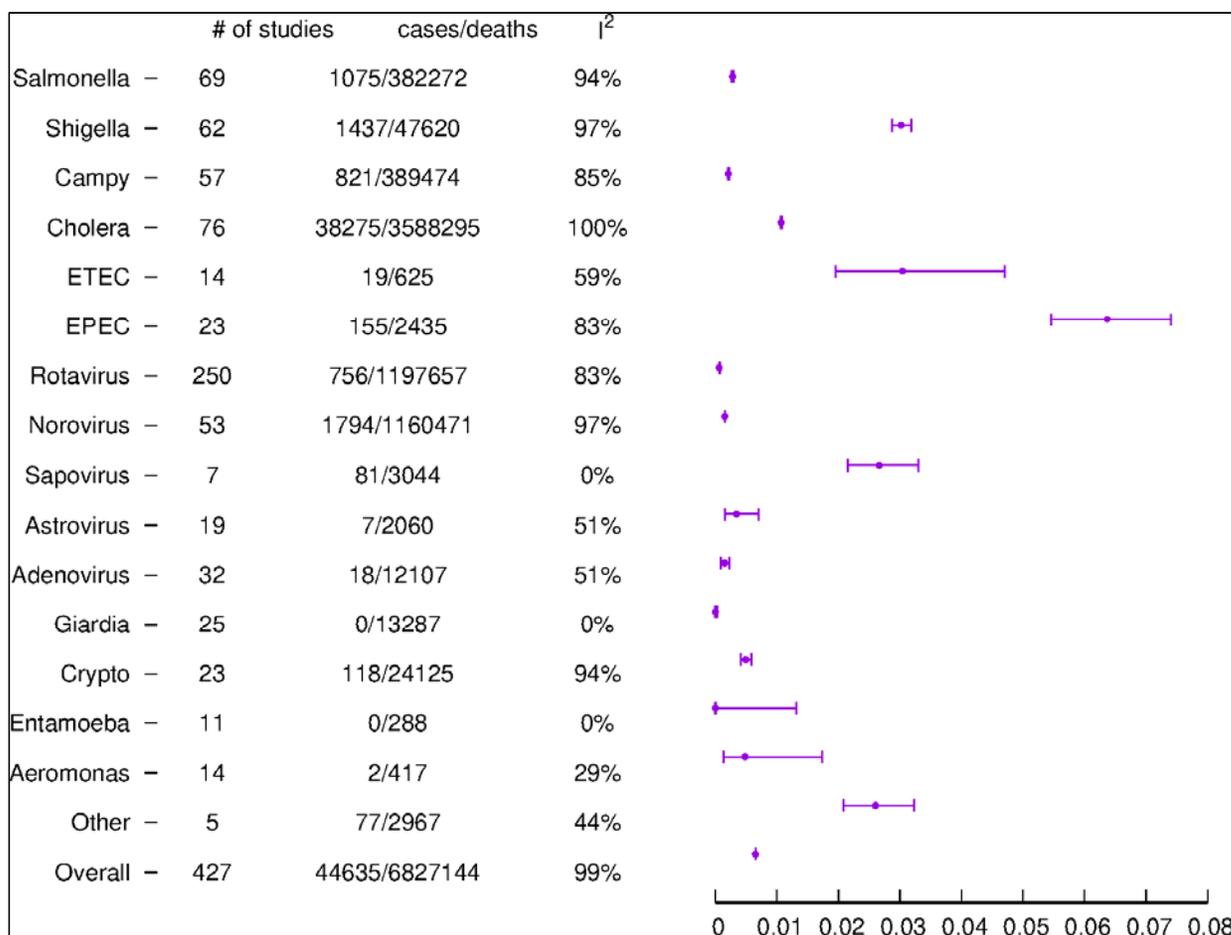
Methodology & analysis

- Data on the case fatality rates for 15 pathogens
 - Systematic review of literature (1990-2019), University of Washington START Center
 - 427 studies, 15 pathogens
- Potential CFR predictors: age group (<1, <5, ≥5, other), country U5MR, setting (hospital/ community), study year, before or after rotavirus vaccine introduction
- Fixed effects models
 - Binomial-normal GLMs to estimate the CFR for each pathogen
 - Calculate I^2 statistic to measure heterogeneity
 - Stratified analyses: age group, U5MR, setting, before/after rotavirus vaccine introduction (for pathogens with at least 50 studies)
- Multilevel mixed effects model for overall CFR

$$\text{logit}(CFR_{i,j}) = \beta_0 + \beta_p(\text{pathogen}_{i,j}) + \beta_a(\text{age group}_{i,j}) + \beta_m(\text{U5MR}_{i,j}) + \beta_s(\text{setting}_{i,j}) + \epsilon_i + \zeta_j$$

- Continuity correction: +0.1

Results – CFR by pathogen



Key takeaways

Overall CFR: 0.65% (0.65-0.66%)

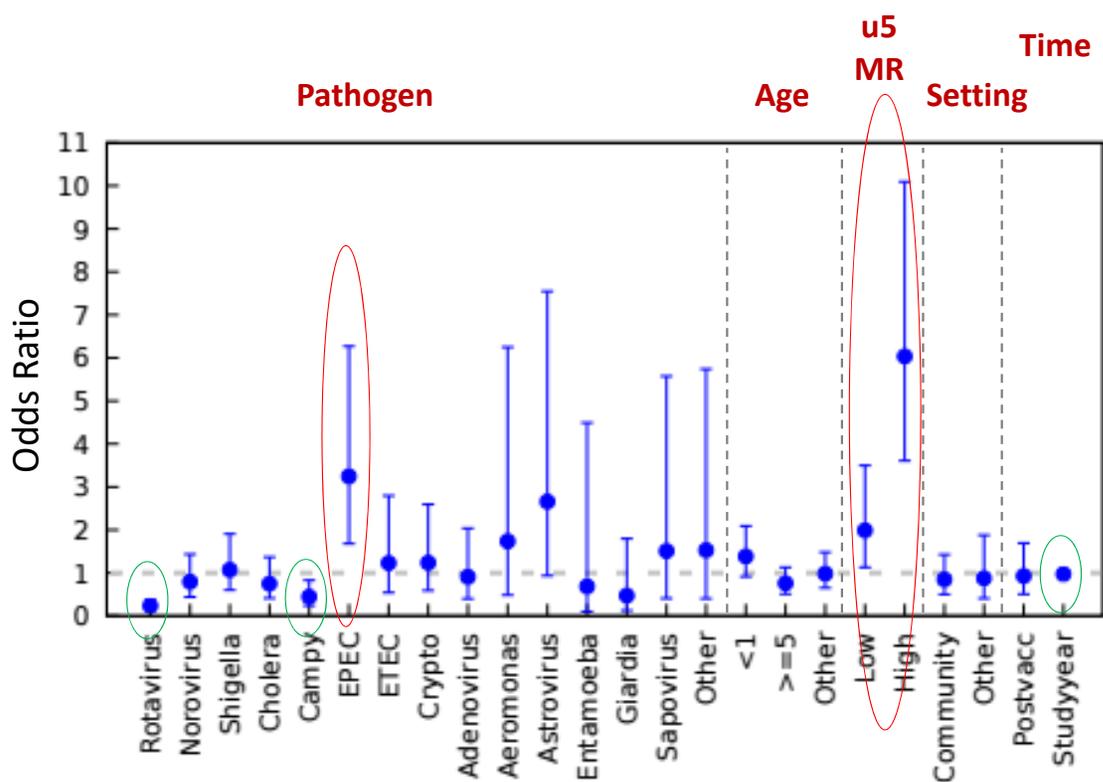
Significant heterogeneity both within and between pathogens

EPEC has highest CFR ~6.3%

ETEC, Shigella, Sapovirus have also high CFRs

Low CFR for **Salmonella, Campylobacter, Rotavirus, Norovirus, Giardia**

Multilevel mixed-effects model results



Key takeaways

- CFR is **lower** for rotavirus, campylobacter, **higher** for EPEC
- CFR is **higher** in high under-5 mortality countries
- CFR is **lower** over time (study year)

Reference groups

- Salmonella
- <5 year age group
- Very low mortality strata
- Hospital-based studies
- Pre-vaccination

Summary

Key results:

Substantial heterogeneity in the estimated CFR both within and between pathogens

For some pathogens, CFR was higher for:

- Age group <1 yr
- Higher u5 mortality rate strata
- Community-based studies (viral pathogens) or hospital-based studies (bacterial pathogens)
- Older studies

Heterogeneity is not fully explained by predictors

Output:

A publication that summarizes the pathogen specific CFRs is in preparation

Study overlap and quality analysis



Egle Butkeviciute

Holly Prudden

Mateusz Hasso

Study rationale, aims, expected outcomes

Rationale:

- The type and quality of studies used to estimate U5 mortality estimates is not known. Low quality studies may skew observed estimates

Aims:

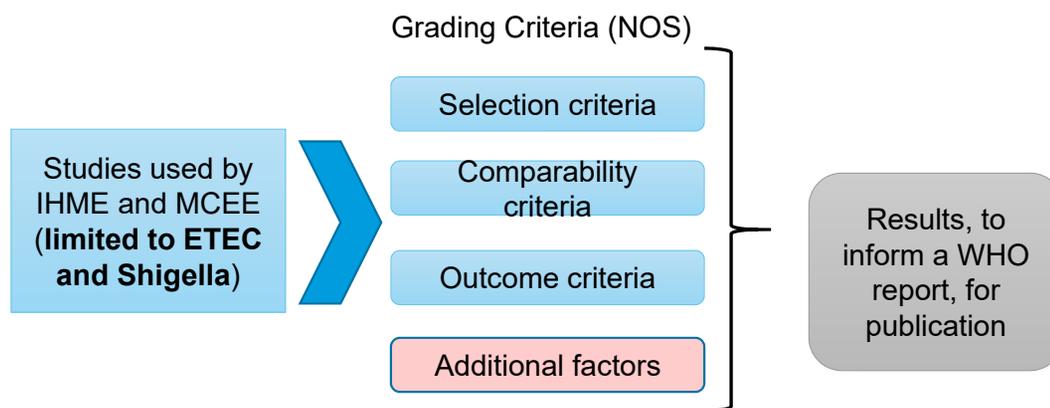
- To conduct a grading review to improve our understanding of the quality of studies and data used by both IHME and MCEE groups.
- To conduct a sensitivity analysis of low quality studies and measure their impact on mortality estimates
- The analysis includes only **ETEC** and **Shigella** studies.

Outcomes:

- A summary of quality of studies used to estimate the U5 mortality
- Revised burden estimates which exclude studies of low quality

Methodology

Together with the BoED WG, a modified Newcastle-Ottawa Scale to assess the quality of IHME and MCEE studies was developed



Study Overlap Analysis: Results

Pathogen	Total number of studies (2016)	Number of studies used by MCEE (2016 ¹)	Number of studies used by IHME (2016 ²)	Number of studies used by IHME and MCEE (2016)
ETEC	36	7	29	0
Shigella	72	31	41	0

¹Studies conducted in 1990-2013 were used to generate MCEE estimates for 2016.

²Studies conducted (study midpoint) between 2011-2021 were used to generate IHME estimates for 2016.

² Mostly studies published up to the year of the estimate were included.

Key takeaways

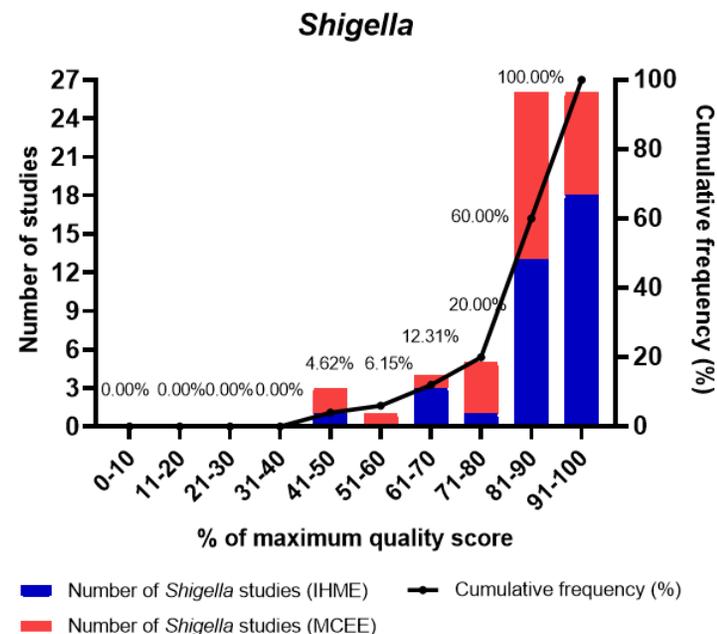
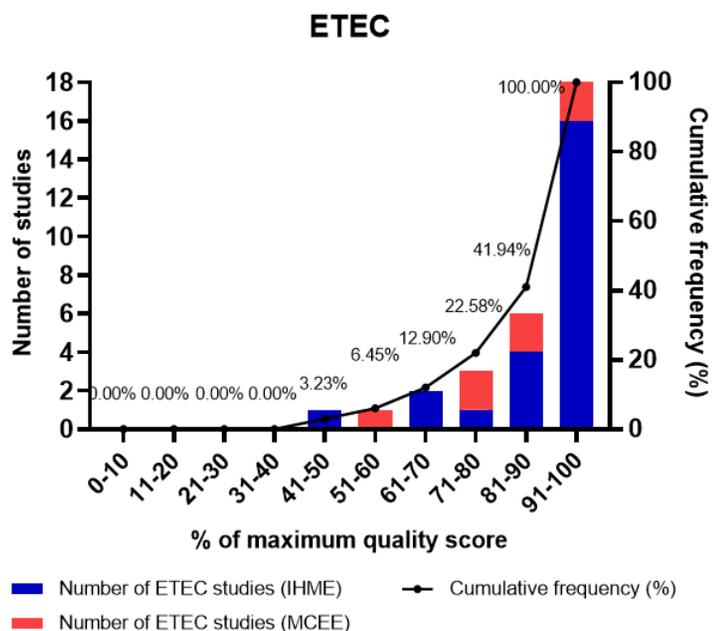
- None of the studies are used by both IHME and MCEE to calculate the 2016 mortality estimates
- The lack of overlap reflects different inclusion criteria applied by both groups

Lack of overlap reflects different inclusion criteria applied by both groups



Criteria	MCEE	IHME
Study setting or stratification	Excludes studies which do not stratify data by inpatient, outpatient or community settings.	Includes studies which do not stratify data by inpatient, outpatient or community settings. Uses non-stratified data and adjusts for sample population in the model.
Laboratory methods	Excludes studies which used non-standard laboratory methods.	Includes studies which used all laboratory methods.
Single pathogen studies	With the exception of rotavirus, excludes studies that test for a single pathogen only.	Includes all studies and applies an adjustment factor if the data are from studies that test for a single pathogen only.
Strain differentiation	Excludes studies that fail to differentiate norovirus GI/II, atypical and typical EPEC, LT/ST-EPEC.	Includes all studies regardless of whether they differentiate strains or serotypes.
Study dates	Includes studies published between 1990-2014.	Includes studies of which midpoint falls five years prior the year for which mortality or morbidity estimates were calculated (2011-2016)

Study Quality Analysis: Results



Key takeaways

- 58% of studies received the maximum quality score
- Similar quality scores observed for studies used by both groups

Key takeaways

- 40% of studies received the maximum quality score
- Similar quality scores observed for studies used by both groups

Summary

Key results:

- None of the studies are used by both IHME and MCEE to calculate the 2016 mortality estimates
- The lack of overlap reflects different inclusion criteria applied by both groups
- 58% of ETEC studies and 40% of Shigella studies received the highest quality scores
- The distribution of the quality score was similar between MCEE and IHME

Outputs:

- IHME and MCEE shared their study databases, and where relevant, future estimates will include studies used by both groups
- IHME is conducting a sensitivity analysis to measure the impact of taking out studies with quality <70/100 on mortality estimates
- Results from both analyses will inform an overarching publication that summarizes suggested inclusion and exclusion criteria for future studies to be included in mortality estimates.

Meta-Analysis of IHME/MCEE study input data and IHME model-based adjustments



**Sarah Elwood and
James Platts-Mills**

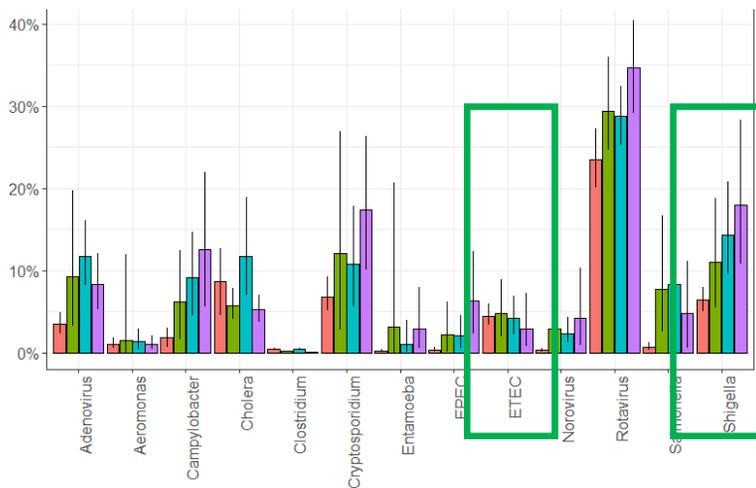
Study rationale, aim, expected outcome



Rationale:

Disparate estimates for *Shigella* and ETEC mortality between the two major diarrhea mortality modeling groups

IHME 2010 estimates: four iterations



Pathogen	MCEE 2017 (unpublished)	IHME GBD 2016 (Lancet 2018)
ETEC	44,078 (32,848 – 58,054)	18,700 (9,800 – 30 659)
Shigella	25,008 (17,148 – 35,878)	63,700 (41 191 – 93 611)

Aims:

To understand differences in pathogen prevalence between MCEE and IHME before model adjustments are applied

To understand the impact of IHME adjustments on mortality estimates

Outcome:

A summary of the impact of IHME adjustments on mortality estimates

Courtesy of Chris Troeger/IHME, Bob Black/MCEE, Birgitte Giersing/WHO

Background: Components of pathogen-specific diarrhea mortality estimates – a simple schema



Group	Pathogen prevalence	Inference to etiology	Mortality incidence
MCEE	Prevalence in hospitalized diarrhea in multi-pathogen studies of hospitalized diarrhea using “standard” diagnostics (includes both PCR and other methods)	Use pathogens associated with diarrhea in GEMS, force sum of proportions to 1 (include % unknown)	Incidence of fatal diarrhea
IHME	Prevalence in hospitalized diarrhea in multi-pathogen studies with qPCR diagnostics (by applying adjustments to incorporate: 1) “ community diarrhea ” (non-hospitalized) studies, 2) single-pathogen studies, 3) studies with non-qPCR diagnostics)	Calculate population attributable fractions (AFs) using GEMS odds ratios	Incidence of fatal diarrhea

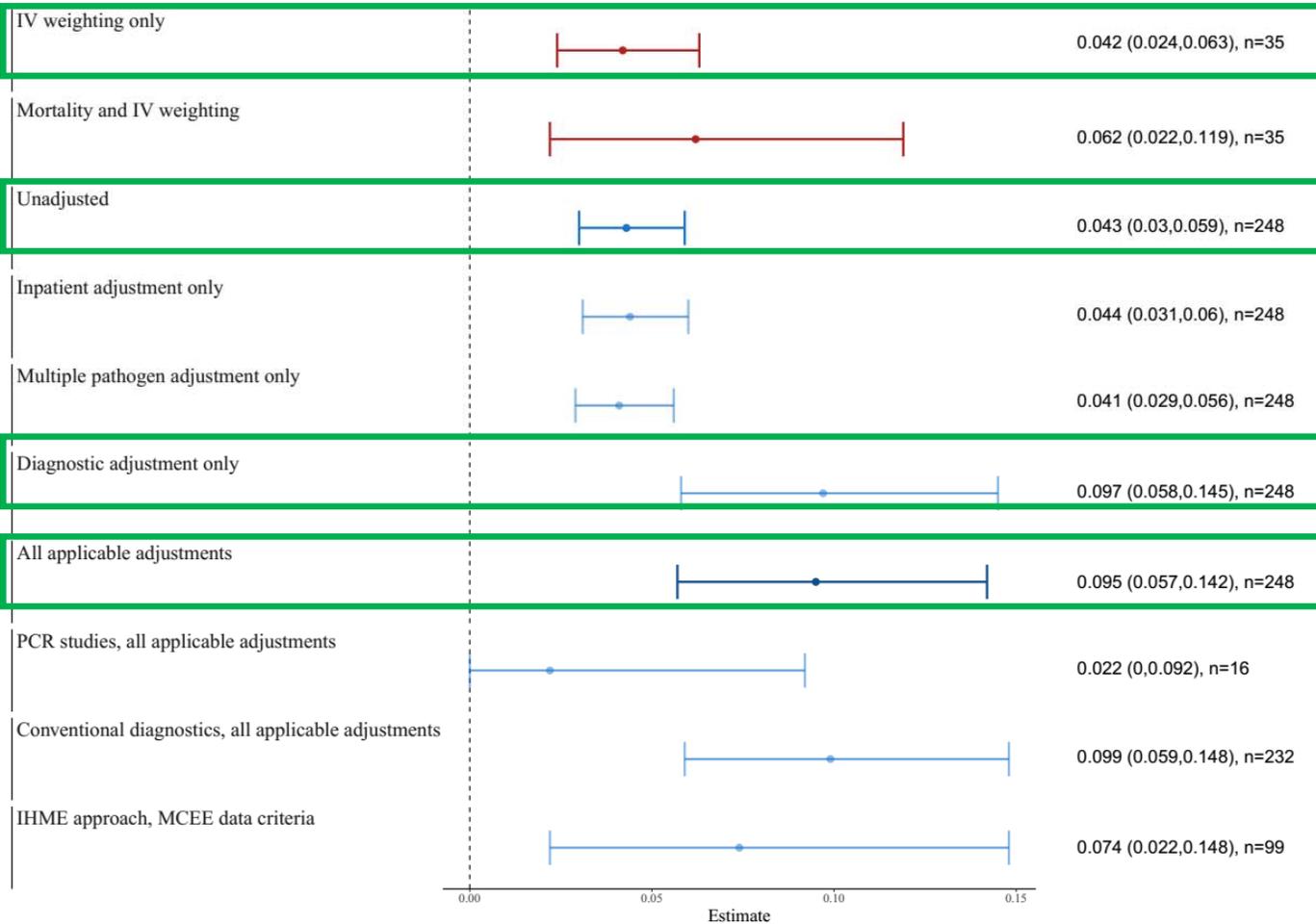
Methods: Meta-analysis and application of IHME adjustments



- High-level meta-analysis of both groups' age-adjusted data
 - Random effects meta-analysis using the Tukey-Freeman double arcsine transformation for the raw proportion data (internally validated with simulations)
 - Weighted by the product of the inverse variance and country-level mortality for each study
- Apply IHME adjustments and examine impact on prevalence estimates
 - Scalar adjustments for **community vs. hospital studies**, and **single- vs. multi-pathogen studies**
 - Diagnostic adjustment for **non-qPCR studies**: sensitivity and specificity of culture vs qPCR is calculated and used to adjust non-qPCR observed prevalence to the expected "true" prevalence using qPCR
 - Apply **odds ratios from GEMS** to calculate population attributable fractions

Results: *Shigella*

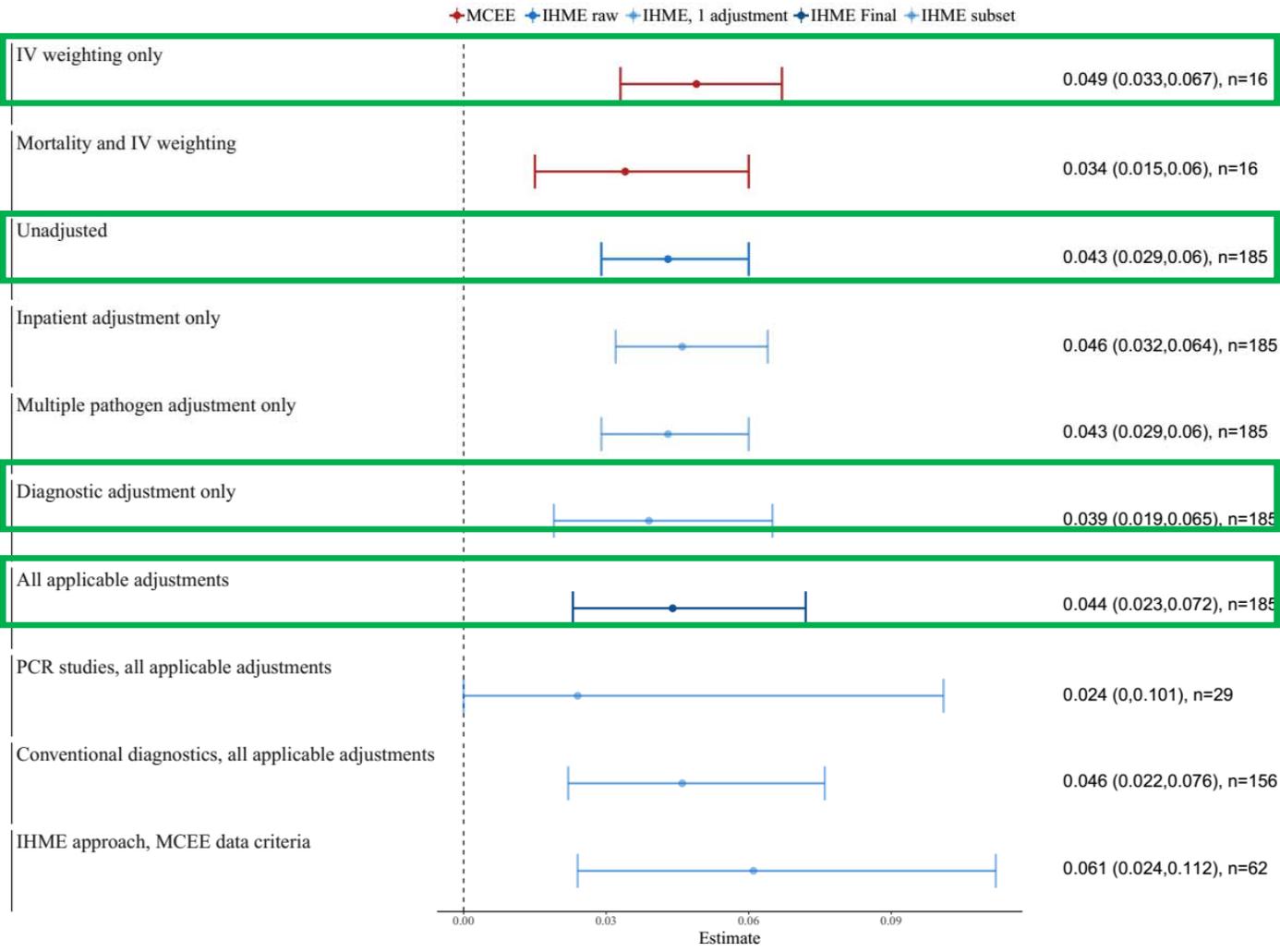
◆ MCEE ◆ IHME raw ◆ IHME, 1 adjustment ◆ IHME Final ◆ IHME subset



Key takeaways

- For *Shigella*, IHME and MCEE estimates similar before model adjustments
- IHME diagnostic adjustment increases the prevalence of *Shigella* more than twofold
- When all IHME adjustments are applied the number of estimated U5 deaths in this meta-analysis for *Shigella* is 50,700 (0.095 * ~534,000 = ~50,700)

Results: ETEC



Key takeaways

- For ETEC, MCEE estimated prevalence slightly higher than IHME before model adjustments
- IHME diagnostic adjustment slightly decreases the prevalence of ETEC
- When all applicable adjustments are applied the number of estimated U5 deaths for ETEC is 23,500 (0.044 * ~534,000 = ~23,500)

Summary

Key results

- The IHME diagnostic test adjustments increase the *Shigella* mortality estimate by approximately twofold but do not increase the ETEC estimate; these increases are conservative when compared to the GEMS/MAL-ED re-analyses (which increased *Shigella* estimates 2.5-5x, and ETEC 1.5-2x)
- The other IHME adjustments have a negligible impact on the estimates
- Incorporation of a diagnostic test adjustment in the MCEE methodology will likely bring the estimates for these (and other) pathogens into closer alignment

Outputs

- Collaboration with IHME to revise the methodology of the diagnostic adjustment
- Collaboration with MCEE to develop and implement a methodology for diagnostic adjustment

Perspectives from MCEE and IHME

- Analyses and results are useful and fill in important data gaps in the area of enteric pathogens
- Analyses will iterate methodologies to calculate U5 mortality estimates for enteric pathogens
- Both groups MCEE and IHME expressed intent to incorporate the results of the BoED work and publish revised mortality estimates in 2021

Proposed list of publications (mortality)

Already published:

Meeting Report: WHO workshop on modelling global mortality and aetiology estimates of enteric pathogens in children under five (**Lead: Holly Prudden**)

To be published:

1. Results from the OR systematic review (**Lead: Ben Lopman & Julia**)
2. Results from the CFR systematic review (**Lead: Ginny Pitzer & Ernest**)
3. Results from the meta-analysis (**Lead: James Platts-Mills & Sarah**)
4. A high-level publication that describes inclusion and exclusion criteria for mortality estimates studies (incorporating results from the grading analysis and IHME sensitivity analysis) (**Lead: Mateusz Hasso & Egle Butkeviciute**)
5. An overarching publication that describes the exercise, summarises key results from workstreams, includes perspectives from modellers on the impact of findings. (**Lead: Mateusz Hasso & Rob Breiman & Gitte**)

Questions to IVIR-AC

Do these workstreams potentially impact the assessment of pathogen mortality, and therefore relative value of vaccines against these pathogens?

Does IVIR-AC agree that results of the mortality workstreams should be included in future enteric mortality modelling estimates?

Expansion of the BoED scope to morbidity



Mateusz Hasso-Agopsowicz, Birgitte Giersing and Ibrahim Khalil

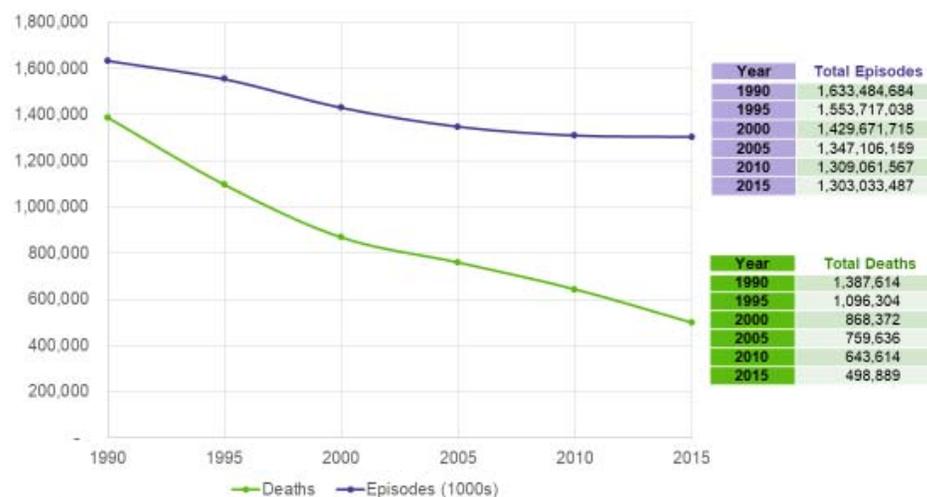
IVIR-AC Meeting

24 September, 2020

Underestimation of Overall Diarrhea Burden: how to quantify long term burden?

Mortality burden declining, but not morbidity..

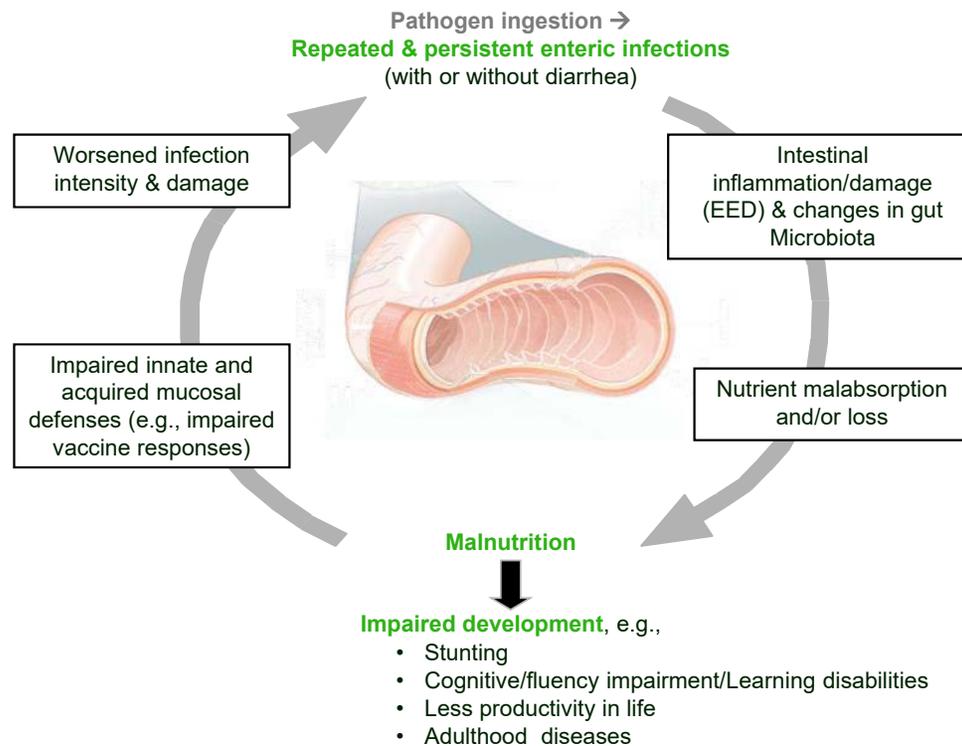
- *Despite a steep reduction in diarrhea death rates, incidence of diarrhea remains consistently high over years*



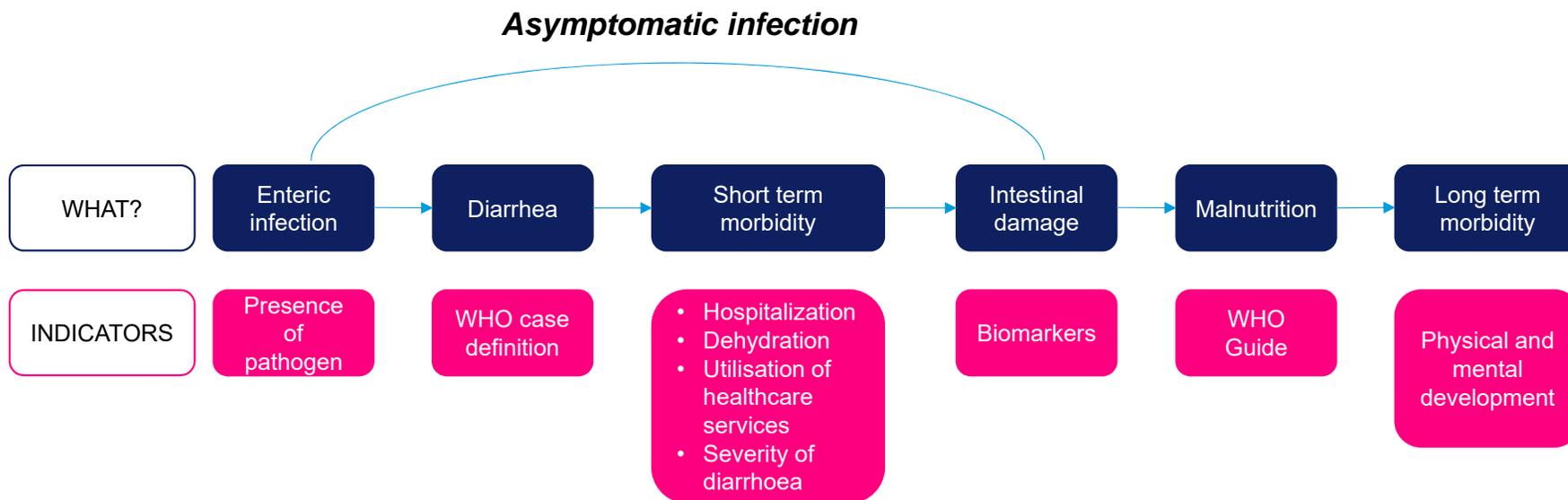
Estimating the overall global burden of diarrheal disease is essential to articulate the full value of vaccines (FVVA) and to guide strategic investments

The vicious circle of diarrhoea, malnutrition, and impaired development...

Strong evidence links both symptomatic and asymptomatic diarrheal pathogen infections with long term consequences



The Pathway to Long term Morbidity

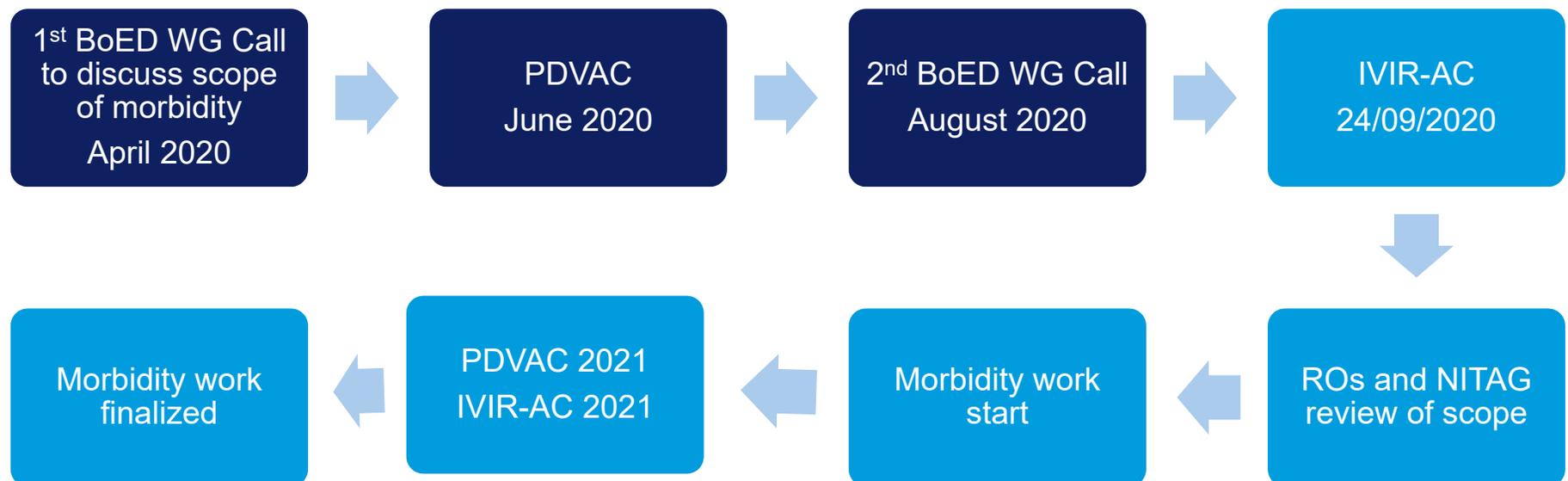


Metrics and Methods

Disability adjusted life years (DALYs): YLLs and YLDs

- Composite measure of overall disease burden, with some limitations expressed as the number of years lost due to ill-health, disability or early death- perfect health is weighted as zero disability, and disability weights progress up to one, the equivalent of death
- Facilitates comparisons of health outcomes Analysis of cost-effectiveness of alternative interventions in terms of cost per DALY averted
- Additional IHME Analysis for diarrhea long-term morbidity burden:
 - Counterfactual analyses of the three common markers of growth: weight-for-age z-scores (WAZ), weight-for-height z-scores (WHZ), and height-for-age z-scores (HAZ).
 - Diarrhoea day was associated with HAZ (-0.003, 95% Confidence Interval [CI]: -0.002 to -0.004), WAZ (-0.008, 95% CI: -0.006 to -0.010), and WHZ (-0.010, 95% CI: -0.007 to -0.013). After adding the DALYs due to the long-term sequelae as a consequence of undernutrition, the burden of diarrhoeal diseases increased by 40% and was responsible for 55,778,000 DALYs (95% Uncertainty Interval: 49,125,400-62,396,200) among children under 5
 - Quantifying the contribution of individual pathogens to growth shortfalls has not been examined
 - Need to incorporate new DALYs estimates in the GBD study

BoED morbidity: Process to identify workstreams



PDVAC Feedback and Recommendations

- PDVAC agrees with the proposed scope of morbidity work;
- This work is needed to inform strategic decisions around vaccine development investment, provide guidance on the kind of data that could inform policy recommendation, vaccine introduction and use.
- Engage early with NITAGs, RITAGs, SAGE, vaccine developers, GAVI to ensure that results from the proposed workstreams, and investments should they be made, will be valuable for decision making;
- Utilise existing studies to inform the morbidity work (ABCD, CHAIN, IHME, GPDS)
- Develop consensus on methodologies to measure the impact of pathogens on morbidity;
- Reflect the AMR component in the morbidity assessment;
- Align with Full Value of Vaccines Assessment concept, IHME, MCEE;

Proposed workstreams

Workstream 1 (2020-2021): assessment of evidence of impact of enteric pathogens or diarrhoea on long term morbidity

- Conduct a systematic review to examine the evidence for the pathologic pathway leading to long term sequelae (inflammation biomarkers, EED, stunting...etc.) of enteric infections and diarrhoea;
- If appropriate, active engagement with study investigators to identify, extract and analyse evidence from historical and ongoing studies to inform the impact of enteric pathogens on morbidity;
- Assessment of robustness of all evidence and proposal to conduct further research studies where appropriate

Output: Summary and assessment of robustness of evidence of the impact of enteric pathogens on long term morbidity, with recommendations for future studies.

Workstream 2 (2020-2021): assessment of methodologies to measure long term morbidity

- Conduct a systematic review to identify indicators and methodologies (variables, metrics, types of tests performed, etc.) to measure the impact of enteric pathogens and diarrhoea on long term morbidity;
- Identify critical data gaps and propose research studies/methodologies that may improve the assessment of the impact of enteric pathogens on long term morbidity

Output: Summary of indicators and methodologies to measure the impact of enteric pathogens on long term morbidity, and critical data gaps with proposed research studies or methodologies.

Proposed workstreams

Workstream 3 (2021-2022), tentative:

- Assess whether the evidence collected on disease impact, and the existing studies/methods to measure morbidity could inform the development of a standardised framework to quantify the burden
- If possible, analyse datasets identified in WS1 using indicators and methodologies revised in WS2

Output: Manuscript or a meeting report to describe the framework to quantify the long term burden, and additional evidence to inform the impact of enteric infections on long term morbidity

We are suggesting not to:

- Collect evidence or assessing the methodologies to measure the short-term morbidity- modelling groups already addressed this
- Looking at non-diarrhoeal outcomes- Guillain Barre syndrome is already accounted for, others are very rare
- Assess the socio-economic impact- we need to understand and collect evidence on long term morbidity to incorporate into socio-economic impact.

Questions to the IVIR-AC



- Does IVIR-AC recommend the proposed scope of work to measure the impact of enteric pathogens on morbidity?
- Is the proposed scope of work considered appropriate next step for further evaluating the full burden, and ultimately the value, of enteric vaccines?

Thank you



World Health
Organization

WHO

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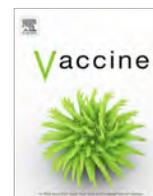
Closing slide



WHO

20, Avenue Appia
1211 Geneva

Switzerland



Conference report

Meeting Report: WHO Workshop on modelling global mortality and aetiology estimates of enteric pathogens in children under five. Cape Town, 28–29th November 2018

H.J. Prudden^a, M. Hasso-Agopsowicz^a, R.E. Black^b, C. Troeger^c, R.C. Reiner^c, R.F. Breiman^d, M. Jit^{e,f,g}, G. Kang^h, L. Lambertiⁱ, C.F. Lanata^{j,k}, B.A. Lopman^d, W. Ndifon^l, V.E. Pitzer^m, J.A. Platts-Millsⁿ, M.S. Riddle^o, P.G. Smith^e, R. Hutubessy^a, B. Giersing^{a,*}

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ABSTRACT

Investment in vaccine product development should be guided by up-to-date and transparent global burden of disease estimates, which are also fundamental to policy recommendation and vaccine introduction decisions. For low- and middle-income countries (LMICs), vaccine prioritization is primarily driven by the number of deaths caused by different pathogens. Enteric diseases are known to be a major cause of death in LMICs. The two main modelling groups providing mortality estimates for enteric diseases are the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, Seattle and the Maternal Child Epidemiology Estimation (MCEE) group, led by Johns Hopkins Bloomberg School of Public Health. Whilst previous global diarrhoea mortality estimates for under five-year-olds from these two groups were closely aligned, more recent estimates for 2016 have diverged, particularly with respect to numbers of deaths attributable to different enteric pathogens. This has impacted prioritization and investment decisions for vaccines in the development pipeline.

The mission of the Product Development for Vaccines Advisory Committee (PDVAC) at the World Health Organisation (WHO) is to accelerate product development of vaccines and technologies that are urgently needed and ensure they are appropriately targeted for use in LMICs. At their 2018 meeting, PDVAC recommended the formation of an independent working group of subject matter experts to explore the reasons for the difference between the IHME and MCEE estimates, and to assess the respective strengths and limitations of the estimation approaches adopted, including a review of the data on which the estimates are based.

Here, we report on the proceedings and recommendations from a consultation with the working group of experts, the IHME and MCEE modelling groups, and other key stakeholders. We briefly review the methodological approaches of both groups and provide a series of proposals for investigating the drivers for the differences in enteric disease burden estimates.

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1. Background

Whilst it is estimated that diarrhoeal mortality has decreased by more than 20% from the decade between 2005 and 2015, the burden of diarrhoea is still significant and predominantly affects sub-Saharan Africa and South Asia in populations with poor access to primary healthcare, clean water and sanitation [1].

Today, diarrhoeal diseases with the highest burden in under five-year olds are considered to be rotavirus, *Shigella* and *Salmonella* species. *Cryptosporidium* and enterotoxigenic *Escherichia coli* (ETEC) also contribute significantly to overall burden [1]. In 1975, the WHO recommended oral rehydration solution globally as the standard immediate treatment for acute diarrhea [2], yet recent evidence suggests that recognition by caregivers may be poor, and uptake remains low [3]. The routine use of antimicrobials for diarrhoea in children is only recommended by WHO in clinically severe cases for cholera, shigellosis, dysenteric presentation of campylobacteriosis and non-typhoidal salmonellosis, or when the host immune status is severely compromised by severe malnutrition or chronic disease [4]. However, with the recognition and continued emergence of antimicrobial resistance (AMR) [5], particularly amongst diarrhoea-related pathogens [6,7], additional approaches to tackling childhood diarrhoea, particularly in LMICs, must be sought. Future research and development of vaccines against diarrhoeal pathogens have been highlighted as key priorities to reduce global disease burden [8,9]. There are currently licensed vaccines for rotavirus and cholera; however, vaccines are not currently available for any of the other major diarrhoeal pathogens, although all have candidates in clinical development.

The estimated global burden of disease, and in-particular the mortality attributable to each pathogen, impacts priority setting for investment in vaccine research and development (R&D), as well as policy recommendations for introduction of new vaccines into immunization programmes. It is important, therefore, that the methodology used to derive the estimates is well understood, and accepted, by global stakeholders, including product developers and policy-makers. Two modelling groups, IHME and MCEE, have generated estimates of mortality due to the different causes of diarrhoea. Historically, the global diarrhoea mortality estimates for children under 5 years of age (U5s) from both groups have been similar with broad and overlapping confidence intervals [10–12]. However, the most recent iteration of estimates from IHME, GBD 2017 for the year 2016, have diverged from previous IHME estimates, particularly with respect to the numbers of deaths attributed to specific pathogens, mainly as a result of revisions to the estimates in high-population, high-burden countries. With the adoption of new detection technology for diarrhoeal pathogens in stools and changes to the methodological approach, estimates of the mortality associated with some pathogens has shifted so significantly that investment in some vaccine candidates that are approaching late-stage clinical testing has been reduced [13]. Because of the implications of changes in disease burden estimates, in 2018, WHO's Product Development for Vaccines Advisory Committee (PDVAC) recommended that an independent working group be established to evaluate diarrhoeal burden models and estimates [14].

The enteric burden of disease working group (WG) was established and convened in 2018. The initial focus of the WG has been on the aetiology of diarrhoeal deaths in children U5. Morbidity and long-term sequelae, though constituting a significant proportion of the burden from enteric pathogens in this age group, have not yet been considered by the WG, nor has mortality in older age groups. However, these factors need to be included in the assessment of the global burden of various diarrhoeal pathogens and the potential public health value that a vaccine could offer.

This report summarizes the findings from the first meeting of the WG.

2. Objectives of the workshop

The IHME GBD and the MCEE models were reviewed with the objectives to:

- (I) Identify areas of commonality and divergence across methodologies and assumptions.
- (II) Develop recommendations and identify areas for further work that may inform future iterations of the diarrhoeal aetiology-specific mortality assessments for U5s.
- (III) Increase the transparency and understanding of how aetiology estimates are derived.

The sections below outline the main methodological approaches of the two modelling groups, highlighting similarities and differences. We use *Shigella* and ETEC as examples to show the divergence in modelled estimates between the groups. Reference will be made to two large landmark epidemiology studies, namely the Global Enteric Multicentre Study of Diarrheal Disease (GEMS) [15] and the Aetiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development study (MAL-ED) [16] (see Box 1). Finally, a set of proposals are presented as future work to explore variations in the model outputs and to provide updated evidence for key assumptions applied by both modelling groups.

Box 1 Description of two large landmark epidemiology studies of diarrhoeal disease aetiology, GEMS and MAL-ED.

The Global Enteric Multicentre Study of Diarrheal Disease (GEMS)

The GEMS study was a 3-year, prospective, age-stratified, case-control study to estimate the population burden and microbiologic aetiology of acute moderate-to-severe diarrhoea (MSD). Children aged 0–59 months seeking care for diarrhoea as outpatients or inpatients at health care centres (cases) were compared with non-diarrhoeal community controls. In addition, cases were followed up after 2 months to study short-term mortality after an episode of MSD. The research was carried out in seven field sites in Southern Asia and sub-Saharan Africa, using qPCR as a diagnostic tool in cases and controls to detect evidence of different pathogens in stool samples and these results were used to estimate the fraction of moderate-to-severe diarrhoea attributable to each pathogen.

The Aetiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED)

The MAL-ED study was a birth cohort study at eight sites in South America, sub-Saharan Africa, and Asia. It used a prospective longitudinal design to assess diarrhoea, subclinical enteropathogen carriage and undernutrition up to the age of 2 years in a community setting. Among the factors evaluated were enteric infections (with or without diarrhoea) and other indicators including micronutrient levels, diet, socioeconomic status, gut function and environment. The study examined these factors, their inter-relationships and overall impact on health outcomes. Because participants were selected in the community, rather than from among hospital patients, few children with severe, dehydrating diarrhoea were observed.

3. Overview: modelling estimates of mortality due to enteric infections

Both the IHME and MCEE modelling groups employ a step-wise process for generating under-five all-cause and pathogen-specific diarrhoea mortality estimates. The first stage is to generate estimates for all-cause mortality in U5s. This is then disaggregated into the percentage of U5 deaths due to diarrhoea, and then, estimates for deaths attributed to individual pathogens are generated (Fig. 1). Table 1 compares differences in these first two key outputs from the two modelling groups and provides information on differences in data sources and inclusion and exclusion criteria applied to generate the estimates. In addition, estimates for ETEC and Shigella are provided, comparing 2011 estimates for MCEE and 2013 for IHME from earlier studies, as an example of deaths attributed to different pathogens during the third stage. Data from IHME 2016 are also shown, data for MCEE 2016 will not be made publicly available. In this section, we outline the first two stages shown in Fig. 1 and then provide a more detailed overview of the third stage employed by each group to generate estimates of the numbers of diarrhoeal deaths attributable to different aetiologies, highlighting key similarities and differences in Section 4.

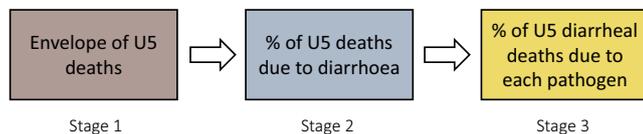


Fig. 1. Three stage process for generating U5 diarrheal deaths due to different pathogens.

Table 1
Differences in data sources used and estimates generated for the envelope of U5 deaths and percentage of U5 deaths due to diarrhoea, by MCEE and IHME. A comparison for the percentage of U5 diarrheal deaths due to Shigella and ETEC are provided as examples to show the variation at the level of aetiology.

Model output	IHME (2016) ¹	MCEE (2016) ²
U5 Mortality Envelope (2017) (Stage 1)	IHME-generated estimates 5.6M (5.4M–5.9M)	Generated by the United Nations Group for Child Mortality Estimates (UN IGME) 5.4M (5.2M–5.8M)
U5 Deaths Due to Diarrhoea (Stage 2)	Data included: • Vital registration studies with >60% data completeness. • Verbal autopsy data from demographic surveillance and surveys 549 K (491–606 K)	Data included: • Vital registration studies with >80% data completeness. • Verbal autopsy data from demographic surveillance and surveys.
U5 Diarrheal Deaths Due to Pathogens: (Stage 3) Shigella: ETEC:	• All hospital and community studies conducted for 12 or more months. • GEMS and MAL-ED studies.	• Hospital inpatient studies conducted for 12 or more months. • GEMS and MAL-ED unpublished studies including data stratified by inpatient vs. outpatient/community.
Model output	IHME (2016)	MCEE (2016)
Shigella	99 680 (59550–161235)	Data will not be made publicly available
ETEC	15 960 (4400–40300)	Data will not be made publicly available
	IHME (2011) ³	MCEE (2013) ⁴
Shigella	33 400 (24 900–43500)	28 000 (12000–53000)
ETEC	23 100 (17000–30400)	42 000 (20000–76000)

Comparison of modelling results and data inputs for IHME and MCEE for Total U5 mortality envelope (2017) and percentage U5 deaths due to diarrhoea (2017). Estimates for percentage U5 diarrheal deaths due to Shigella and ETEC (2016 GBD IHME, 2017 MCEE (unpublished)) are also shown.

¹ Data extracted from GHDx website for the Global Burden of Disease 2017 Model, reporting data for 2016.

² Data from Pneumonia and Diarrhea Progress Report, 2018. John Hopkins, International Vaccine Access Centre.

³ Data from Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015, Jan 10; 385(9963): 117–171.

⁴ Data from Global Causes of Diarrheal Disease Mortality in Children <5 Years of Age: A Systematic Review. PLOS One 2013, 4 Sept. 8(9).

3.1. Generation of the total global envelope for all-cause U5 mortality globally

For the 2017 iteration, the IHME model uses IHME-generated estimates for all demographic inputs. The MCEE model uses United Nations Inter-agency Group for Child Mortality Estimation (UN IGME) modelled estimates, generated using UN Population Division demographic data of population, fertility, migration and mortality by age, sex, location and time, from national censuses and specialised surveys [17]. Despite these differences in the source data, the overall U5 mortality estimates generated by each group are similar; 5.6M (95%UI, 5.4M–5.9M) for IHME and 5.4M (90%UI, 5.2M–5.8M) for MCEE. However, it should be noted that there are significant differences between the mortality estimates in different geographic locations. Thus, differences in the all-cause envelope at a country or regional level, used by the IHME modellers, could lead to differences in the estimated number of total diarrhoea deaths for individual regions between IHME and MCEE. For each revision of the GBD estimates, both groups update all of their values for previous years.

The second output is an estimate for the percentage of U5 deaths due to diarrhoea. Both IHME and MCEE use vital registration, verbal autopsy and surveillance system data to inform the estimate of percentage of U5 deaths due to diarrhoea. However, there are differences in the data used by each of the groups, with respect to inclusion and exclusion criteria and access to unpublished data. The MCEE group have more stringent inclusion and exclusion criteria for the threshold completeness of vital registration data: MCEE only accepts studies with >80% data complete whereas IHME includes studies with > 60% data completeness.

To generate diarrhoeal-specific estimates, IHME redistributes deaths that cannot be attributed to a pathogen to specific causes of death (like diarrhoea) and uses an internal model called the Cause of Death Ensemble model (CODEm), a Bayesian hierarchical model to generate, by location, age group (four age groups under

5 years), sex, and year, estimates of the percentage of deaths due to diarrhoea. Table 1 provides information on the data sources used for the first two stages in the process.

The procedures used by both groups to generate the percentage of U5 diarrheal deaths due to different pathogens, which was the major focus of the workshop. Differences in methodological approaches between groups at this stage are most likely to contribute to the divergence seen in pathogen-specific mortality estimates (aetiology). In Section 4, each step in the process is summarised and an explanation of similarities and differences in the modelling approaches are reviewed, highlighting the strengths and limitations of the methodologies used by each group.

4. Process for calculating the percentage of diarrheal deaths due to individual pathogens

4.1. Generation of a diarrheal mortality proxy

Due to a lack of representative datasets in which deaths due to specific diarrhoeal pathogens have been identified, the initial step in the process of attributing diarrhoeal deaths to specific pathogens is to identify a proxy measure. Both groups use the proportion of diarrheal episodes in which a particular pathogen is detected as the proxy measure; however, IHME use data from both hospital inpatient and outpatient studies and MCEE uses only data from hospital inpatient studies, assuming that hospitalization is a more accurate proxy for mortality and that aetiological fractions differ between inpatient and outpatient studies. Both groups only use studies which were conducted for 12 or more months. Studies which did not stratify data from inpatients, outpatients and the community were excluded by MCEE. Facility-based studies of both inpatients and outpatients are thus only included if inpatient-specific proportions are reported or raw data are available to allow subset analysis with the exception of the GEMS and MAL-ED studies, for which unpublished stratified data were obtained. Both IHME and MCEE include only diarrhoea proportion data from studies with a minimum of 100 samples tested and conducted for longer than one year, and not restricted to specific subpopulations. The proportion positive in hospitalised and 'severe' episodes are tracked, and all data meeting inclusion criteria is used in the models [18]. All data for hospitalised/severe diarrhoea relative to community/outpatient are included in the model, including all eligible GEMS data. A summary is given in Table 2.

4.1.1. Strengths and limitations

The approach of IHME is to use all available data with limited restrictions, whilst MCEE have stringent inclusion and exclusion criteria for data. The inclusion of 'severe' cases as well as hospitalised cases allows both inpatient and outpatient data to be used for IHME's model estimates. However, there is variation between studies in what may constitute a 'severe' case (i.e. the case definition), and the interpretation of this, which may limit data quality. The IHME approach uses more data compared to MCEE, although there is likely to be a large proportion of studies that were included by both modelling groups. A comparative analysis of the criteria for data inclusion, data sources and data quality of the modelling groups could help to optimize approaches for the next iterations

of models, ensuring that future diarrhoeal disease models abide to a high and consistent standard of data quality.

4.2. Validity of epidemiology studies to be included

Both groups use systematic literature reviews that date back to 1985 (IHME) or 1990 (MCEE), to extract pathogen prevalence from studies meeting their inclusion and exclusion criteria. This includes, where available, data from scientific literature on different aetiologies, hospital data, population survey data, and data from unpublished sources, including detailed data for the GEMS and MAL-ED studies and more recent cohort studies.

4.2.1. Strengths and limitations

The validity of using studies dating back to the 1980's by both groups, in terms of robustness and reproducibility of diagnostic methods compared to more recent studies, is highlighted as a potential limitation. The improvement over time in culture-based and other diagnostic techniques as well as likely shifts in the aetiology of diarrhoeal disease, due to initiatives such as Water, Sanitation and Hygiene (WASH), may suggest that, for contemporary estimates, a greater weighting should be placed on more recent studies [19]. Additionally, evidence from GEMS shows that using qPCR to test stools for different pathogens is more sensitive than culture-based methods, compared to culture-based methods [20], with the consequence that older diagnostic reporting from older studies may underestimate the prevalence of pathogens which require more sensitive techniques for detection. There is a need for sensitivity analysis to test for reliability of these data, and groups should consider the potential effect of attributing greater weighting to more recent studies or incorporating time and/or time-varying covariates in the models [21], given the improvement in diagnostics.

4.3. Data processing methodologies and the use of qPCR data

4.3.1. IHME approach

The final step in the generation of estimates for individual pathogen mortality is data adjustment and processing. In the case of IHME, epidemiological data extracted from the literature, hospital data, and population survey data are analysed using their DisMod tool (Bayesian hierarchical meta-regression tool) to estimate the proportion of diarrhoeal cases that are caused by different organisms. In order to adjust for the different pathogen detection methods used, GEMS and MAL-ED data are used to calculate the sensitivity and specificity of laboratory diagnostic tests, such as culture and immunoassay, relative to qPCR, for each pathogen and a qPCR adjustment factor is applied to the pathogen-specific proportions after the model is run. A major short-coming of diarrhoeal disease studies conducted prior to GEMS has been the failure to perform comprehensive assessment of major enteric pathogens, due to demanding technical approaches, in settings with high burdens, often lacking the necessary laboratories and diagnostics [22]. The correction factor generated from GEMS and MAL-ED is then applied to the modelled results and adjusted for sensitivity and specificity based on this estimate. The modelled proportion of diarrhoeal cases by aetiology are adjusted and produce estimates for each location, year, age, and sex. IHME then use a counterfactual

Table 2
Summary of data used by IHME and MCEE for generating diarrheal mortality proxy.

Model Methodology	IHME	MCEE
Generation of diarrheal mortality proxy	Include hospitalised and 'severe' diarrheal episodes. Include inpatient, outpatient, and community-based data. All eligible GEMS and MAL-ED data included.	Included only hospitalised episodes. Include only inpatient data. Only GEMS and MAL-ED inpatient data included

approach to calculate a population attributable fraction (PAF) for each pathogen, which represents the relative reduction in hospitalised diarrhoea episodes (as a proxy for deaths) if exposure to a given aetiology was to be eliminated. In order to generate this, GEMS case-control data are used to calculate pathogen-specific odds ratios (ORs) by age where the OR is the odds of diarrhoea given the presence of that pathogen in the stool at a diarrhoea-attributable quantity as detected by qPCR, divided by the odds of diarrhoea without the detection of the pathogen at a diarrhoea-attributable quantity. This is combined with the qPCR-adjusted proportion of diarrhoea cases positive for a given aetiology to calculate the pathogen-specific PAF. Such that:

$$PAF = Proportion * \left(1 - \frac{1}{OR}\right)$$

The PAF is applied to calculate deaths due to diarrheal aetiologies by location, year, age, and sex. The schematic in Fig. 2, below, summarises the IHME data processing methodology.

For all pathogen aetiologies except *Vibrio cholerae* and *Clostridium difficile*, the PAF is calculated from the proportion of diarrhoea cases that test positive for each aetiology and the OR of having diarrhoea if the pathogen is detected. Since diarrhoea can be caused by co-infections with multiple pathogens, PAFs can overlap and therefore add up to more than 1. The purpose of using ORs is to address the issue of subclinical carriage, namely that enteric pathogens are frequently detected in the absence of diarrhoea. For each pathogen, PAFs and uncertainty intervals are multiplied by the diarrhoea mortality envelopes to estimate age-, sex-, location- and year-specific pathogen deaths.

4.3.2. MCEE approach

MCEE takes a different approach. They do not adjust studies and data where pathogens are detected using non-qPCR detection methods to match with those detected by qPCR. However, MCEE uses pathogen positivity according to GEMS qPCR to define pathogenicity. Organisms with <2 site- and age-specific attributable fractions that were different to 1 (not associated with causing diarrhoea) in the GEMS qPCR re-analysis [20] (including norovirus G1, atypical EPEC, LT-EPEC, Giardia, EAEC) were excluded from the analysis. Mean age-adjusted pathogen-specific proportions were calculated from hospital data, with age-group conversion factors applied to convert pathogen-specific proportions reported for narrower age ranges than 0–59 months, based on data from studies that reported estimates across age ranges. A global median was used to estimate pathogen-specific proportions for regions with missing data. The pathogen proportions (in addition to the unknown proportion, derived from GEMS qPCR hospital inpatient data) are constrained to add up to 1 overall and by region (Fig. 3). Uncertainty bounds are generated using bootstrap techniques. Final pathogen-specific proportions and uncertainty intervals are multiplied by regional diarrhoea mortality envelopes by year to generate regional estimates of pathogen-specific deaths.

4.3.3. Strengths and limitations

Samples from the GEMS study have recently been reanalysed using qPCR methods rather than the culture-based and other microbiological methods that were used in the original study. This has led to a re-estimation of the percentage of diarrhoea attributable to a named pathogen, with 89% of all episodes attributed to a pathogen, compared to 52% in the original GEMS analysis [20]. In

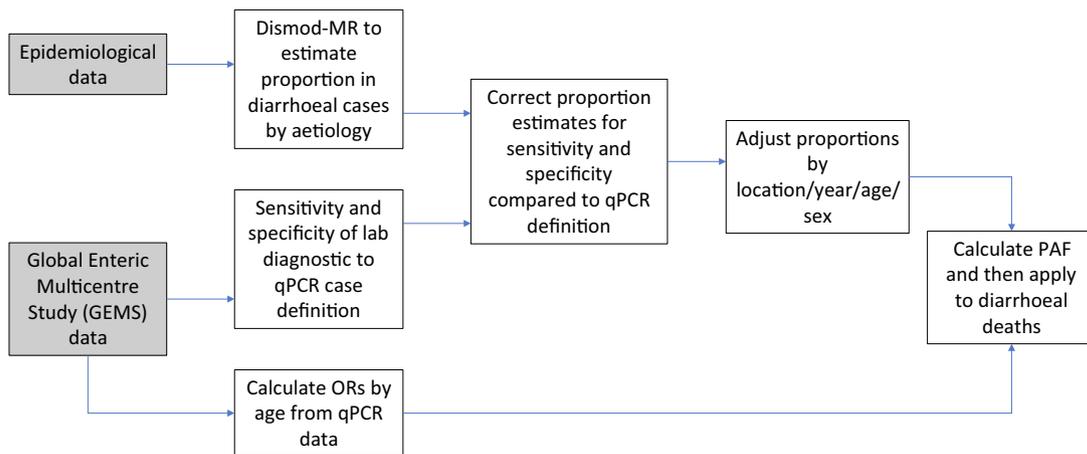


Fig. 2. Data processing mechanism for IHME data (adapted from GBD Diarrhoeal Diseases Collaborators. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Infect Dis 2017).

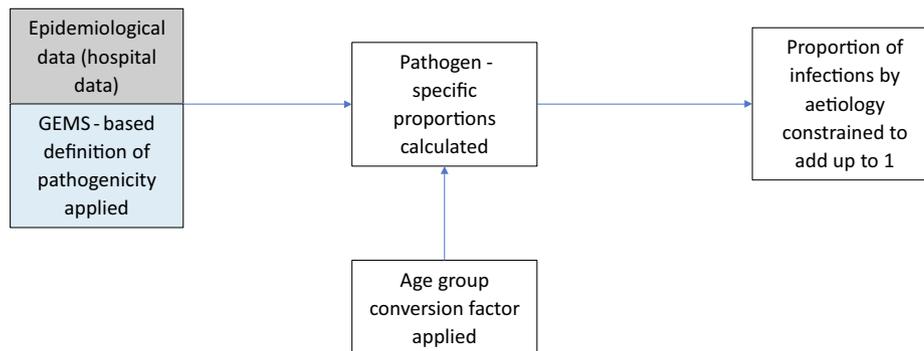


Fig. 3. Data processing mechanism for MCEE data.

the modelling analysis, IHME uses these reanalysed GEMS data to adjust for differences in sensitivity and specificity for all PCR and non-PCR estimates, whilst MCEE does not, but plans to do so in the future. There are two main limitations in using the GEMS data. Firstly, the use of a single adjustment for each pathogen derived from GEMS ignores substantial heterogeneity across studies in the relative sensitivity between diagnostics. Secondly, the absence of diagnostic metadata in the IHME database combined with the increasing incorporation of molecular diagnostics may lead to over-correction, particularly among more recent studies that use PCR.

4.4. Approaches to infer aetiology in the presence of high-rates of subclinical pathogen detection

4.4.1. The use of PAF versus pathogen prevalence

Currently, only IHME uses ORs to calculate the pathogen-specific mortality and population attributable risk, whilst MCEE use the pathogen prevalence (the prevalence of individual pathogens from the studies). Both groups consider evidence from multiple pathogen studies, thereby addressing the issue of mixed aetiologies. This gives rise to the issue of subclinical carriage, where a pathogen may be present but is not responsible for symptoms. This approach relies heavily on the assumption that the ratio of the prevalence of a pathogen in cases compared to controls is a clear indicator of pathogenicity. This assumption may be too conservative, especially in high incidence settings [23,24] and in particular for pathogens that commonly cause reinfection. Such is the case for many enteric pathogens that often cause asymptomatic or subclinical infection.

IHME does not constrain the PAFs to add up to 1, and therefore they assume that in instances where multiple pathogens are detected, diarrhoea would still occur even if one of the pathogens was removed. MCEE also considers mortality attribution may be a result of multiple pathogens, but they do constrain the pathogen prevalence envelope to add up to 1 minus the proportion of diarrhoea without a known cause (restricting to the inclusion of pathogens that were statistically significantly associated with diarrhoea in the GEMS qPCR re-analysis). Burden estimates could be significantly inflated, if subclinical carriage (presence of a pathogen, which is not severe enough to present observable symptoms) is not considered, by way of calculating attributable fractions. In addition to this there may be variation in pathogen load needed to cause infection between sites, i.e. variations in the probability of clinical symptoms caused by a certain pathogen in different settings, which would lead to a restriction in the generalizability of assumptions. It therefore remains unclear how often 'true' aetiological mixed infections occur. Evidence from qPCR shows high variation in durations of carriage of subclinical infections, and there is also evidence to suggest infections could be sequential rather than mixed [25,26]. The implications of this are that, in cases where a pathogen is consistently shed and there are high levels of detection but suspected low levels of pathogenicity within a site, country, or region, the OR may be over- or under-estimated.

4.4.2. Strengths and limitations

A strength of the current approach of both groups is the consideration of sub-clinical infections, but there is a lack of knowledge on how to interpret the information and estimates of the burden of sub-clinical infections which are not generated by either group. The presence of sub-clinical infection may vary geographically for individual pathogens, such that the occurrence of one pathogen may cause symptoms in one setting but not in another. A further limitation is lack of knowledge on whether co-infections enhance the probability of clinical symptoms and how different pathogens interact and impact aetiology in the presence of others. This is

potentially further complicated by geographical variations and a lack of understanding on whether infections are 'mixed' or 'sequential'. For IHME, these combined factors may result in heterogeneity of ORs that complicates the use of a single 'global' median OR for each pathogen to calculate PAFs, currently adopted by IHME. A potential solution, to strengthen the approach adopted by IHME, may be to generate ORs across similar geographical regions and population archetypes, based on the proportion of pathogens excreted in diarrheal and non-diarrheal stools. However, the sparsity of data on pathogen prevalence that is currently available from healthy controls limits this option, and additional control samples from geographical areas would need to be generated. This is also a limitation for the MCEE group, who considers that mortality may be attributed to multiple pathogens, with pathogen prevalence informing aetiology. Additional information on pathogen prevalence in healthy controls, would likewise help to also strengthen MCEE's approach.

4.5. Other key strengths and limitations in the generation of individual pathogen estimates

4.5.1. Data extrapolation

In order, to produce global estimates for individual pathogen estimates, IHME extrapolate the ORs derived from children under 5 years of age from Africa and Asia (GEMS) to all estimates, including adults and in developed countries. Prevalence of each pathogen is estimated for both ages and locations where data do not currently exist, and models are continually updated. Whilst in many instances, sub-regional data may be able to predict country-level burden attribution with a high degree of confidence, it is possible that outliers, where data quality is poor or is not reflective of sub-regional estimates, may result in inaccurate estimates for some countries. MCEE use a global median to estimate pathogen-specific proportions for regions with missing data. This is reliant on the data being a good proxy for other regional estimates, and it is not clear if this is always the case.

4.5.2. Assumption of pathogen homogeneity in case fatality ratios

Both modelling approaches assume that the distribution of pathogen aetiology as assessed via each group's accepted proxy measure directly reflects the distribution of mortality, such that detection of every pathogen in a hospitalized or severely ill child is assumed to be equally likely to cause death. MCEE assume that case fatality ratios are the same across all pathogens based on the prevalence estimate they generate when they scale pathogen-specific proportions. The same implicit assumption is made by IHME, when they generate PAFs. If indeed, there is variation between pathogens, this will affect the distribution of pathogen aetiology in patients who die from diarrhoea and may also be dependent on geography, socio-economic status and population. More evidence is needed to explore variations in case-fatality rates for individual pathogens. This is challenging because the majority of data on mortality is obtained in hospital settings and therefore may bias estimates, given that untreated severe diarrhoea within the community, particularly in LMICs, is more likely to result in death, in most cases. Data collected from study sites is also extrapolated at country-level, which may not necessarily be representative. Whilst this is a limitation, to address this issue of generalisability would be particularly difficult.

5. Proposals for addressing knowledge gaps and improving model estimates

There are both strengths and limitations to the methods presented by both IHME and MCEE groups, as outlined above. We believe

that a key outcome of the consultation should be to initially focus on understanding the main reasons for variations in aetiology estimates within the published diarrhoea mortality envelope for U5s. Three key thematic areas were proposed for future investigation.

- (1) How differences in data inputs impact the distribution of U5 aetiology estimates within the mortality envelope.

Identifying the drivers for differences between the modelling outputs produced by IHME and MCEE will be a key step in helping to quantify and assess the source of differences in estimates. Whilst much of the data used by both groups are expected to be common and comparable, there are important differences in the criteria that determine which data are included. An improved understanding of factors that are the strongest determinants of the model estimates is vital to better understanding their accuracy and robustness, since these estimates drive decision-making with respect to vaccine development and introduction. The impact or trade-off of utilising a small number of high-quality studies (as MCEE do) versus a larger number of studies of varying quality (as IHME do), to generate global estimates needs to be investigated. Additionally, the validity of using historical studies that use less sensitive diagnostic techniques, weighted equally within the data analysis, needs reviewing.

To investigate these steps, we propose the following strategies, to be refined in an iterative manner as greater understanding of the processes evolve:

- i. Conduct a systematic comparison of studies and data included in both models, in an effort to understand how data selection criteria and access to data impacts on the quality and quantity of studies used.
 - ii. Agree on a standardised dataset to directly compare how differences in model structure and associated assumptions (rather than input data) impact estimates.
 - iii. Conduct a data grading review to improve understanding of the quality and standard of data used by each group, followed by a model sensitivity analysis to explore the impact of inclusion and exclusion criteria on model estimates.
- (2) How extrapolation of odds ratios from 7 GEMS sites in Africa and Asia impacts global aetiology estimates.

There were concerns regarding potential bias resulting from the use of GEMS data to determine global median ORs or pathogens, given substantial variation in the rates of subclinical pathogen carriage across ages and settings. Concerns were further raised regarding the direct use of odds ratios exclusively from seven GEMS sites and extrapolation of this data regionally and to older age groups (5–99 years, for Global Burden of Disease). There was a desire to improve our understanding of the relationship between the presence of pathogen and diarrhoea by utilising additional data from controls to provide more geographically representative ORs which can be consistently used in future modelling analysis, for both IHME, MCEE and other groups. Recommendations included:

- i. Conduct a systematic review to identify studies that tested for the presence of key diarrheal pathogens among non-diarrheal controls and older age groups.
 - ii. Use the findings to carry out a careful and comprehensive statistical approach using network meta-analysis to assess variability in odds ratios within and across regions and settings, built through consensus with IHME and MCEE.
- (3) Heterogeneity in case fatality ratios (CFRs) for different pathogens.

There is a strong recommendation to assess potential variability in CFRs, particularly in-light of the high number of co-infections and sub-clinical carriage reported in study participants in low- and middle-income countries, and to assess the relationship between the OR of disease and risk of death. This approach will need to account for the different approaches taken by each of the modelling groups, since neither group uses CFR in its current methodology, to ensure the process provides useful information that can be adapted and applied by both MCEE and IHME in the future. A limitation is the potential scarcity of data available for non-hospitalised (community) estimates of death (as previously alluded to), which will likely introduce bias since treatment within a hospital setting is likely to significantly increase chances of survival. Additionally, mortality may be affected by the rate of onset of illness and time to death (which may affect the probability that a child with diarrhoea reaches a facility), and this may vary depending on the pathogen. Factors such as economic status and geography are also important. To address this issue, there was a recommendation to:

- i. Carry out a systematic literature review to identify the CFR for selected enteric pathogens. The review should aim to include both hospital and non-hospital data (with the caveat that the latter may be very limited; and that hospitalization changes the CFR for largely treatable infections, like rotavirus.).

6. Discussion

The global mortality due to diarrhoeal disease is declining, and for some pathogens, such as ETEC, the current (GBD 2017 for the year 2016) IHME burden of disease estimate is now considered too low to warrant prioritization of vaccine development by some stakeholders. However, given the variation between mortality estimates from different groups, the methodology and robustness of each estimate needs to be carefully understood and investigated. For this reason, WHO's PDVAC recommended the formation of an independent working group to evaluate these aspects. As we have discussed here, we identified several elements of the methodology that we suggest, be further investigated.

The proposed systematic review to extract data from healthy controls will help to further explore the relationship between the presence of a pathogen and disease. It is expected there will be a degree of geographical variation within the results, to complement the current GEMS data, which assumes homogeneity across sites for the odds ratios. This additional information may help to better explain geographical differences in the susceptibility of individuals and populations to certain pathogens, and thus provide improved information on burden.

The results from the second systematic review will explore the likelihood of mortality given the presence of disease, known as the case fatality ratio, for individual pathogens. The current strategy employed by both modelling groups is to assume equal likelihood of death regardless of the aetiology. This is likely to over-estimate the risk of mortality for some pathogens and under-estimate the risk for others. A clearer understanding of the variation in case fatality ratio will be of great importance in informing vaccine development, particularly for pathogens which are associated with a higher risk of mortality.

7. Conclusion

The modelling approaches employed by both the IHME and MCEE groups have historically provided well-regarded results that have guided policy recommendations. As new data, diagnostic and

surveillance techniques emerge, the incorporation of new evidence is essential to ensure more reliable estimates. However, the interpretation and use of new evidence should be subject to a high level of scrutiny, and where appropriate, new guidelines developed for its use. In addition, it will be important to address gaps within the data that give rise to inconsistencies and less reliable information. Emerging evidence generated through studies, such as The Child Health and Mortality Prevention Surveillance (CHAMPS) study, designed to track definitive causes of child mortality in sites throughout Asia and sub-Saharan Africa through minimally invasive tissue sampling, will help to provide validation on key measures such as the diarrhoeal mortality proxy. More generally, steps can be taken to assess the quality of data employed by modelling groups, and systematic reviews can be undertaken to address other key gaps in the evidence.

Future modelling work, should also assess the longer-term sequelae of diarrhea [27,28], including growth failure and cognitive impairment in the earlier years of life, as well as metabolic syndrome in the later years of life [29]. There is evidence also that repeated infections may increase risk of death from other unrelated infectious diseases such as pneumonia and malaria [30]. Whilst the GBD estimates include growth deficits in their estimation of diarrhoea-specific DALYs, they do not consider neurodevelopment due to the absences of standard routinely collected metrics of neurodevelopment. Future models should incorporate these longer-term effects and risk factors, in addition to the effects of acute diarrhoea. This will further strengthen the evidence-base for decision-making around prioritizing enteric pathogens for which vaccines would have the greatest public health impact.

There is a clear case for ensuring diarrhoeal pathogen mortality estimates are constantly reviewed and updated, and adequate resources are made available to ensure model comparison exercises, since these are a core component of vaccine priority evaluations. This work will serve as an example of the importance of critically assessing data quality in modelling exercises, whilst identifying and addressing crucial gaps in the evidence which must be addressed.

The proposed work aims to provide a thorough assessment of the current data and approaches used by IHME and MCEE groups. Our hope is that this can include a sensitivity analysis of the model input data to improve understanding of key input variables, potentially leading to improved guidance for data use, and enhanced interpretation of model results to guide decision-making. Whilst the activities outlined above help to better define which pathogens should be prioritized for vaccine development, future work should include assessment of data and model to quantify the impact of longer-term sequelae. Collectively, robust data and burden models are imperative for building the evidence-base to inform prioritization and policy decisions.

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Authors contributions

HJ Prudden and B Giersing contributed significantly to the development of text and content, produced the main figures and

tables and carried out extensive editing. RE Black, C Troeger, and RC Reiner contributed to the development of the methodology and details of the overview (3) section of the paper, as well as additional edits to the main manuscript.

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Title:

Case fatality risk of diarrheal pathogens: a systematic review and meta-analysis

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Abstract

Background

Despite substantial reductions in all-cause diarrhea mortality, diarrhea is still a leading cause of death among children aged <5 years worldwide. In order to prioritize vaccine development and pathogen-specific interventions across diarrheal pathogens, accurate estimation of their relative contribution to all-cause diarrhea mortality is required. We aimed to investigate and estimate the level of heterogeneity in the case fatality risk (CFR) of different diarrheal pathogens.

Methods

We conducted a systematic review for diarrheal pathogen-specific CFR using PubMed, EMBASE and Cochrane databases. The resulting dataset consisted of published studies that reported cases and deaths for 15 enteric pathogens between 1990 and 2019. The primary outcome was diarrheal pathogen-specific CFR stratified by age group, country-specific under 5 mortality rate (U5MR), setting (hospital- or community-based), study year and rotavirus vaccination status (i.e. studies conducted before or after rotavirus vaccine introduction). We developed fixed and multilevel mixed-effects logistic regression models to estimate the pooled CFR overall and for each pathogen, controlling for potential predictors of heterogeneity.

Results

A total of 427 studies met study criteria and were included in the analysis. The overall CFR from the fixed effect model was 0.65% (95% confidence interval (CI): 0.65%-0.66%); pathogen-specific estimates ranged between 0% and 6.4%. There was considerable heterogeneity between and within studies, with an overall I^2 of 99% and pathogen-specific I^2 ranging between 0 and 100%. Studies from countries with a high U5MR exhibited a higher CFR compared with studies

from other countries. Associations with other predictors were inconsistent across the pathogen-specific models and weak in the overall model. When pathogens were included as predictors of the CFR in the overall model, the highest and lowest odds ratios were found for enteropathogenic *E. coli* (EPEC) (OR = 2.91, 95% CI: 1.25-6.80) and rotavirus (OR = 0.23, 95% CI: 0.13-0.39), respectively.

Conclusions

We provide comprehensive estimates of the CFR across different diarrheal pathogens, and highlight the pathogens for which more studies are needed to estimate their true CFR. The results could help prioritize vaccine development and pathogen-specific interventions across diarrheal pathogens.

1. Introduction

Despite an estimated 80% decline in diarrhea mortality among children <5 years between 1980 and 2015 within low- and middle-income countries [1], globally in 2015, diarrhea still caused 1.3 million deaths, making it the fourth and ninth most common of death among children <5 years and all ages, respectively [2]. Thus, there is an urgent need to better understand the factors and pathogens contributing to the overall diarrhea mortality burden.

Studies have shown that diarrhea mortality varies by pathogen, age, mortality strata and income settings [3-7]. Currently, there are two main models that are used to estimate the global mortality associated with diarrheal disease: the Maternal Child Epidemiology Estimation (MCEE; formerly the Child Health Epidemiology Reference Group) model [3-5] and the Institute for Health Metrics and Evaluation (IHME) model [6,7]. The MCEE model assumes that pathogen-specific mortality is proportional to the distribution of pathogens among hospitalized patients, while the IHME model uses the distribution of pathogens among both inpatient and outpatient (with a correction factor) studies to estimate pathogen-specific mortality. Between 2013-2019, the two groups have reported increasingly divergent mortality estimates among children <5 years old, particularly for *Shigella* and enterotoxigenic *Escherichia coli* (ETEC) [8,9]. Such discrepancies impact decisions around vaccine development, introduction and use. Efforts are needed to fully understand limitations and methodologies used to calculate the estimates for both models.

A potential limitation of both models is that they assume that the distribution of pathogens among inpatients is a suitable proxy for the contribution of each pathogen to overall diarrheal deaths. Thus, they implicitly assume the same CFR for “hospitalizable” patients across all diarrheal

pathogens [10]. To improve estimates of pathogen-specific diarrhea mortality and prioritize pathogens for vaccine development, reliable estimates of the CFR are required. In addition, identifying predictors of heterogeneity in the CFR could inform regions or age strata for targeted interventions in an effort to reduce diarrhea mortality.

Most previous meta-analyses of the CFR of diarrheal pathogens have been primarily focused on single pathogens [11-13], or limited to children <5 years [12] or to a specific geographical region [14], with only few studies combining some of these factors [8,9]. Given the variation in estimates of the CFR across various strata and settings, it is important to estimate the diarrhea pathogen-specific CFR and how various factors contribute to pathogen mortality in order to improve our understanding of overall diarrhea mortality across the globe.

2. Data and methods

2.1. Overview

In this study, we conducted a systematic review and meta-analysis to estimate and investigate heterogeneity in the CFR of different diarrheal pathogens. We also examined how the CFR varies by country-specific under-5 mortality rate (U5MR), age group, study setting (hospital- or community-based), study year and rotavirus vaccination status (i.e. whether the study was conducted before or after rotavirus vaccine introduction). Finally, to gain insight about the contribution of each predictor to the estimated CFR, we developed models to estimate the CFR overall and for each pathogen, controlling for potential predictors of heterogeneity.

2.2. Search strategy and selection criteria

We conducted a systematic review to identify studies that could be used to estimate the CFR for 15 enteric diarrheal pathogens using three databases (PubMed, EMBASE and Cochrane). The 15 enteric pathogens included seven bacterial (*Aeromonas spp.*, *Campylobacter spp.*, enteropathogenic *Escherichia coli* (EPEC), ETEC, *Salmonella spp.*, *Shigella spp.*, and *Vibrio cholerae*), five viral (adenovirus, astrovirus, norovirus, rotavirus, and sapovirus) and three parasitic (*Cryptosporidium spp.*, *Entamoeba histolytica*, and *Giardia lamblia*) pathogens; acceptable detection methods and strains for each pathogen are listed in Table S1. The review was restricted to studies that reported cases and deaths published between 1990 and 2019. The search was conducted on July 10, 2019 using pre-specified search strings for each database (see Supplementary Material, file1: pages 3-5). Studies were selected into the review if they presented primary data, if their subjects had a pathogen of interest and diarrhea, and if they either included information about the number of deaths or presented follow-up data for all subjects, allowing the study team to deduce that no subjects died due to enteric pathogens during the study. Inclusion and exclusion criteria are presented in Table 1.

Two independent reviewers screened each title and abstract using the inclusion and exclusion criteria (Table 1). During screening, disagreements between reviewers were settled either by further review between the two reviewers or by reaching team consensus. If the disagreement could not be settled with information available in the title and abstract, the study was passed on to full-text review. The same double-review and conflict resolution procedures were used during full-text review. Data extraction was conducted by a single reviewer per study, with 10% of manuscripts and extracted data set aside randomly for quality control checking by a second reviewer. The full

list of variables extracted is presented in Table S2; the manuscript details instrument and the data extraction protocol are presented in Supplementary File [Y](#).

The primary outcome was the diarrheal pathogen-specific CFR stratified by age group, country-specific under 5 mortality rate (U5MR), study setting, study year and rotavirus vaccination status (i.e. whether the study was conducted before or after rotavirus vaccine introduction).

Table 1. The inclusion and exclusion criteria used for study selection.

Criteria	Study population	Study design	Publication requirements	Outcomes
Inclusion	Humans of any age	Studies with primary data	Articles written in English, French, Spanish, Polish, and Portuguese languages Published between January 1, 1990 and July 9, 2019	CFR from diarrhea caused by any of the 15 pathogens of interest Information about the number of deaths was included and/or follow-up data was presented for all participants
Exclusion	Non-humans Studies within a specific population (e.g. HIV-positive individuals or malnourished children) Subjects were diarrheal but a pathogen of interest was not detected Diarrheal subjects died but a pathogen of interest was not detected Studies of invasive non-typhoidal <i>Salmonella</i> Studies that included fewer than 30 diarrheal patients (all pathogens)	Case-studies Modeling outputs Conference abstracts or poster presentations No mortality or follow-up data was presented	Articles written in other languages Published before 1990 or after July 9, 2019	Selection methods did not allow CFR calculation

2.2. Statistical analysis

For each study, and for strata within each study, we estimated the crude CFR by dividing the number of deaths by the total number of diarrhea cases. We then combined information across studies using fixed effects binomial-normal generalized linear models (GLMs) to estimate the CFR for each pathogen, and compared to the estimate derived from the crude CFR. We investigated heterogeneity among studies using the I^2 statistic [15]; potential publication bias was assessed using funnel plots and Egger's test [16].

To estimate the overall and relative risk of death while controlling for possible predictors as well as between- and within-study variation, we used multilevel mixed-effects logistic regression models. We estimated the CFR for each pathogen individually (Eq.1a) and for all studies together (Eq.1b):

$$\text{logit}(CFR_{p,i,j}) = \beta_0 + \beta_a(\text{age}_{i,j}) + \beta_u(U5MR_j) + \beta_s(\text{setting}_j) + \beta_v(\text{rotavac}_j) + \beta_c(\text{studyyear}_j) + \varepsilon_i + \zeta_j \quad (1a)$$

$$\text{logit}(CFR_{i,j}) = \beta_0 + \beta_p(\text{pathogen}_{i,j}) + \beta_a(\text{age}_{i,j}) + \beta_u(U5MR_j) + \beta_s(\text{setting}_j) + \beta_v(\text{rotavac}_j) + \beta_c(\text{studyyear}_j) + \varepsilon_i + \zeta_j \quad (1b)$$

The outcome variable was the logit-transformed proportion ($CFR_{p,i,j}$ and $CFR_{i,j}$ for the pathogen-specific and overall CFR, respectively) for strata-specific observation i from study j ; a continuity correction factor of 0.1 was added to all strata with 0 deaths. For the predictors, $\text{age}_{i,j}$ was the age group (<1 year, <5 years [reference], 5 years and above, other); setting_j was the study setting (community, hospital [reference], or other); $U5MR_j$ was the U5MR category of the country where

the study took place; *rotavac_j* was the rotavirus vaccine introduction status (pre-vaccination [reference] or post-vaccination); and *studyyear_j* was the year the study was conducted (median for multiyear studies; included as a continuous variable). If the study year was not available, we used the year the study was published. We also investigated how the CFR changed over time by categorizing the study year into four time periods: 1978-1989, 1990-1999, 2000-2009 and 2010-2019. In addition, we assessed variations in the CFR across bacterial, viral and parasitic pathogens and between hospital- and community-based studies. Finally, all models included both observation-level (ε_i) and study-level (ζ_j) random effects.

For the age strata, some studies reported aggregate data for all children <5 years old, whereas others did not; in order to avoid double-counting studies that reported sufficient detail to differentiate between the overlapping age categories (<1 year and <5 years), subjects aged less than 1 were classified as <1 year while those aged 1-4 years were classified as <5 years. U5MR strata were defined by classifying each country where a study was conducted into under-5 mortality quintiles based on the 2005 U5MR (which is the median start year across all studies). The quintiles were categorized as: very low (lowest quintile) [reference]; low (next two quintiles); and high (highest two quintiles). For rotavirus vaccine introduction status, all studies conducted before 2006 were classified as pre-vaccination. Following 2006, if the start year of the study was before or after the date of rotavirus vaccine introduction in the country where the study was carried out, we classified the study as pre-vaccination or post-vaccination, respectively.

Pathogen-specific analyses were limited to pathogens with >50 studies. For the overall model, we included an indicator variable for each pathogen as a predictor; we used salmonella as the reference

pathogen, since it was included in a large number of multi-pathogen studies and had a crude CFR similar to the average CFR for all pathogens. Only main effects without interactions among the predictors were considered.

The statistical analyses were conducted using the "metafor" package in R [17]. For the fixed effects models, we used the `rma.glmm` function; for the multilevel mixed-effects models, we used the `rma.mv` function with the restricted maximum-likelihood estimator. Model code is provided in the Supplementary Material [file1: page 4].

3. Results

3.1. Systematic review

A total of 7556 studies were identified based on the search strategy, of which 427 studies met the criteria and were included in the analysis. Fig. 1 shows the flow diagram of the study selection process. We identified more than twice as many studies for rotavirus ($n = 250$) compared to all other pathogens (Fig. S1); the fewest number of studies were identified for sapovirus ($n = 7$) and "other" pathogens ($n = 5$). There were a considerable number ($n=100$) of multi-pathogen studies included in the final analysis (Fig. S1). Studies from 111 countries were identified; the geographical distribution is presented in Fig. S2. There is a clear disparity in the study distribution, with 9% of studies conducted in India and approximately a third conducted in only seven countries (India ($n=44$), United States ($n=33$), Spain ($n=24$), Bangladesh ($n=19$), Turkey ($n=18$), France ($n=14$) and Kenya ($n=12$)).

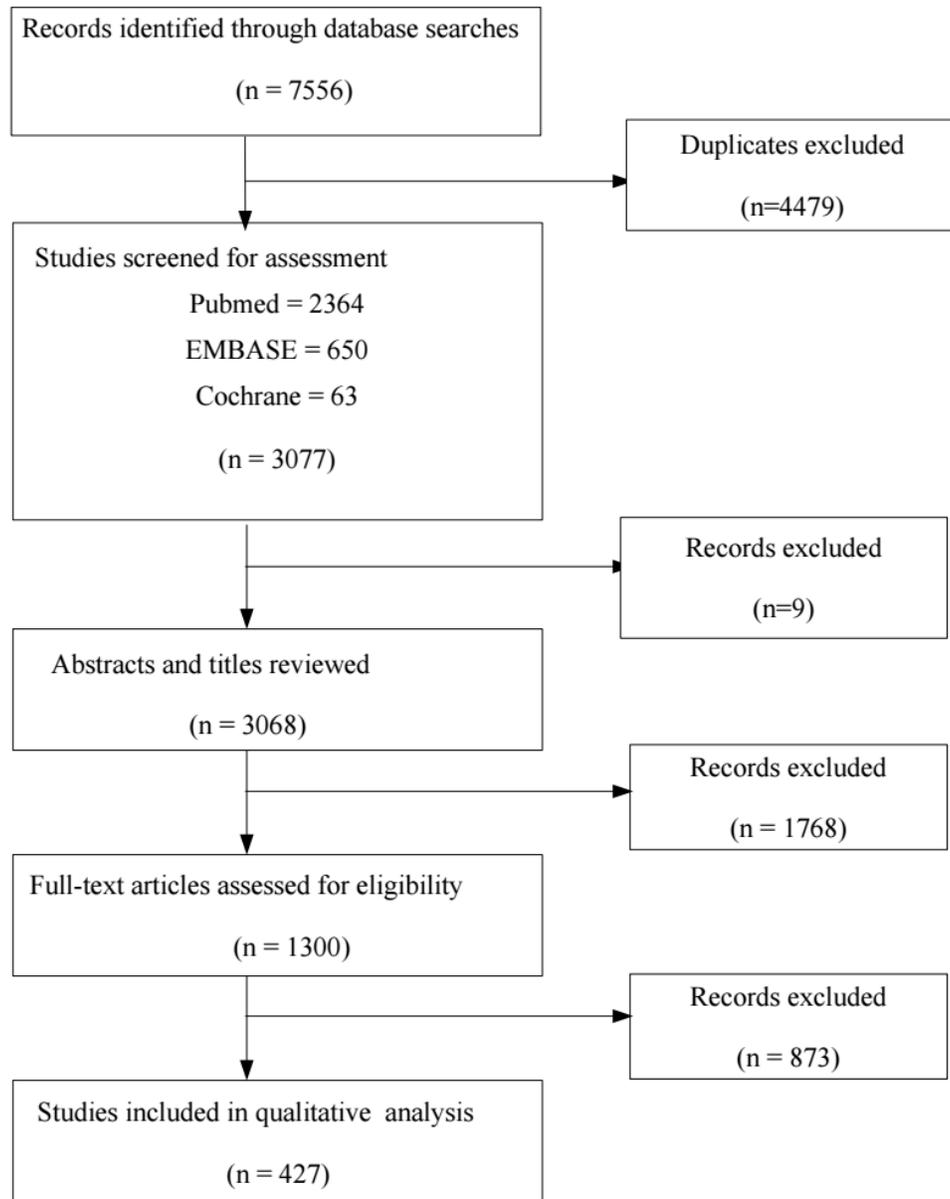


Fig.1. Flowchart of the study selection process.

The majority of studies ($n = 246$) did not provide sufficient detail to stratify cases and/or deaths by age (Fig. S3); of the remaining studies, most observations were for children <5 years ($n = 222$), followed by <1 year ($n = 115$), and 5 and above ($n = 76$). For the U5MR strata, most studies were

from countries in the very low mortality category (n = 169) followed by the high mortality category (n = 153) (Fig. S3). Most studies were hospital-based (n = 334), while we identified 23 studies with unknown setting (“other”). Studies conducted before and after the introduction of rotavirus vaccine accounted for 84% (n = 360) and 16% (n = 67), respectively.

3.2. Meta-analysis

The overall CFR for all diarrheal pathogens was 0.65% (95% confidence interval (CI), 0.65-0.66%) with an I^2 value of 99% indicating high heterogeneity across studies. The pathogen-specific CFR showed significant variation, ranging between 0% for *Giardia lamblia* (95% CI: 0-0.03%) and *Entamoeba histolytica* (95% CI: 0-1.32%) and 6.4% (95% CI: 5.46-7.41%) for EPEC, and I^2 values ranging from 0% to 100% (Fig. 2). Generally, the estimated CFRs for the bacterial pathogens were higher compared with those for both viral and parasitic pathogens (bacterial: 0.95% (95% CI: 0.94-0.96%); parasitic: 0.33% (95% CI: 0.28-0.39%) and viral: 0.11% (95% CI: 0.11-0.12%)). Summary estimates of the CFR and corresponding 95% CIs from the fixed effect models are shown in Fig. 2, while forest and funnel plots showing the study-specific CFRs for each pathogen are included in the Supplementary Material (see file2: Figs. S1-16). The funnel plots were asymmetrical for some pathogens and overall, indicating potential publication biases; the p-values obtained from the Egger's test were statistically significant for 9 out of the 15 pathogen-specific studies and overall (file2: Table S1).

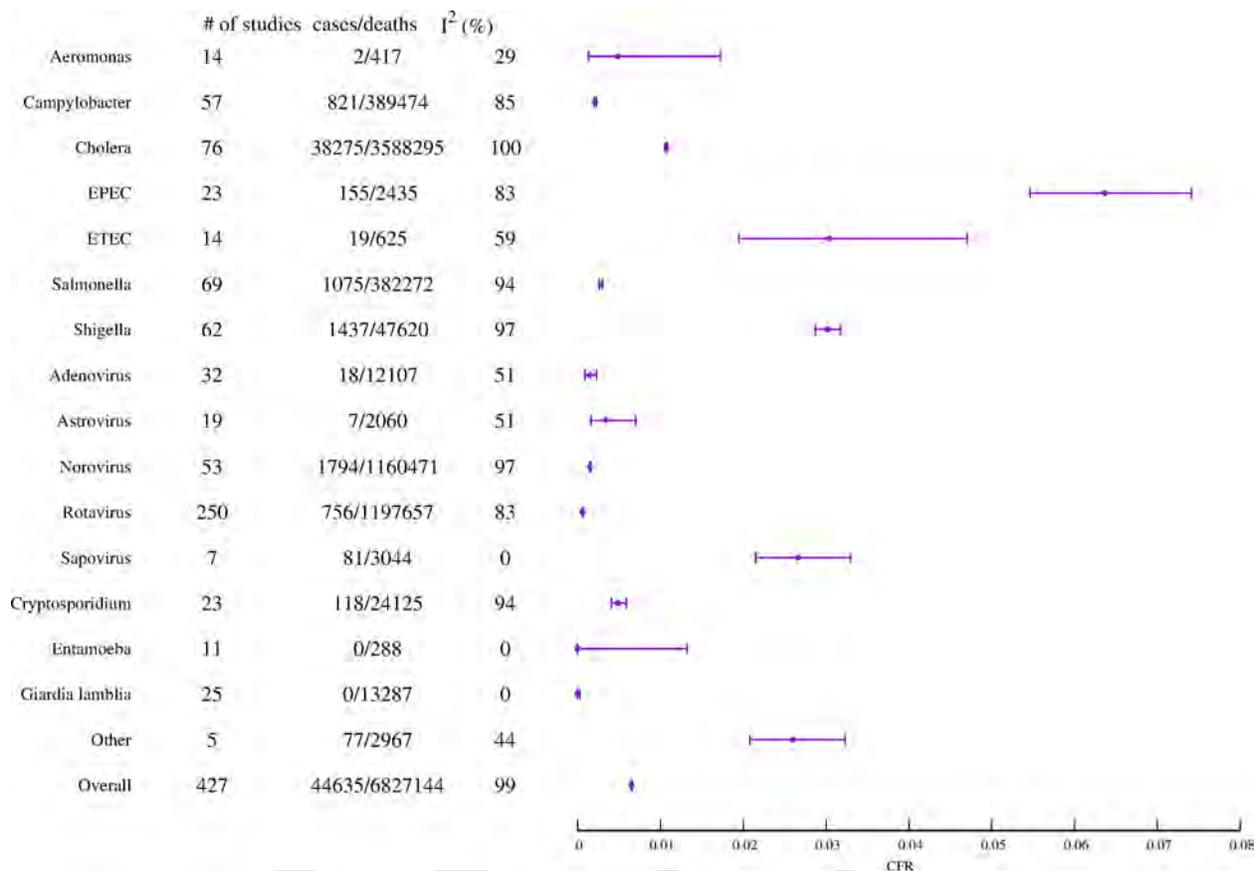


Fig. 2. Summary of CFR estimate for each pathogen and overall fixed effects models. The total number of studies, cases and deaths for each pathogen are indicated, along with the pathogen-specific and overall I^2 measure of heterogeneity.

Pathogen-specific fixed-effects models showed a high variability in the CFR across the different predictors for some of the important pathogens (Fig. 3). A higher CFR was estimated among infants <1 year of age for *Salmonella*, *Shigella* and ETEC, whereas a higher CFR for those aged ≥ 5 years was estimated for cholera; the CFR did not vary by age for norovirus, rotavirus and *Campylobacter* (Fig. 3A). The CFR was lowest in the very low U5MR strata and highest in the high U5MR strata for all pathogens except cholera and ETEC (Fig. 3B). There was no clear pattern in the estimated CFR for different study settings across the pathogens (Fig. 3C), although a slightly higher CFR was estimated for community-based studies for the viral pathogens (rotavirus and

norovirus) and for hospital-based studies for the bacterial pathogens (cholera, *Salmonella*, and ETEC). The estimated CFR was lower after rotavirus vaccine introduction for all pathogens except norovirus (Fig. 3D), although this mostly reflected a decline in the CFR over time rather than the specific impact of rotavirus vaccine introduction (Fig. S4). Results for pathogen-specific multilevel mixed-effects models (across the 6 pathogens with >50 studies) showed a similar influence for the various predictors (Table S3).

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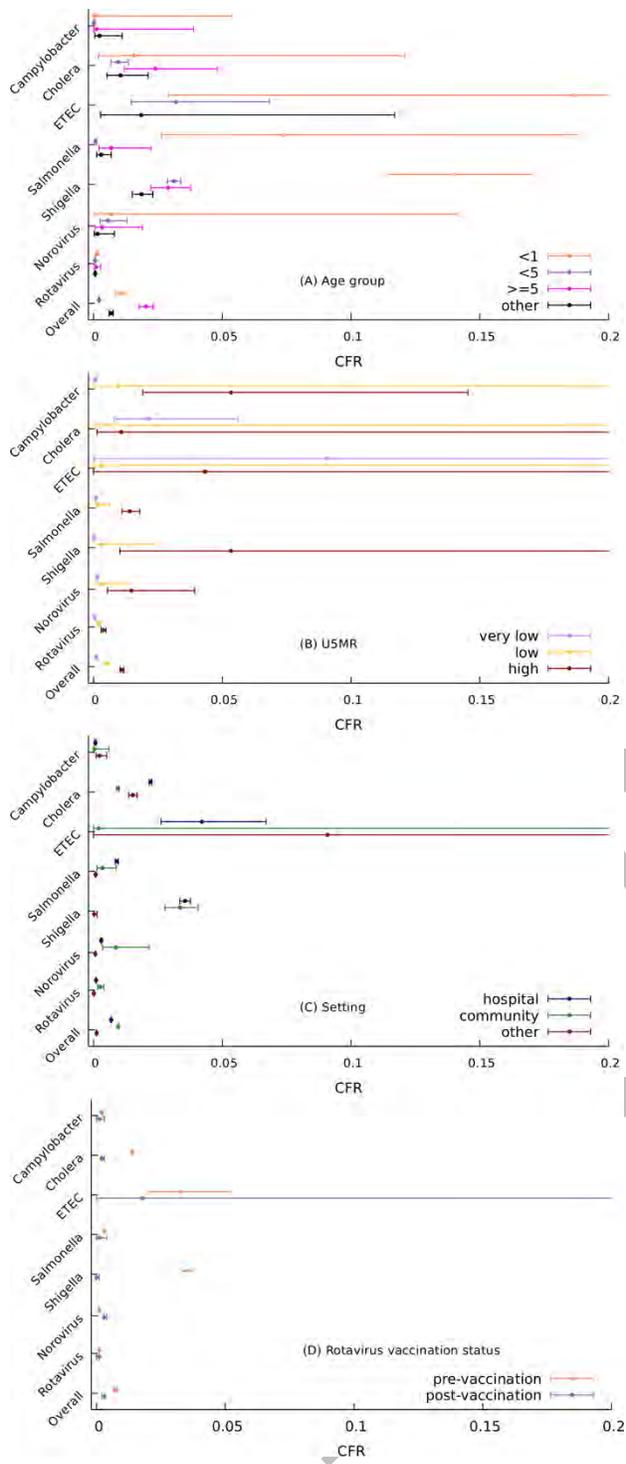


Fig. 3. Fixed-effect model estimates of CFR stratified by the predictors of interest overall and for seven important pathogens. The predictors include (A) age group, (B) country U5MR, (C) study setting, and (D) country rotavirus vaccine introduction status. The colors represent the strata within each predictor.

The results from the overall multilevel mixed-effects model incorporating all the predictors are shown in Fig. 4. Compared to *Salmonella* (reference pathogen), the CFR was estimated to be significantly higher for EPEC (OR = 2.91, 95% CI: 1.25-6.80) and significantly lower for rotavirus (OR = 0.23, 95% CI: 0.13-0.39) and *Campylobacter* (OR = 0.48, 95% CI: 0.24-0.98). The estimated CFR was slightly higher among infants <1 year of age (OR = 1.31, 95% CI: 0.83-2.08) and slightly lower among children and adults 5 years and older (OR = 1.20, 95% CI: 0.71-2.01), but the differences were not significant. Our model revealed a strong gradient across U5MR strata, with the estimated CFR for the low and high categories about two-fold (OR = 2.13, 95% CI: 1.23-3.68) and seven-fold (OR = 6.94, 95% CI: 4.20-11.47) higher, respectively, compared to the very low (reference) category. The estimated CFR from community-based and other studies was slightly lower than hospital-based studies (OR = 0.88, 95% CI: 0.53-1.46 and OR = 0.78, 95% CI: 0.37-1.63, respectively), but again the differences were not significant. The estimated CFR for studies carried out after rotavirus vaccine introduction was slightly lower than pre-vaccination (OR = 0.94, 95% CI: 0.52-1.68), but the difference was not significant when controlling for the decline in CFR associated with study year (OR = 0.97, 95% CI: 0.95-0.99). For the study decade, relative to 1978-1989 [reference], the odds ratio was 1.67 (95% CI: 0.173-1.040) for 1990-1999, 0.183 (95% CI: 0.078-0.431) for 2000-2009, and 0.291 (95% CI: 0.119-0.709) for 2010-2019.

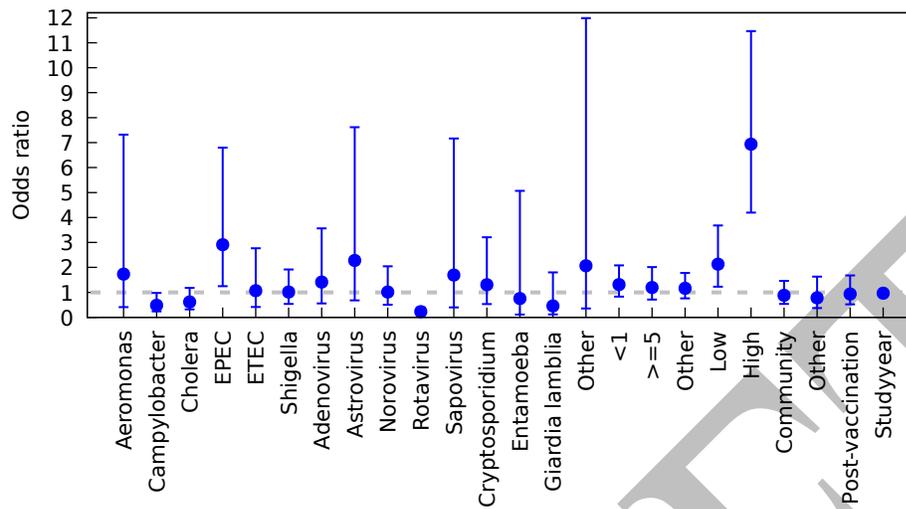


Fig. 4. Odds ratios for overall multilevel mixed-effects logistic regression model. The reference explanatory categorical variable was *Salmonella* (pathogen), under 5 (age group); very low (U5MR strata), hospital (setting) and pre-vaccination (rotavirus vaccine introduction status).

Discussion

Our analyses highlight the extent to which diarrhea-specific CFRs vary across pathogens, as well as by age group, country U5MR, study setting (community- or hospital-based), rotavirus vaccine introduction status, and study year. Overall, the CFR was <1%, but there were significant differences in the estimated CFR across pathogens and, in addition, considerable heterogeneity between studies that could not be fully explained by any of the predictors we examined. The pathogen-specific and overall models showed differences in the strength and direction of associations between CFRs and the explanatory variables used in the regression analyses.

Our results should be interpreted with caution when attempting to rank diarrheal pathogens by the estimated CFR due to disparities in the number of studies for each pathogen (ranging from 5 to

250) and the potential for publication bias. For example, although the highest CFR was estimated for EPEC, there was significant heterogeneity ($I^2 = 83\%$) among the 23 studies that contributed to this estimate. Most studies with non-zero deaths were conducted in higher mortality settings (e.g. for EPEC, two and three out of the five studies with non-zero deaths were conducted within low and high U5MR settings, respectively) or conducted only among children <5 years of age (e.g. for EPEC, four out of the five studies with non-zero deaths were conducted among children <5 years of age). Studies conducted in these settings are usually associated with higher CFRs [6,18,19]. Second, pathogens represented by a smaller number of studies may be at higher risk of publication bias (i.e. studies reporting a higher number of deaths may be more likely to be published), such that the high overall estimated CFR may be due to a few isolated studies with high CFR (e.g. EPEC had five studies with non-zero deaths out of the 23 studies). Nevertheless, for multi-pathogen studies involving EPEC and other diarrheal pathogens with a non-zero CFR, the estimated CFR for EPEC was either first or second highest [20-22]. Pathogens with low estimated CFRs also had fewer studies, e.g. *Giardia lamblia* (25) and *Entamoeba histolytica* (11). However, most of these studies were conducted in very low U5MR countries (*Giardia lamblia*: 69% and *Entamoeba histolytica*: 38%) and were not limited to children <5 years old (e.g. 88% of *Giardia lamblia* and 69% of *Entamoeba histolytica* observations were for the “other” age category, which typically included individuals of all ages or only adults). More studies are required for pathogens such as EPEC, ETEC and sapovirus, for which a limited number of studies suggest a higher CFR, to better quantify their relative contribution to overall diarrhea deaths.

The estimated CFR for rotavirus was significantly lower than that of other diarrheal pathogens (OR=0.23, $p<0.0001$ compared to *Salmonella*). This may in part be driven by the large number of

studies for rotavirus, including many from countries with a very low U5MR (46%), and a low risk of publication bias. It may also be because rotavirus diarrhea can be effectively treated through oral rehydration salts (ORS) [23,24], as indicated by the lower CFR among hospital-based studies compared to community-based studies for rotavirus. Furthermore, a reduction in the severity of rotavirus infections following the introduction of rotavirus vaccination in many countries may have contributed to the overall decline in rotavirus mortality among children [25-27].

The widely available predictors we examined could explain some but not all of the variability in the estimated CFR across pathogens. The CFR was consistently higher in studies conducted in high U5MR countries, which could indicate poorer access to health care in these settings. The CFR was slightly higher for hospital-based studies relative to community-based studies overall. However, the CFR was higher in community-based studies for viral pathogens (rotavirus and norovirus), which may reflect their acute presentation, such that most deaths occur among individuals whose access to healthcare is limited or delayed. The overall CFR also tended to be slightly higher among infants <1 year old. This is consistent with a previous systematic review [28], and may result from infants having a less fully developed immune system or being more prone to dehydration. In contrast, the results for cholera showed a slightly higher CFR among those aged 5 and above. Most of these studies were conducted in cholera-endemic settings [29-31], indicating that cholera mortality occurs among older age groups in endemic regions. A similar high CFR has been found among adults older than 60 years for *Shigella* [6] and all-cause diarrhea [32].

Our results indicate that the CFR from diarrhea has decreased over time. This may be partly due to improvements in water, sanitation and hygiene (WASH) infrastructure and socioeconomic development (leading to reductions in childhood malnutrition) over time causing a reduction in the severity of diarrheal episodes [33-35]. In addition, improvements in healthcare quality and access over time could have contributed to reductions in the CFR [36]. Further reductions in the CFR of diarrhea overall and for non-rotavirus pathogens also occurred following the introduction of rotavirus vaccination, suggesting that preventing rotavirus gastroenteritis may have added benefits of decreasing vulnerability to severe disease caused by other diarrheal pathogens, although most reductions were not significant. However, our estimates of the impact of rotavirus vaccine introduction may be biased due to misclassification. We assumed all studies carried out after rotavirus vaccine introduction in the country were post-rotavirus vaccination; however, some of these studies may have been carried out within an unvaccinated population (e.g. older age groups).

Model-based estimates of mortality caused by different diarrheal pathogens assume that deaths caused by each pathogen are proportional to the distribution of pathogens among severe and/or hospitalized cases [3-7]. Thus, the models implicitly assume that the CFR is the same for all diarrheal pathogens after accounting for severity leading to hospitalization. Nevertheless, our analysis suggests that there may be additional variability in the CFR for different diarrheal pathogens. Accounting for differences in the risk of death among severe cases may help to improve estimates of global mortality caused by different pathogens.

5. Conclusions

To our knowledge, this is the first global study to estimate the CFR across multiple diarrheal pathogens. Our estimated overall CFR of 0.65% is substantial, suggesting the need to scale up and

sustain the ongoing control strategies. In addition, our results highlight the existence of marked heterogeneity in the estimated CFR both within and between studies and across pathogens. Our results not only provide an updated and comprehensive estimate of the CFR across different diarrheal pathogens, but also highlight pathogens for which more studies are needed, particularly those with fewer studies and a higher CFR. Developing vaccines for important diarrheal pathogens will help to reduce overall diarrhea burden and may have benefits that extend beyond pathogen-specific reductions in mortality. Our results could help prioritize vaccine development and pathogen-specific interventions across diarrheal pathogens.

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Table S1. Acceptable detection methods and strains for each pathogen.

Pathogen	Acceptable detection methods	Strains measured
<i>Aeromonas spp</i>	Identification with enzyme immune assay (EIA) (including enzyme-linked immunoassay ELISA), or electronic microscopy, or PCR	All
<i>Campylobacter spp.</i> or Campylobacter enteritis	Isolation by use of transport media with antibiotics (Skirrow's supplement or similar) and inoculation into 5% sheep blood with antibiotics (Butzlers supplement or similar), cultivated at 42C in micro-aerobic atmosphere, or PCR	All
<i>Vibrio cholerae</i> or cholera	Isolation by alkaline peptone water enrichment and subculture at 8 hrs into thiosulfate-citrate-bile salts -sucrose agar (TCBS), or PCR	O1, O139
Enterotoxigenic <i>Escherichia coli</i> (ETEC)	Isolation from MacConkey agar and identification of ETEC by DNA probes or polymerase chain reaction (PCR) for heat-labile (LT) or heat stable (ST) toxins, cell cultures (Y1, CHO cells), ileal loop or mouse models	LT-ETEC, ST-ETEC
Enteropathogenic <i>Escherichia coli</i> (EPEC) or typical enteropathogenic <i>Escherichia coli</i> (tEPEC)	Isolation by the use of Hep 2 cell cultures or the presence of the plasmid for adherence (BFP) and the intimin gene (eae) identify in DNA probes or by PCR	All
<i>Salmonella (enterica) spp.</i> or salmonellosis	Isolation in salmonella agar, xylose-lysine-deoxycholate agar, Hektoen enteric agar, selenite enrichment for salmonella, or PCR	All Salmonella (enterica) spp. except <i>Salmonella typhi</i>
<i>Shigella spp.</i> or shigellosis	Isolation in shigella agar, xylose-lysine-deoxycholate agar, and Hektoen enteric agar, or PCR	All
Adenovirus (enteric)	Identification with enzyme immune assay (EIA) (including enzyme-linked immunoassay ELISA), or electronic microscopy, or PCR	40, 41
Astrovirus	Identification with enzyme immune assay (EIA) (including enzyme-linked immunoassay ELISA), or electronic microscopy, or PCR	All
Calicivirus (Norovirus)	Identification with enzyme immune assay (EIA) (including enzyme-linked immunoassay ELISA), or electronic microscopy, or PCR	Group I, Group II
Calicivirus (Sapovirus)	Identification with enzyme immune assay (EIA) (including enzyme-linked immunoassay ELISA), or electronic microscopy, or PCR	All
Rotavirus or rotavirus gastroenteritis (RVGE)	Identification with enzyme-linked immunoassay (ELISA) or enzyme immune assay (EIA), electronic microscopy, or PCR	All
<i>Cryptosporidium spp.</i>	Identification by EIA/ELISA, or the modified Ziehl-Neelsen stain for microscopy, or PCR	All
<i>Entamoeba histolytica</i> (amoebiasis)	Identification by direct microscopic examination, or PCR	All
<i>Giardia lamblia</i>	Identification by direct microscopic examination, or zinc-sulfate concentration from direct stools or by EIA/ELISA, or PCR	All

Table S2. Full list of extracted variables and brief description.

Variable	Description	Variable	Description
covidence_num	Covidence Number (ID)	adeno_detect	Adenovirus Detection Method
author	First Author	giar_strain	Giardia Strain
year_pub	Year Published	giar_detect	Giardia Detection Method
title	Title	crypto_strain	Cryptosporidium Strain
country	Country	crypto_detect	Cryptosporidium Detection Method
region	Region	enta_strain	Entamoeba Strain
month_began	Month Study Period Began	enta_detect	Entamoeba Detection Method
year_began	Year Study Period Began	aero_strain	Aeromonas Strain
month_ended	Month Study Period Ended	aero_detect	Aeromonas Detection Method
year_ended	Year Study Period Ended	path_other	Other pathogens
design	Study Design	lab_qc	Were standardized or validated laboratory methods mentioned and used?
design_other	Specify study design	setting	Study Presentation (setting)
age_min	Age minimum of all study subjects	fac_num_hosp	Number hospitalized
age_max	Age Maximum of all study subjects	fac_num_outp	Number of outpatients
spec_death	Did the study specifically mention screening for death?	age_min_strata	Age Band Min (in years)
diarr_def	Case definition for diarrhea	age_max_strata	Age Band Max (in years)
diarr_def_other	If other please specify	rotavirus_vacc	Country Rotavirus Vaccination Status
sampling	Were either all cases or a representative sample of cases included in study?	severity_scale	Severity Scale
valid_tx	Did study describe diarrhea presentation and/or treatment?	severity_est	Point Estimate
valid_detection	Did the study describe a laboratory method for pathogen detection?	severity_cilow	Lower bound
valid_score	Validation Score (calculation)	severity_cihigh	Upper bound
gems_or_maled	Is this a GEMS or MAL-ED Study?	severity_unit	Severity Measure Metric
comment_1	Comments	severity_qual	Qualitative severity description
note1	Criteria for Stratification	qual_scale_ref	To what is the qualitative description referring?
data_year_start	Year Data Collection Started	hiv	HIV status of study participants
data_year_end	Year Data Collection Ended	treat	Was treatment given?
pathogen	Pathogen detected	perc_treat	Percentage of Patients Treated
salm_strain	Salmonella Strain	treat_type	Treatment type
salm_detect	Salmonella Detection Method	treat_type_exp	Specify experimental treatment:
shig_strain	Shigella Strain	other_tx_type	Specify other treatment type:
shig_detect	Shigella Detection Method	presentation	Presentation of Diarrhea
campy_strain	Campylobacter Strain	presentation_spec	If other, please specify
campy_detect	Campylobacter DetectionMethod	note2	End Stratification Criteria
chol_strain	Cholera Strain	cases	Total number of cases
chol_detect	Cholera Detection Method	deaths	Total number of deaths
etec_strain	ETEC Strain	all_diarr	Were all deaths attributed to diarrhea?
etec_detect	ETEC Detection Method	deaths_nondiarrhea	Number of deaths not attributed to diarrhea
epec_strain	EPEC Strain	cfr	CFR (if provided)
epec_detect	EPEC Detection Method	q_rt_per	Was qPCR or rtPCR used? If so, please record the values here.
rota_strain	Rotavirus Strain	fu_time_min	Minimum follow-up time
rota_detect	Rotavirus Detection Method	fu_time_max	Maximum follow-up time
noro_strain	Norovirus Strain	fu_units	Units of follow-up time
noro_detect	Norovirus Detection Method	duration_time	Duration onset to death
sapo_detect	Sapovirus Detection Method	duration_units	Units
astro_strain	Astrovirus Strain	sample_time_max	Maximum time of sample taken
astro_detect	Astrovirus Detection Method	sample_units	Units of sample time
adeno_strain	Adenovirus Strain	comment	Special notes/comments

Search strategy used in PubMed, EMBASE and Cochrane databases.

The search string used in PubMed was:

(death*[tiab] OR CFR[tiab] OR fatalit*[tiab] OR hospitalization[tiab] OR hospitalisation[tiab])

AND

(aeromonas[tiab] OR entamoeba[tiab] OR cryptosporidium[tiab] OR giardia lamblia[tiab] OR adenovir*[tiab] OR astrovir*[tiab] OR sapovirus[tiab] OR norovirus[tiab] OR rotavirus[tiab] OR escherichia coli[tiab] OR etec[tiab] OR epec[tiab] OR E. coli[tiab] OR cholera*[tiab] OR campylobacter[tiab] OR shigell*[tiab] OR salmonell*[tiab])

AND

(diarrh*[tiab] OR gastroenteritis[tiab] OR enteric infection[tiab])

AND

1990:3000[pdat] NOT

(animals[mh] NOT humans[mh])

The search string used in EMBASE was:

(death:ti,ab OR CFR:ti,ab OR fatalit*:ti,ab OR hospitalization:ti,ab OR hospitalisation:ti,ab) AND
(aeromonas:ti,ab OR entamoeba:ti,ab OR cryptosporidium:ti,ab OR 'giardia lamblia':ti,ab OR
adenovir*:ti,ab OR astrovir*:ti,ab OR sapovirus:ti,ab OR norovirus:ti,ab OR rotavirus:ti,ab OR
'escherichia coli':ti,ab OR etec:ti,ab OR epec:ti,ab OR 'E. coli':ti,ab OR cholera*:ti,ab OR
campylobacter:ti,ab OR shigell*:ti,ab OR salmonell*:ti,ab)

AND

(diarrh*:ti,ab OR gastroenteritis:ti,ab OR 'enteric infection':ti,ab)

AND [1990-3000]/py

NOT

('animal'/exp NOT 'human'/exp)

The search string used in Cochrane was:

ID Search

#1 death OR fatalit* OR CFR OR hospitalization OR hospitalisation

#2 aeromonas OR entamoeba OR cryptosporidium OR giardia lamblia OR adenovir* OR
astrovir* OR sapovirus OR norovirus OR rotavirus OR escherichia coli OR etec OR epec
OR E. coli OR cholera* OR campylobacter OR shigell* OR salmonell*

#3 diarrh* OR gastroenteritis OR 'enteric infection'

#4 #1 and #2 and #3

Model code

Overall model

```
library(metafor)
```

```
#read data
```

```
complete_data <- read.table("complete_data_for_overall_model.txt", header = TRUE, sep = "", dec = ".")
```

```
dat <- escalc(measure="PLO", xi=Deaths, ni=Cases, data=complete_data, method="REML")
```

```
overall_model <- rma.mv(yi, vi, mods = ~relevel(factor(pathogen), ref="Salmonella") + relevel(factor(Age),  
ref="under5")+relevel(factor(U5MR), ref="verylow") + relevel(factor(Setting), ref="hospital") +  
relevel(factor(vacc_status), ref="prevacc") + studyyear, random = list(~ 1 | effectsizeID, ~1 | studyID), tdist=TRUE,  
data=dat, method="REML")
```

```
summary(overall_model, digits=4)
```

```
#pathogen-specific model
```

```
pathogen_data <- read.table("Rotavirus_final_data.txt", header = TRUE, sep = "", dec = ".")
```

```
pdat <- escalc(measure="PLO", xi=Deaths, ni=Cases, data=pathogen_data, method="REML")
```

```
pathogen_model <- rma.mv(yi, vi, mods = ~relevel(factor(Age), ref="under5") + relevel(factor(U5MR),  
ref="verylow") + relevel(factor(Setting), ref="hospital") + relevel(factor(vacc_status), ref="prevacc") + studyyear,  
random = list(~ 1 | effectsizeID, ~1 | studyID), tdist=TRUE, data=pdat, method="REML")
```

```
summary(pathogen_model, digits=4)
```

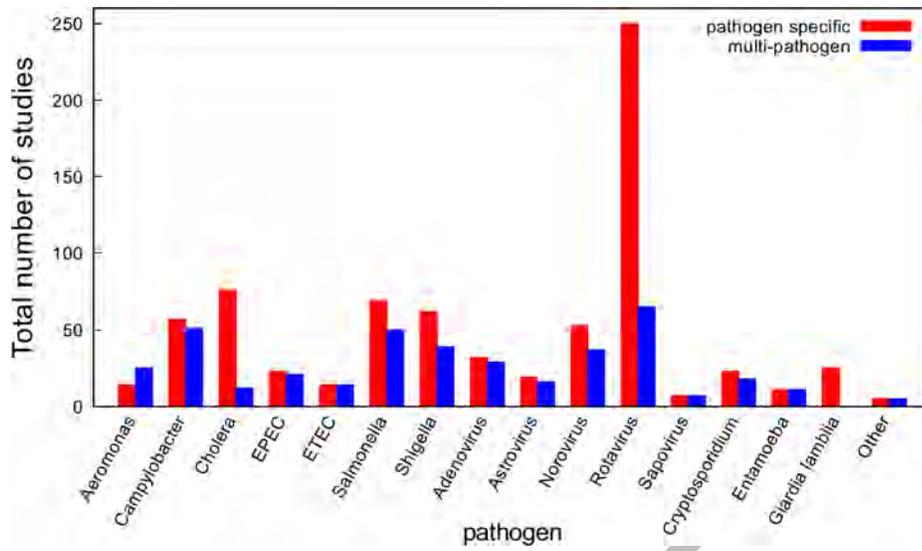


Fig. S1. Comparison of total number of studies included in the study for each pathogen. Red and blue represents the number of pathogen-specific and multi-pathogen studies, respectively.

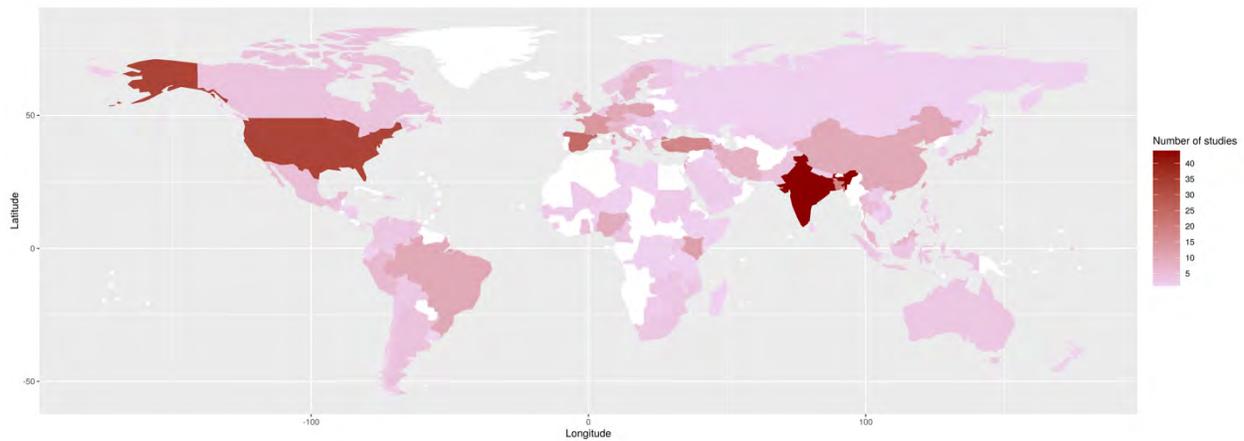


Fig. S2. Geographical distribution of the included studies.

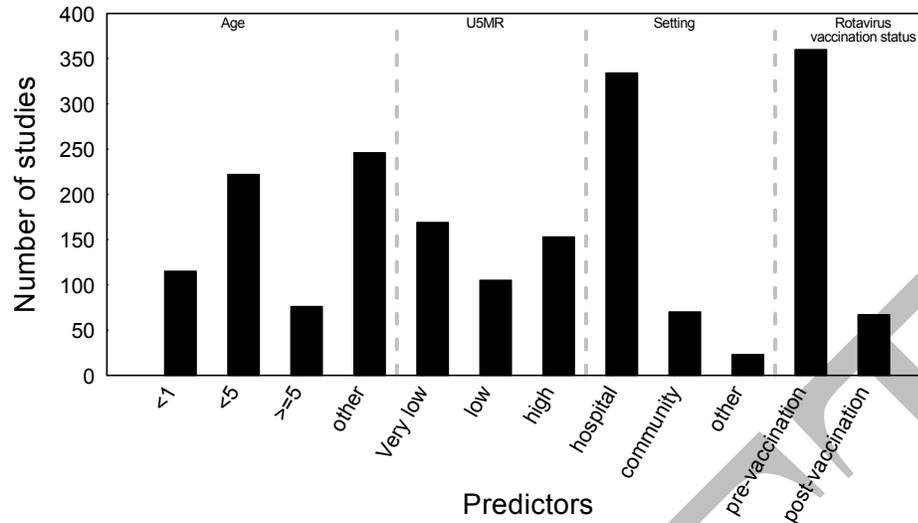


Fig. S3. Comparison of the number of studies for each predictor category used in the model.

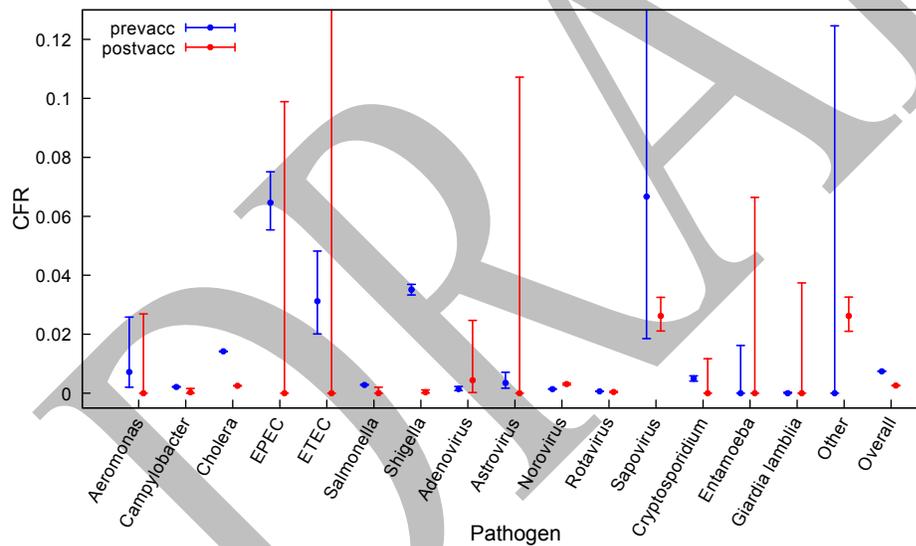
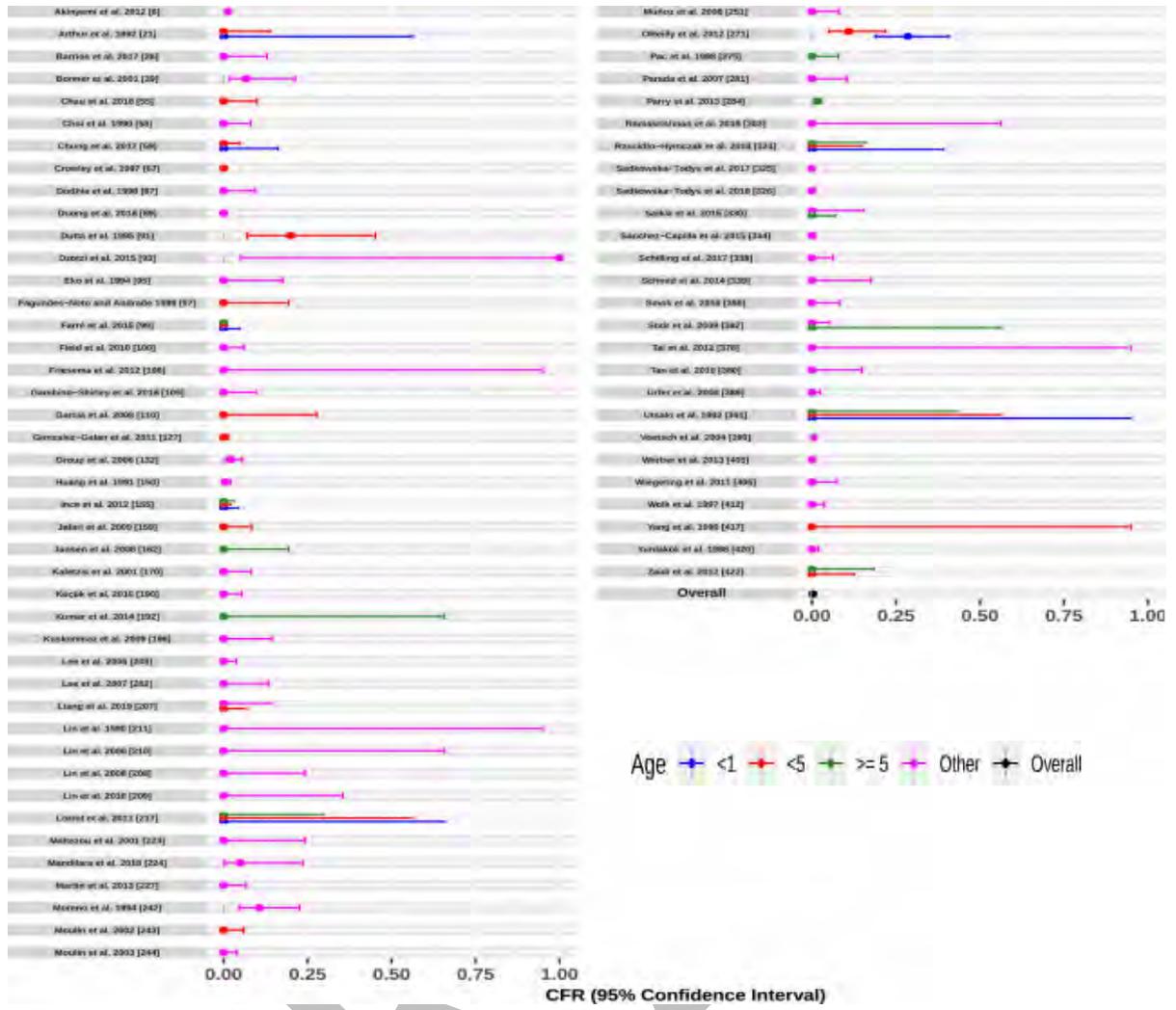


Fig. S4. Comparison of pathogen-specific CFR for studies carried out before (blue) and after (red) rotavirus vaccination.

The figures below are the results of pathogen-specific forest plot stratified by age (Fig. S1A - S16A) and funnel plots (Fig. S1B - Fig.S16B). The references of the included studies are listed. The results from the Egger's test are summarized in Table S1 below.

DRAFT

(A)



(B)

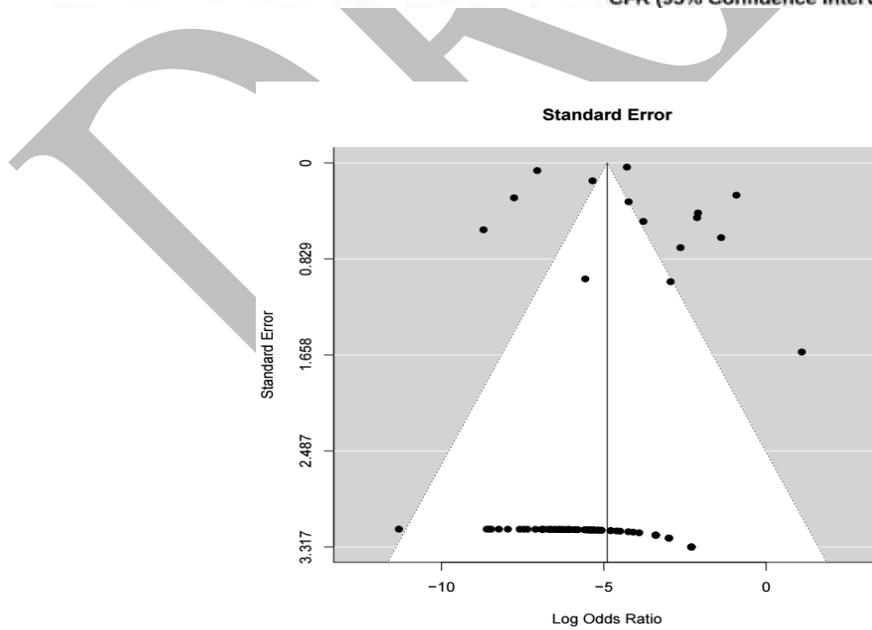
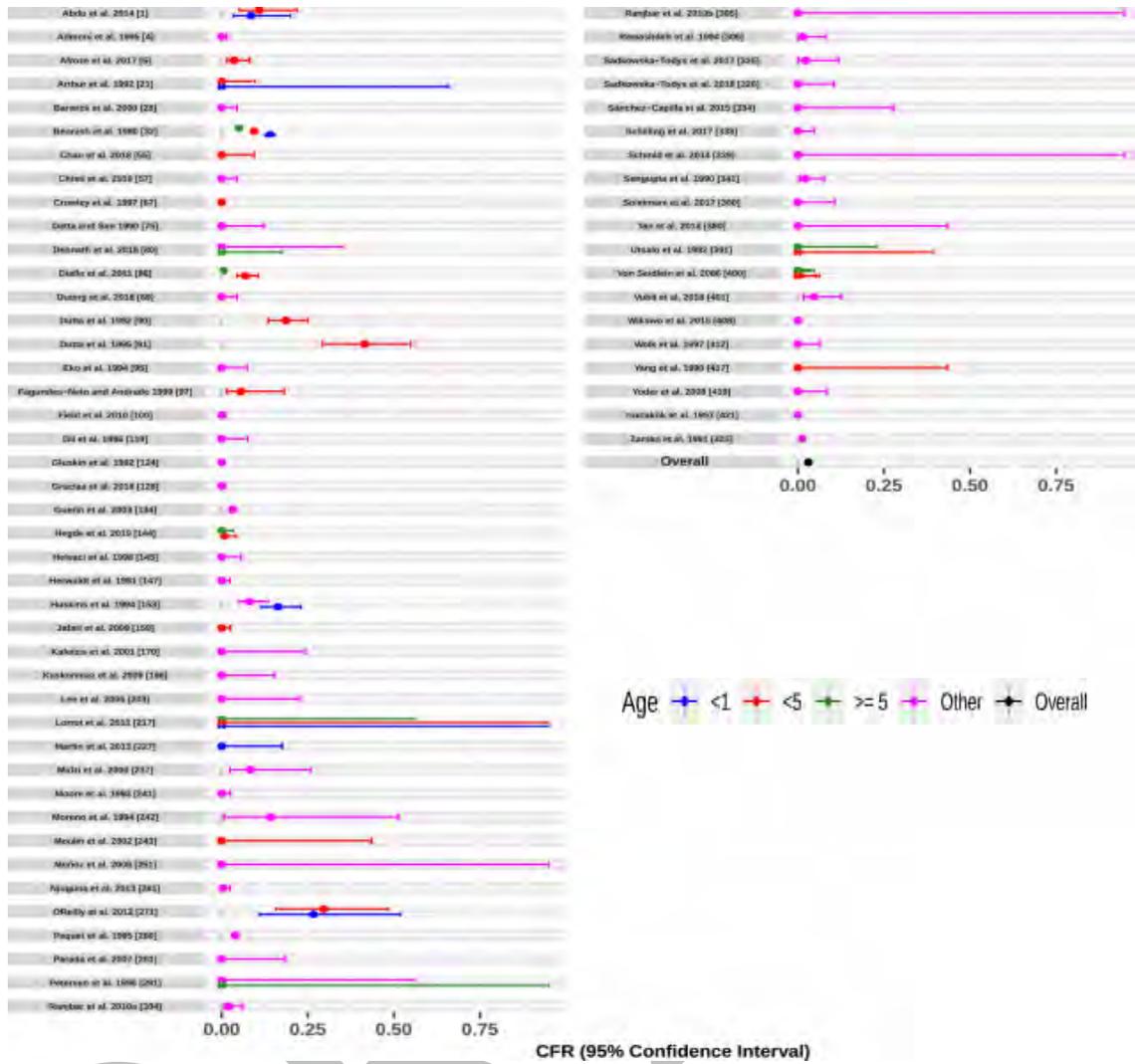


Fig. 1. Salmonella

(A)



(B)

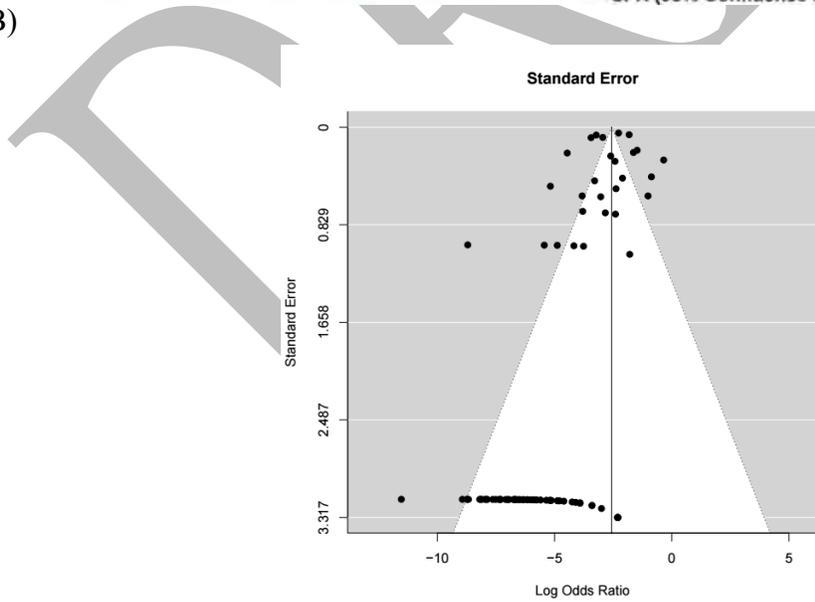
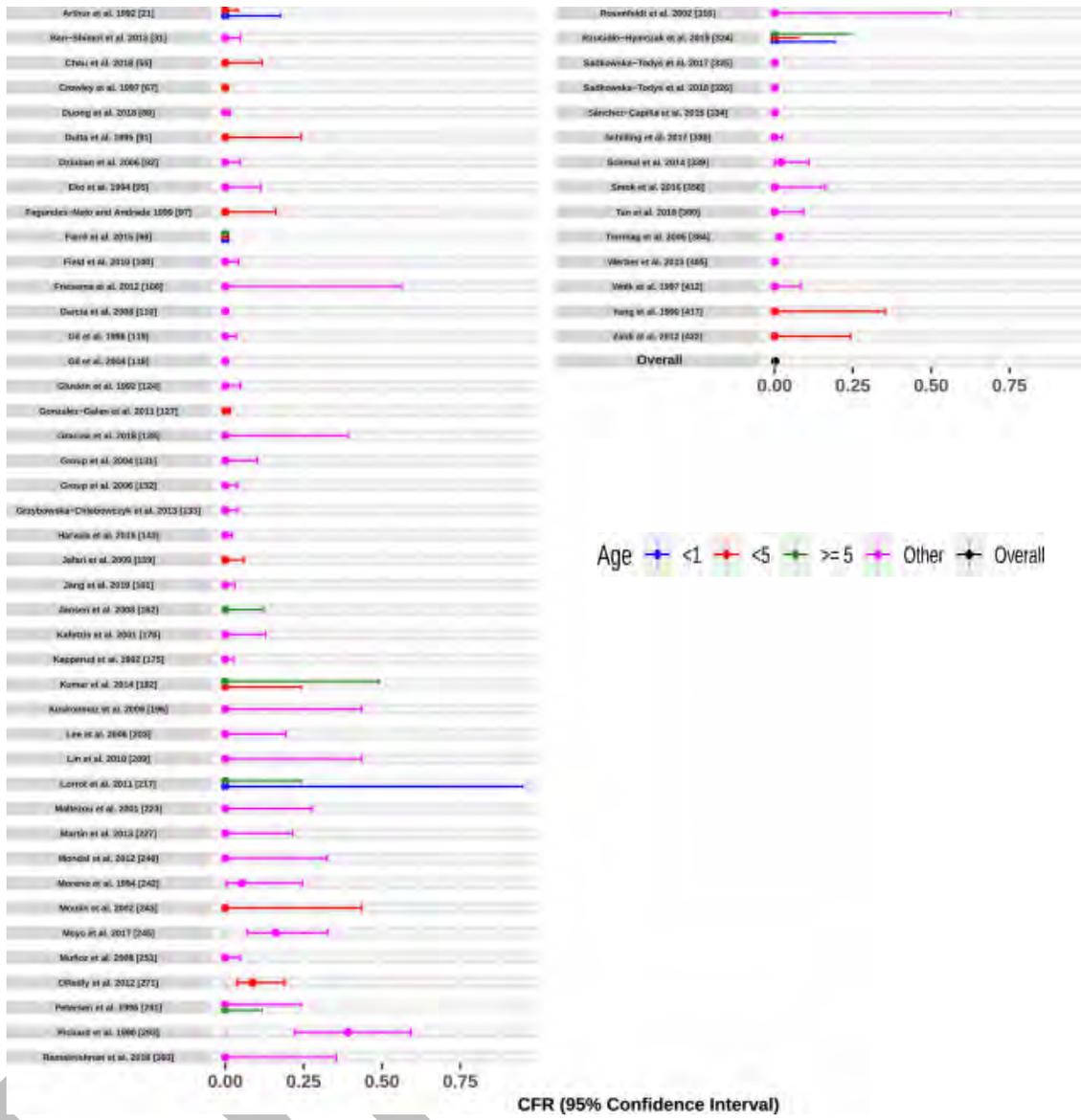


Fig. 2. Shigella

(A)



(B)

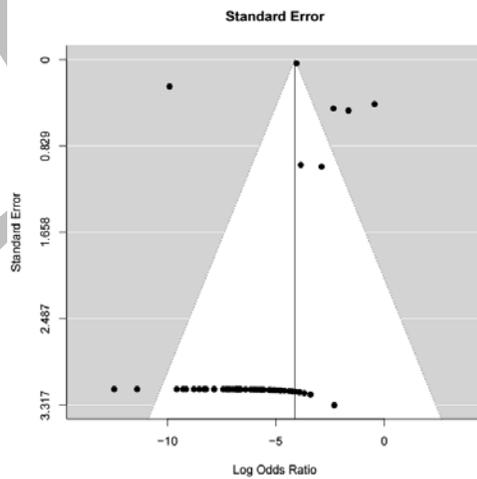
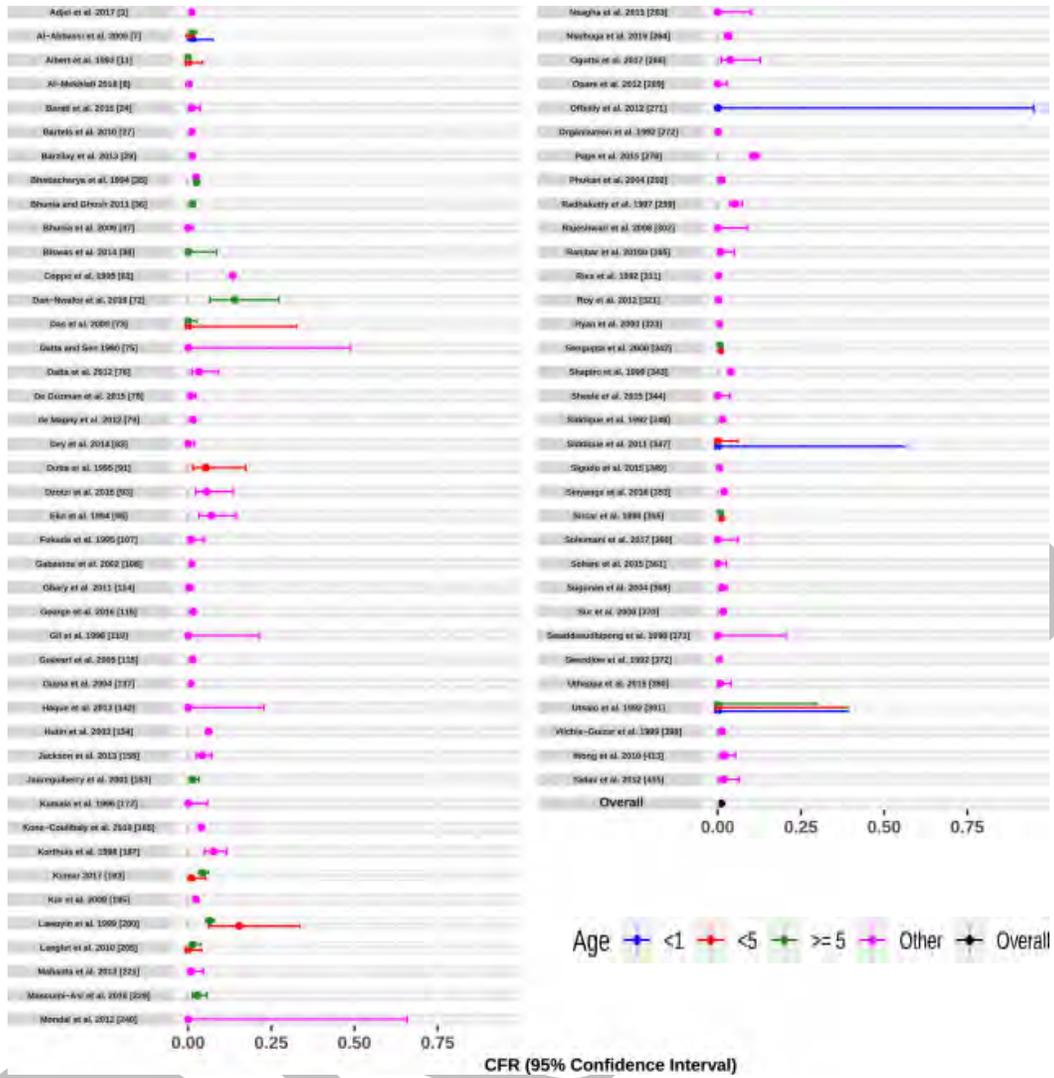


Fig. 3. Campylobacter

(A)



(B)

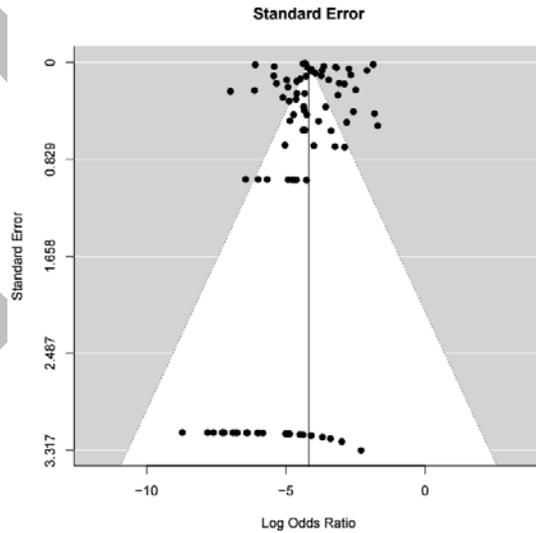
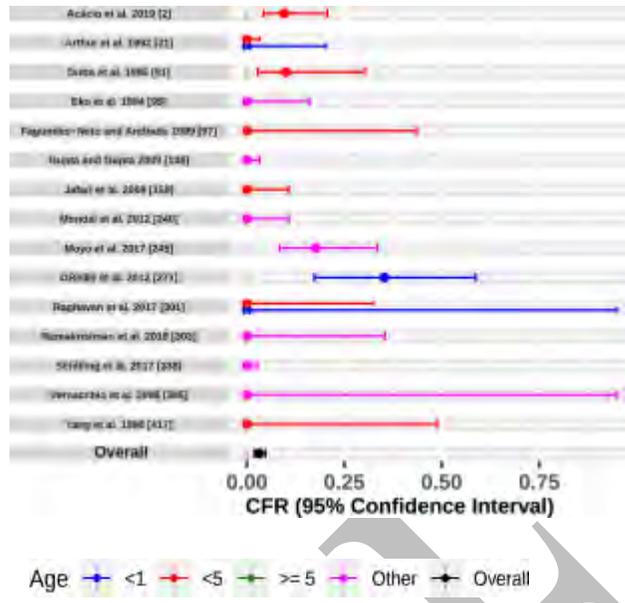


Fig. 4. Cholera

(A)



(B)

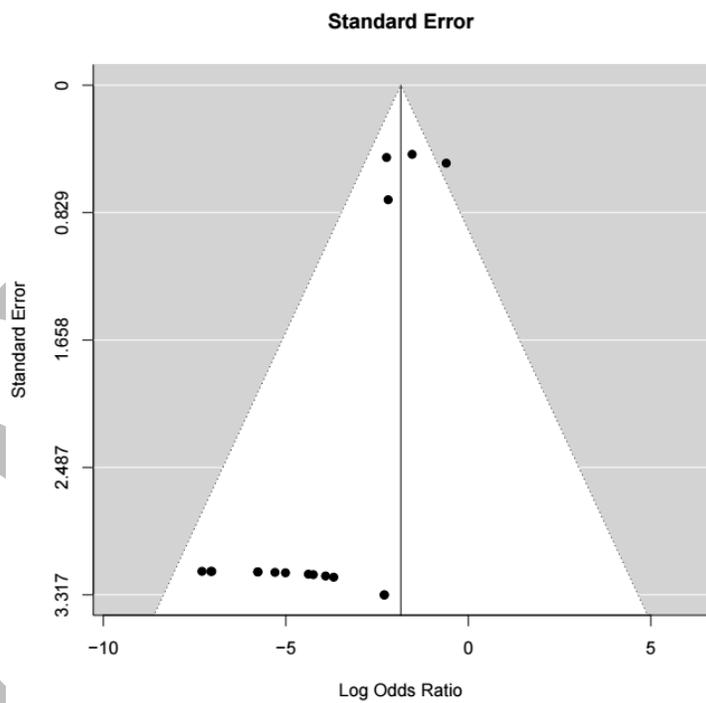
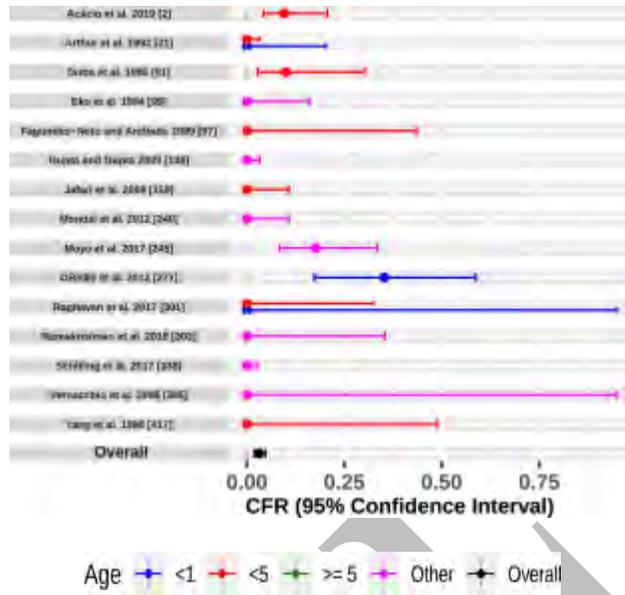


Fig. 5. ETEC

(A)



(B)

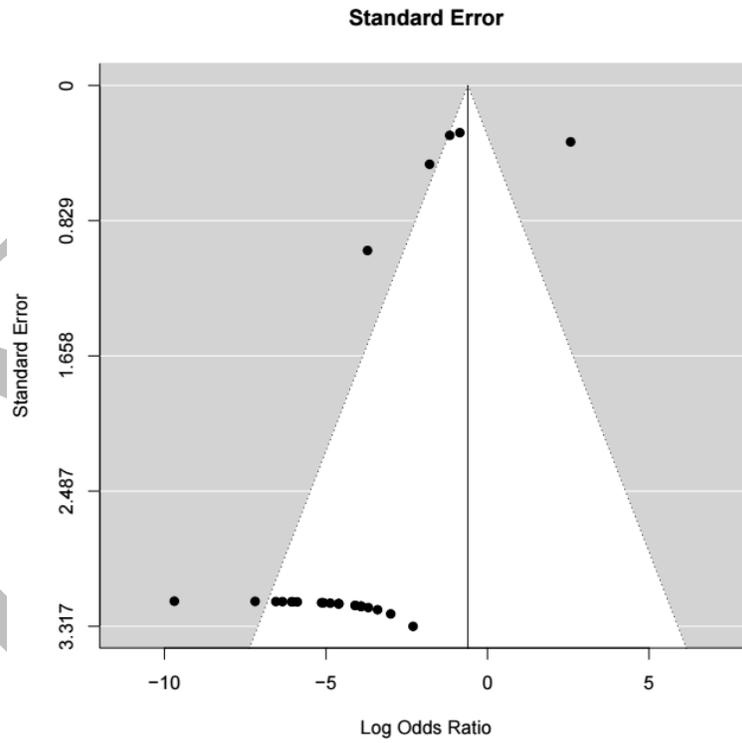
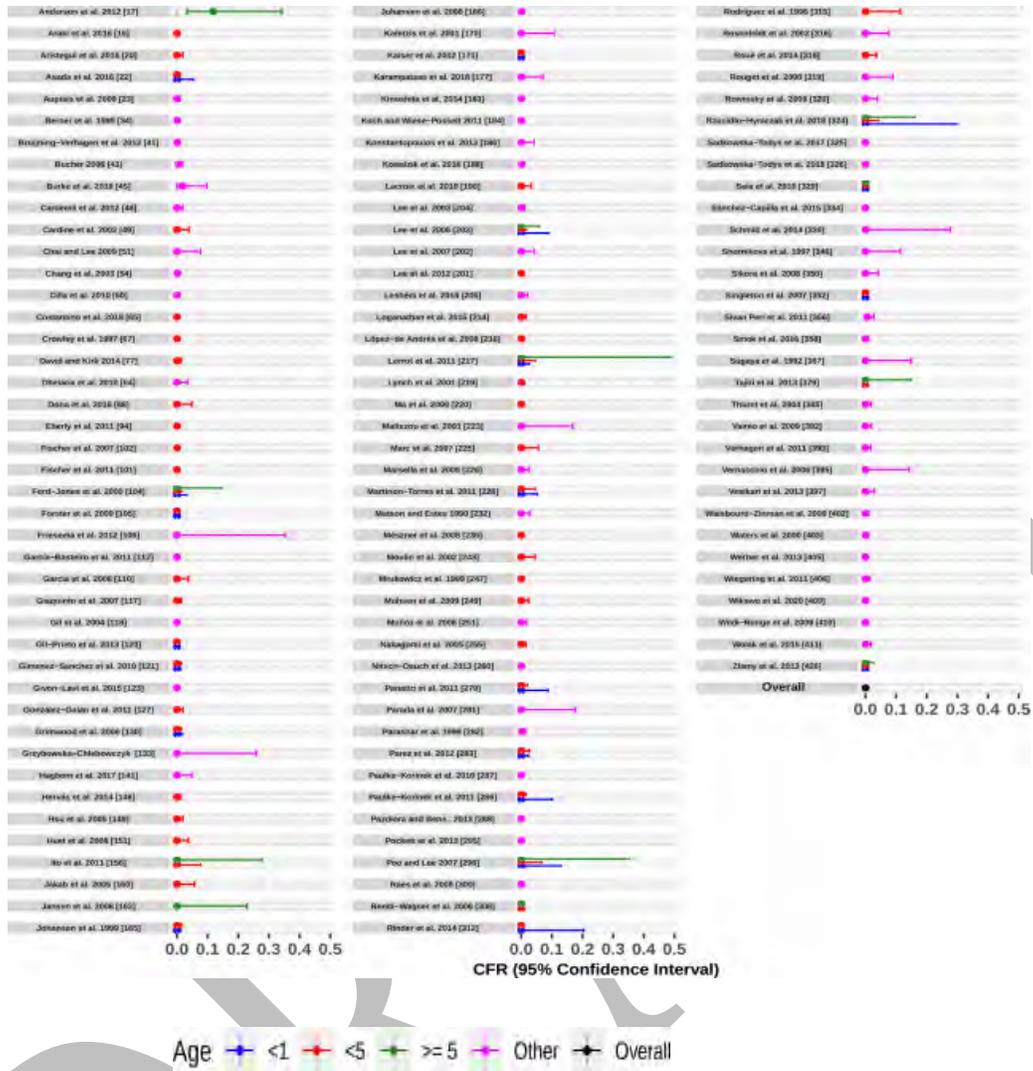


Fig. 6. EPEC

(A)



(B)

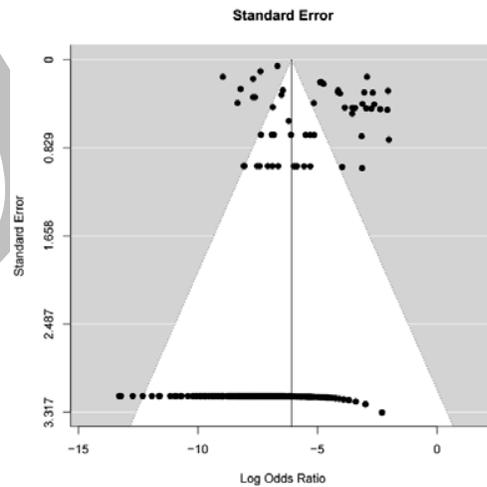


Fig. 7a. Rotavirus (U5MR – very low)

(A)



(B)

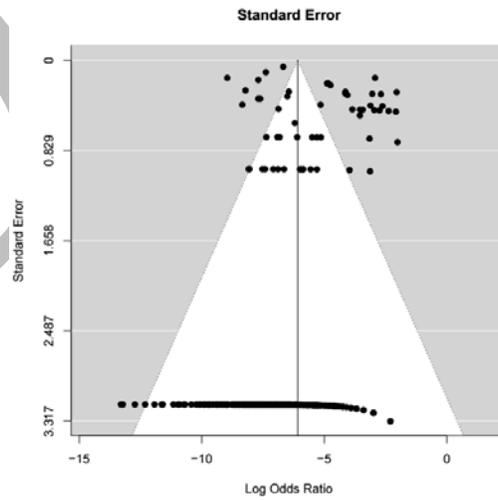


Fig. 7b. Rotavirus (U5MR – low)

(A)



(B)

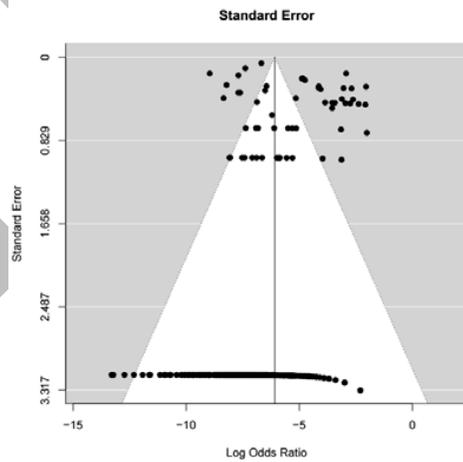
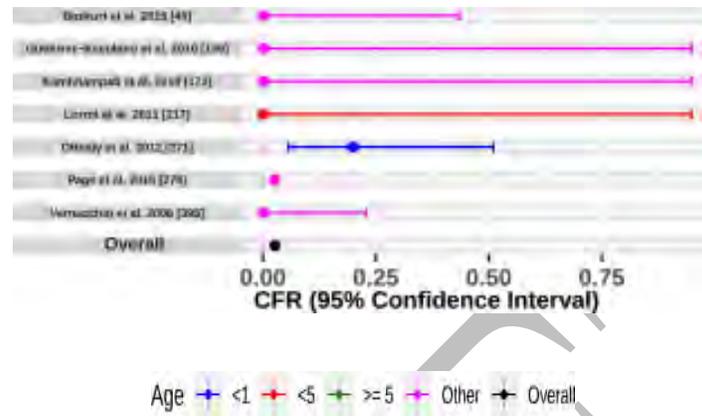


Fig. 7c. Rotavirus (U5MR – high)

Fig. 8. Norovirus

(A)



(B)

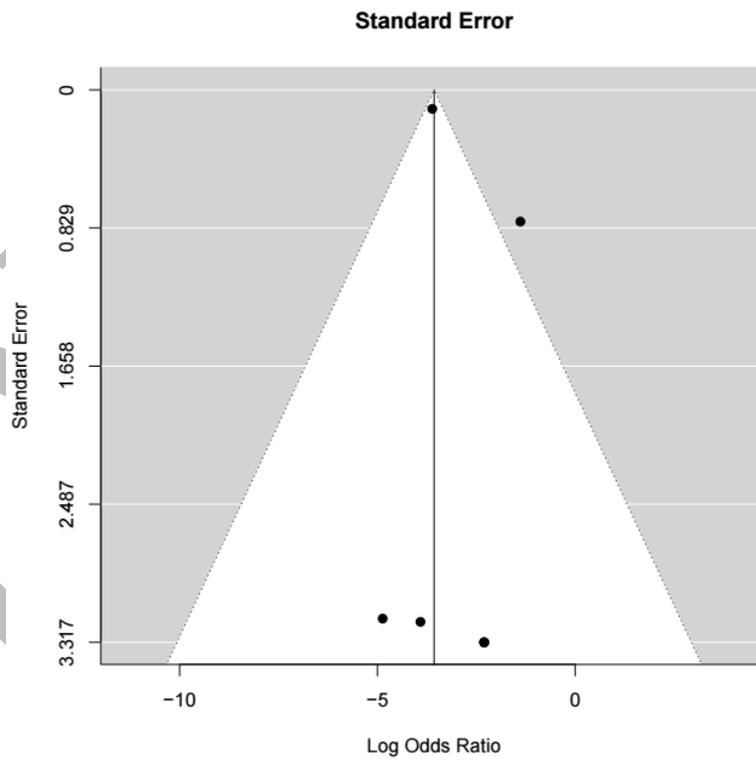
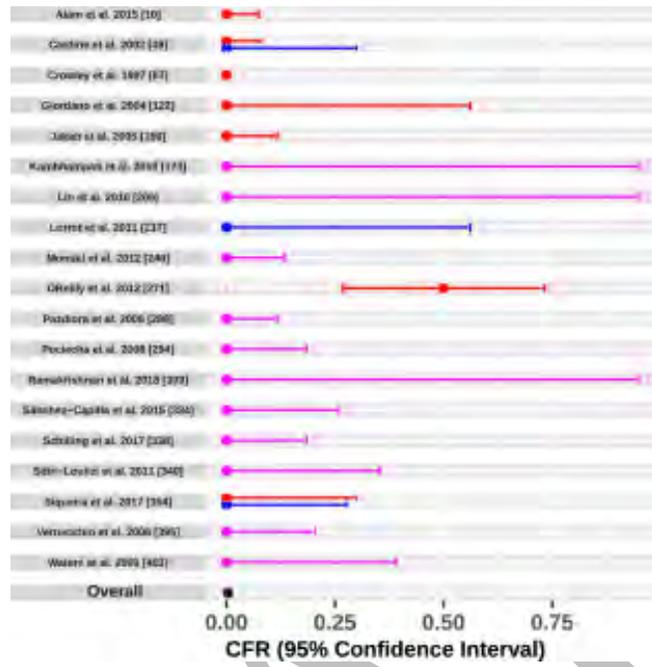


Fig. 9. Sapovirus

(A)



(B)

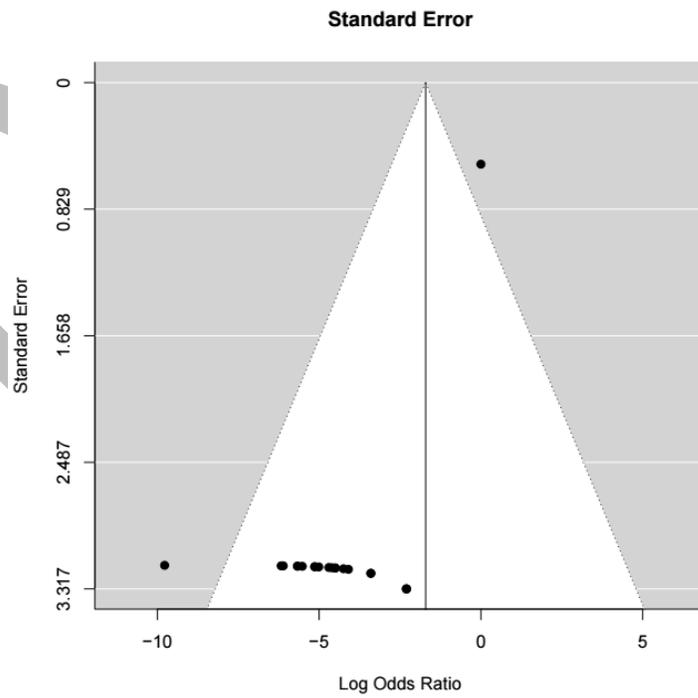
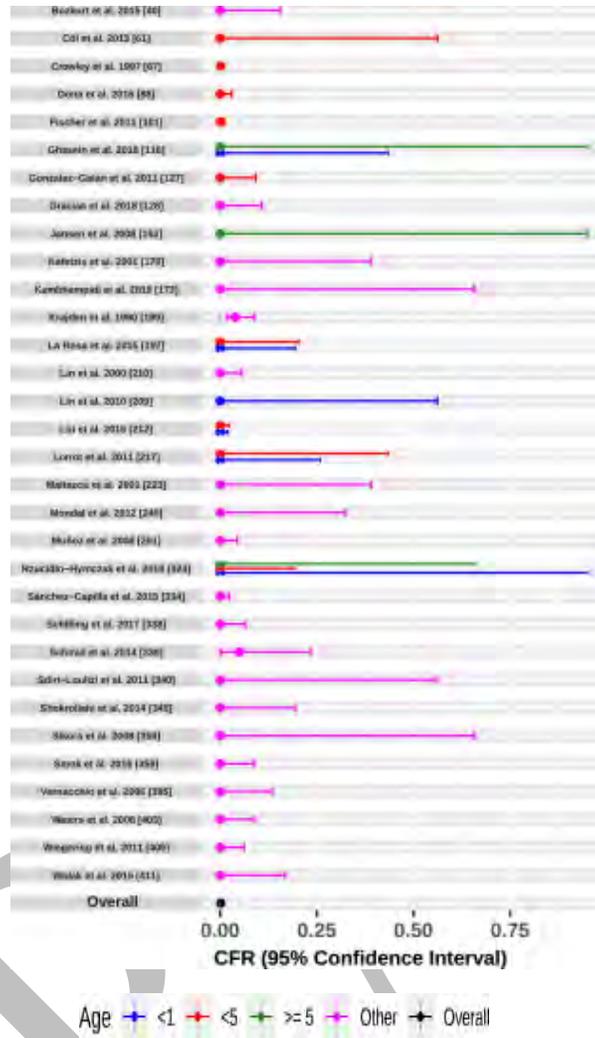


Fig. 10. Astrovirus

DRAFT

(A)



(B)

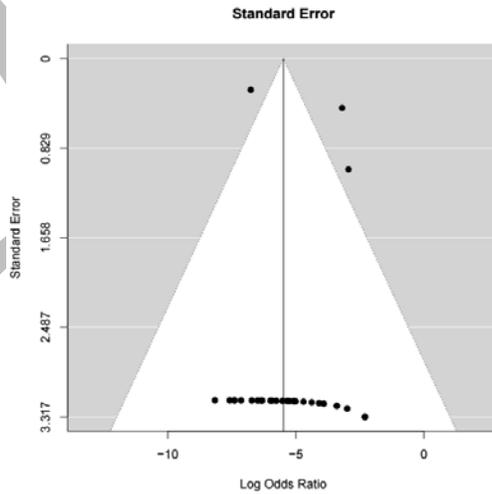


Fig. 11. Adenovirus

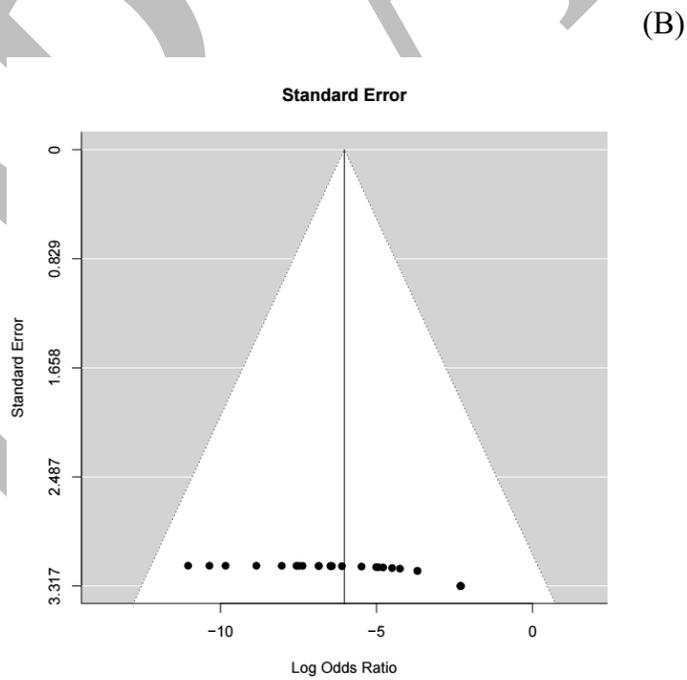
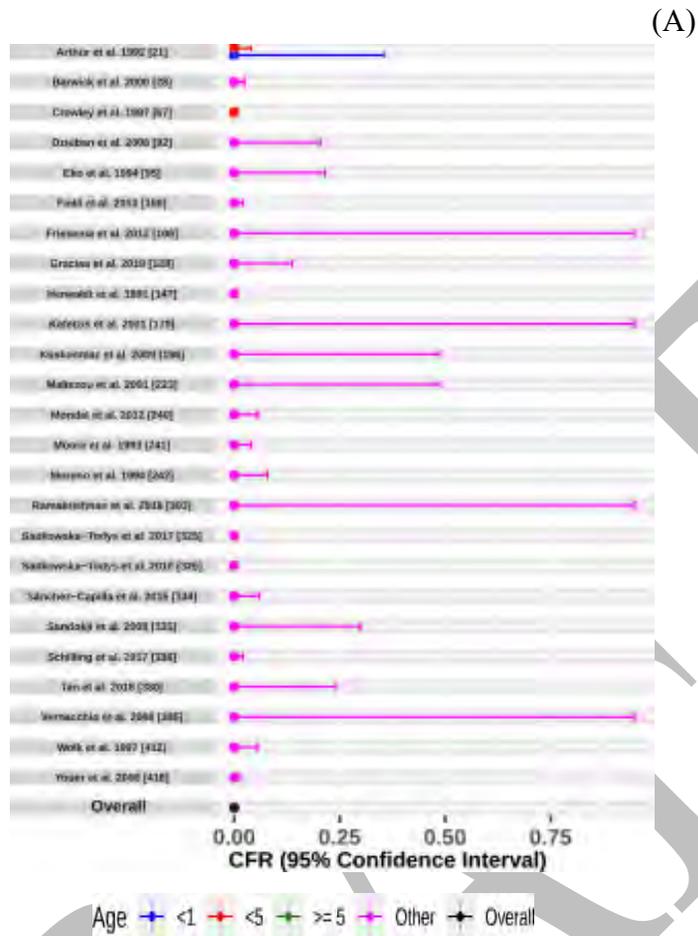
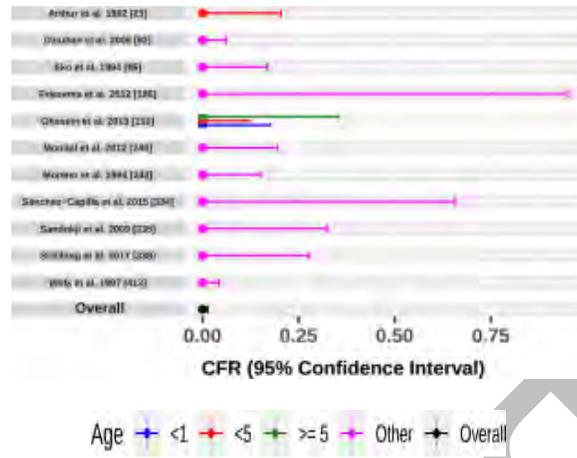


Fig. 12. Giardia lamblia

(A)



(B)

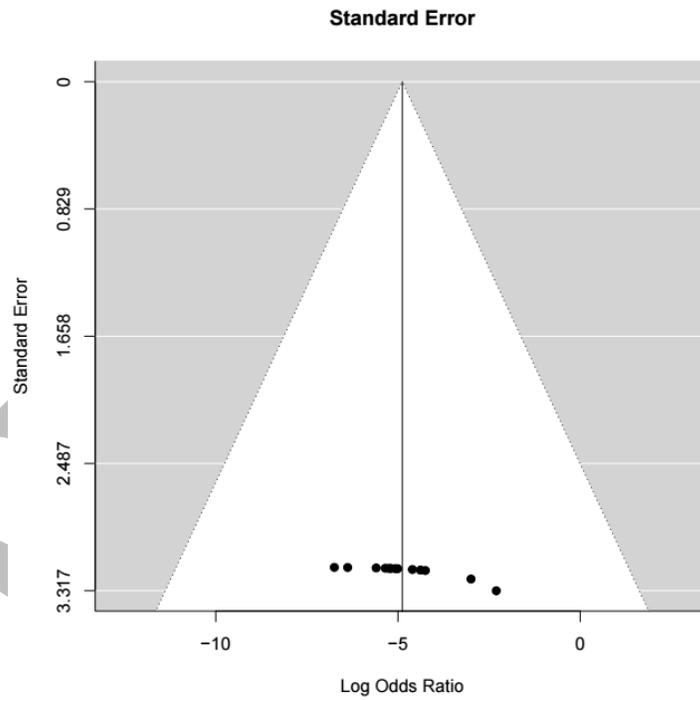
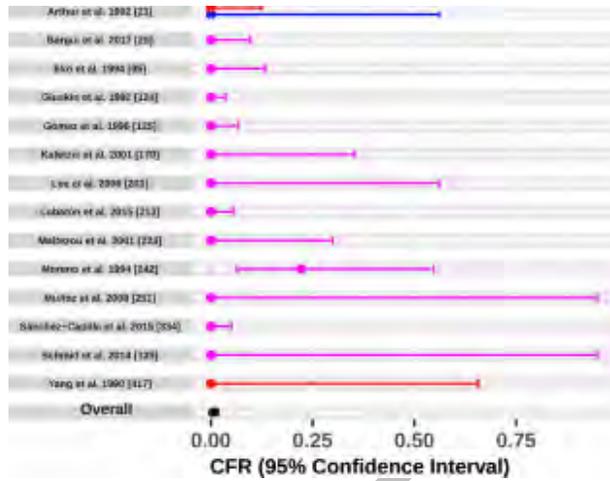


Fig. 14. Entamoeba

(A)



Age <1 <5 >=5 Other Overall

(B)

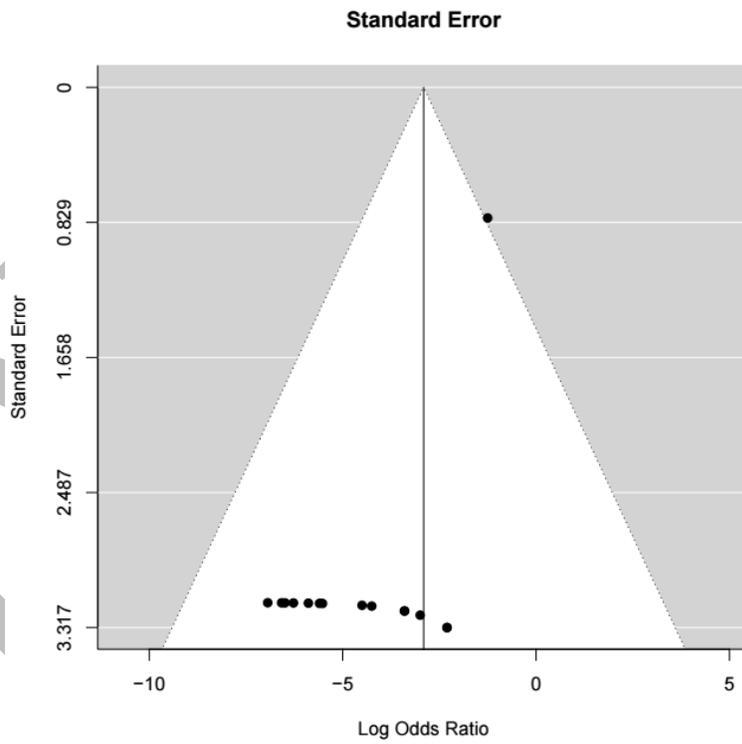
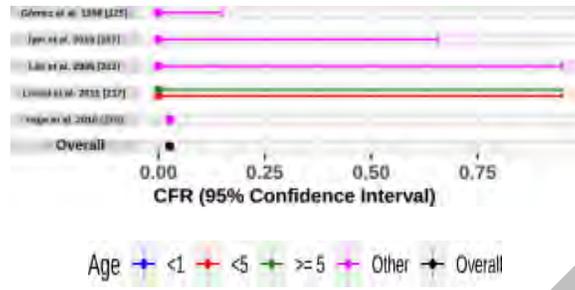


Fig. 15. Aeromonas

(A)



(B)

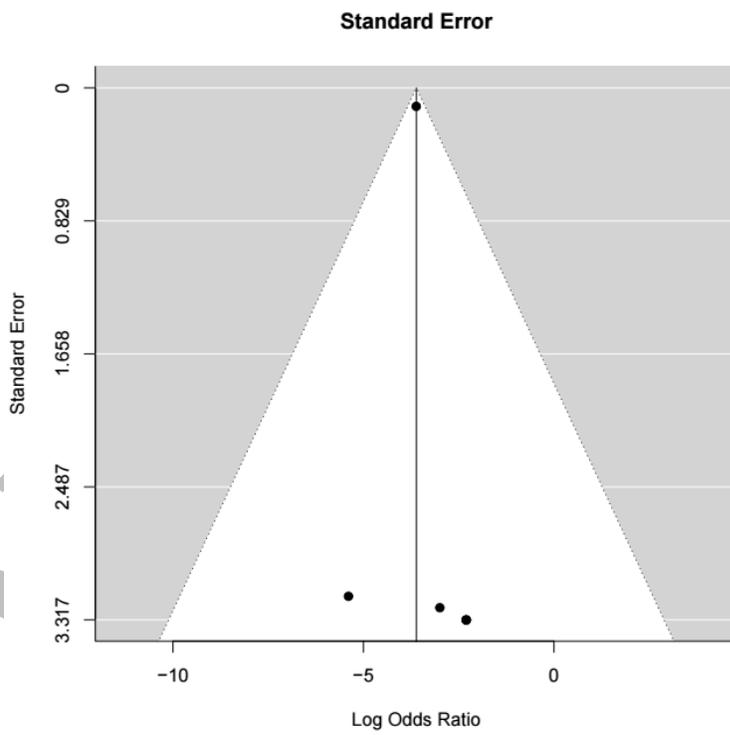


Fig. 16. Other

Table S#: The results of the Egger's test. The test indicates a publication bias if P-value <0.05.

Pathogen	Z	Pval
Salmonella	-0.6448	0.5191
Shigella	-8.9615	<0.0001
Campylobacter	-4.9068	<0.0001
Cholera	8.5271	<0.0001
EPEC	-7.0605	<0.0001
ETEC	-3.665	0.0002
Rotavirus	-0.2229	0.8236
Norovirus	3.4495	0.0006
Adenovirus	1.8884	0.059
Aeromonas	-2.9687	0.003
Astrovirus	-5.2977	<0.0001
Cryptosporidium	-4.8369	<0.0001
Entamoeba	1.1126	0.2659
Giardia	2.8376	0.0045
Sapovirus	1.2875	0.1979
Other	0.3654	0.7148
overall	-10.7437	<0.0001

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**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)
Virtual Consultation 2: Update from the Burden of Enteric Diseases working group
11 May 2020**

Participants:

WHO: Martin Friede, Birgitte Giersing*, Geraldine Griffin, Mateusz Hasso-Agopsowicz*, Erin Sparrow, Adam Cohen

Chair of SAGE: Alejandro Cravioto

PDVAC: Isabelle Bekeredjian-Ding (for Klaus Cichutek), Sinead Delany-Moretlwe, Bernard Fritzell, Barney Graham, Gagandeep (Cherry) Kang*, Ruth Karron, David Kaslow (Chair), Jerome Kim, Claudio Lanata*, Mark Papania (apologies), Shabir Mahdi (apologies), Yiming Shao, Peter Smith*, Marian Wentworth, Beno Nyam Yakubu

Observers and non-member participants: Julia Baker*, Louis Bourgeois, Robert Breiman*, Matt Doxey, Robert Black, William Hausdorff, Ibrahim Khalil, Jens Kieckbusch, Hmwe Kyu, Benjamin Lopman*, Cal MacLennan, Sophie Mathewson, Deepali Patel, Virginia Pitzer*, James Platts-Mills*, Duncan Steele

*denotes BoED working group members

Executive Summary

Rationale for topic: In 2018, PDVAC recommended that an expert working group be established to explore the differences between IHME and MCEE under 5 mortality estimates, and to assess the respective strengths and limitations of the estimation approaches adopted, including a review of the data on which the estimates are based.

General conclusions:

- Results from systematic reviews of odds ratios (ORs) of developing diarrhoea when a pathogen is detected in stool, and pathogen-specific case fatality rates (CFRs) were presented. Results are stratified by a pathogen, child mortality strata, detection method, and study setting. There is heterogeneity between pathogens for both CFRs and ORs. Suggestions were made how results of these analyses could inform future iterations of mortality estimates;
- Results from the study quality grading analysis were presented. The majority of studies for ETEC and Shigella are considered of good quality (>70% of quality score). A sensitivity analysis will be conducted to measure the impact of low-quality studies on mortality estimates;
- The IHME diagnostic test adjustments increase the Shigella mortality estimate by approximately twofold but do not increase the ST-ETEC estimate; the other IHME adjustments have a negligible impact on the estimates;

- IHME and MCEE expressed enthusiasm about the presented work and presented ideas on how these results could improve future mortality estimates;
- PDVAC felt that the outcomes of the BoED WG will lead to improved understanding of data processing and data inputs that inform the mortality estimates, and could improve their robustness and credibility;

PDVAC Recommendations:

- *A set of publications with proposed recommendations for inclusion and exclusion criteria for studies will be an important contribution.*
- *Results of all analyses should be represented visually on a map to highlight countries with no data or countries where data quality is low;*
- *Additional PCR, hospital-based, multi-pathogen studies, such as from GPDS, should inform future mortality estimates.*
- *By the time a vaccine for ETEC or Shigella is developed and licenced, mortality might be one of the drivers in the full value of vaccine assessment (FVVA), and it should be considered together with other components such as morbidity, educational attainment, antimicrobial resistance, economic burden and healthcare utilisation;*
- *PDVAC agrees with the proposed scope of morbidity work; however, the committee highlighted that the scope should be focussed to inform strategic decisions around vaccine development investment, policy recommendation, and vaccine introduction and use.*
- *PDVAC recommended to engage early in the process with multiple stakeholders (NITAGs, RITAGs, SAGE, vaccine developers, GAVI) to ensure that results from the proposed morbidity workstreams will drive decision making*
- *Identify elements in the FVVA that are specific to particular enteric pathogens and the ones that are applicable to a broader group of pathogens.*

1. Context and format of the meeting

Investment in vaccine product development and policy decisions for introduction are informed by the impact that the vaccine is expected to have on disease burden, which currently is mainly driven by the mortality burden. However, there is often a lack of epidemiological data to inform vaccine impact assessments and cost-effectiveness studies, and decisions are based on burden models that extrapolate from specific studies in which disease data are collected. Policy decisions are mostly informed by the extent to which a vaccine might reduce mortality and do not adequately consider the effect the vaccine may have on the morbidity burden, or broader population-based implications.

A number of enteric vaccine candidates are in clinical product development, including those to address the burdens of *Shigella*, enterotoxigenic *E.coli*, norovirus and non-typhoidal *Salmonella*. As part of its mission to advance vaccine development that addresses significant unmet public health need globally, WHO is embarking on efforts to better evaluate and communicate the full value of vaccines, while candidates are in the early stages of product development. The Full Vaccine of Vaccines Assessment (FVVA) is a concept that describes the full value of a vaccine and aims to articulate all direct and indirect effects. The intent of FVVA is to support decision-making across the continuum of vaccine development and uptake, with a line-of-sight to sustainable socio-economic and public health impact.

Two main modelling groups provide mortality estimates for enteric pathogens: the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, Seattle, and the Maternal Child Epidemiology Estimation (MCEE) group, led by Johns Hopkins Bloomberg School of Public Health. In 2018, PDVAC reviewed the global diarrhoea mortality estimates for under five-year-olds from these two groups. While estimates from the two groups a decade ago were closely aligned, more recent estimates for 2016 have diverged, particularly with respect to numbers of deaths attributable to different enteric pathogens. This has impacted prioritisation and investment decisions for candidate vaccines in the development pipeline. For this reason, PDVAC recommended the formation of an independent working group of subject matter experts to explore the reasons for differences between the IHME and MCEE estimates, and to assess the respective strengths and limitations of the estimation approaches adopted, including a review of the data on which the estimates are based.

While infections with enteric pathogens result in substantial mortality, the morbidity impact due to malnutrition, stunting, and cognitive impairment can last long after the initial infection took place. To comprehensively assess the full vaccine value and inform vaccine prioritisation and use, both mortality and morbidity need to be explicitly quantified. However, there is a lack of consensus on how to measure, analyse and present morbidity associated with enteric infections, and as such, the value of enteric vaccines is under-estimated.

This PDVAC session reviewed the outputs of the BoED WG group since the 2018 PDVAC recommendation and discussed the potential expansion of the scope of this group to evaluate current data and methodology to assess morbidity for these pathogens.

Objectives of the meeting

The objectives for the virtual PDVAC meeting on 11 May 2020 were to:

1. Review the status of workstreams related to improving quantification of the under-five mortality caused by individual enteric pathogens;
2. Discuss the impact of findings and their potential implications for the future under-five mortality estimates;
3. Provide an overview of the proposed expansion of the working group scope to evaluate the data and methodology to quantify the morbidity burden of enteric pathogens.

2. Summary of workstreams and the BoED process to date

The BoED WG was convened in November 2018 to assess the differences in the methods used to derive the U5 mortality estimates, increase the understanding of data incorporated into the models, and increase the transparency and credibility of the estimates. The WG proposed to engage in four workstreams, and all were later reviewed and endorsed by both PDVAC and IVIR-AC:

1. Data Gaps – to identify and address areas of commonality where additional evidence may improve future estimates.
2. Study Quality Exercise – to improve the understanding and quality of the studies included in the modelling process.
3. Data Processing Exercise – a high-level assessment of similarities and differences in study data included in the models and how it is processed.
4. Model Comparison Exercise – to address structural and methodological differences in models: on hold, pending results from workstreams 1-3.

3. Workstream 1: Data Gaps

Rationale: the purpose of this workstream is to identify and address areas of commonality between the IHME and MCEE methods, where additional evidence may improve future estimates. The BoED WG recommended to conduct two systematic reviews:

- 1) Systematic review and meta-analysis of odds ratios of developing diarrhoea when a pathogen is detected in stool;
- 2) Systematic review and meta-analysis of pathogen-specific case fatality rates.

3.1. Results from the systematic review of odds ratios of developing diarrhoea when a pathogen is detected in stool.

Rationale: The IHME estimates for the number of episodes and deaths attributable to each pathogen are the product of the total number of diarrhoea episodes and deaths, and the population attributable fraction (PAF) for that aetiology. To calculate PAF, odds ratios (ORs) of developing diarrhoea when a pathogen is detected in stool are used. IHME uses ORs from

seven sites of The Global Enteric Multicenter Study (GEMS) and extrapolates them globally. Consequently, the BoED WG proposed to conduct a systematic review to better understand the heterogeneity of pathogen-specific ORs across under 5 (U5) mortality strata, age groups, and pathogen detection methods.

Methodology: The START Centre at the University of Washington conducted a systematic review of the literature (1990-2019) and identified 145 suitable studies, including 1324 observations for 15 pathogens. GEMS and Malnutrition and Enteric Disease Study (MAL-ED) studies were included. Julia Baker and Benjamin Lopman (Emory University) developed a model to calculate ORs stratified by pathogen, age group, detection method, and child mortality strata.

Results: There is substantial heterogeneity of ORs by pathogen, age, child mortality strata and pathogen detection method. ORs reflect the frequency of exposure, asymptomatic infection, development of immunity, and they may be adapted and used as inputs in burden models. Table 1 summarises results of the OR analysis.

Table 1. Summary of results for the systematic review of odds ratios of developing diarrhoea when a pathogen is detected in stool (unpublished, confidential).

Pathogen	Unadjusted*		0-5 years**						> 5 years*	
			V. low mortality		Low mortality		High mortality			
	Est.	CI	Est.	CI	Est.	CI	Est.	CI	Est.	CI
Adenovirus	2.1	1.8-2.6	6.4	1.0-38.8	4.1	1.9-8.8	1.3	0.8-2.1		
Astrovirus	1.9	1.6-2.3			0.6	0.1-3.0	1.7	0.9-3.1		
Norovirus	1.7	1.4-2.0			9.8	1.7-57.3	2.9	1.4-6.0	3.2	1.3-7.6
Norovirus GI	1.4	0.7-3.0			1.6	0.5-5.2	0.8	0.5-1.2	1.4	0.4-4.4
Norovirus GII	2.1	1.6-2.9			4.6	2.6-7.9	0.9	0.3-2.8	3.4	1.3-8.8
Rotavirus	6.4	5.6-7.3	7.9	1.9-32.9	7.2	3.5-15.2	5.9	4.1-8.4	2.9	1.3-6.5
Sapovirus	1.8	1.5-2.1			2.0	1.4-2.8	1.0	0.5-1.8		
Aeromonas	2.4	1.7-3.3					3.7	3.2-4.2		
Campylobacter	1.7	1.5-1.9	8.8	1.3-59.2	2.3	1.2-4.4	1.7	1.3-2.2	5.1	2.6-10.0
Cholera	5.3	1.6-17.1								
EPEC	1.4	1.2-1.6	1.8	1.2-2.7	2.8	0.6-13	1.4	0.9-2.0	1.2	0.9-1.7
ETEC	1.8	1.6-1.9	2.0	0.8-5.1	0.5	0.3-0.9	1.5	1.2-1.9	1.4	0.1-24.7
ST ETEC	2.2	1.9-2.6	2.4	0.7-8.1	0.9	0.5-1.5	1.6	1.1-2.5	4.8	1.7-14.2
LT ETEC	1.1	1.0-1.3	0.6	0.3-1.4	0.4	0.2-1.0	1.0	0.7-1.4	1.2	0.2-6.3
Salmonella enterica	1.9	1.4-2.5			1.4	0.9-2.0	1.4	0.8-2.5	0.9	0.6-1.3
Shigella	5.5	4.3-7.1			4.6	2.1-9.8	4.2	2.4-7.3	2.8	1.5-5.5
Cryptosporidium	2.2	1.9-2.4	2.5	1.2-5.2	1.0	0.3-3.2	1.9	1.7-2.2	3.4	1.2-9.6
E. histolytica	1.3	1.1-1.6			0.6	0.2-1.9	1.7	1.1-2.7	1.2	0.6-2.3
Giardia lamblia	1.0	0.9-1.1	1.1	0.4-3.0	2.0	0.9-4.4	0.8	0.6-1.1	1.2	0.6-2.3

*All age groups, all mortality strata

**Controlling for pathogen detection method, study design

Next steps: The analysis is finished and will be published together with other manuscripts as a series of publications related to this work. WHO together with Benjamin Lopman and Julia Baker will work closely with IHME and MCEE to understand how the results of this analysis may be incorporated into future modelling estimates.

Discussion:

- Due to the heterogeneous study design of this meta-analysis, pathogens were treated independently and the impact of multiple pathogen infections on ORs was not investigated;
- The OR that a pathogen was associated with diarrhoea was more strongly determined by prevalence in controls than prevalence in cases. This finding points out the limitation of using ORs as a measure of pathogenicity for enteric pathogens that confer incomplete immunity;
- Higher ORs are reported for ST-EPEC in very low or low mortality setting vs high mortality settings; however, for Shigella, OR was high and consistent in low to high mortality settings and in over 5 year olds;
- Large uncertainty represented by wide confidence intervals should be taken into account when analysing results;
- The results provide a more granular OR stratification across pathogens, ages and mortality strata, and add to the currently used ORs based only on the GEMS study.

3.2. Results from the systematic review of pathogen-specific case fatality rates (CFRs)

Rationale: Global burden of diarrhoea models assume that deaths from enteric pathogens occur in proportion to the distribution of pathogens in hospitalised (MCEE) or severe (IHME) cases. The estimates do not take into account potential differences in the risk of death from different pathogens. Consequently, the BoED WG proposed to conduct a systematic review to better understand the heterogeneity of CFRs among pathogens, WHO regions, age groups and study settings.

Methodology: The START Centre at the University of Washington conducted a systematic review of the literature (1990-2019) and identified 430 studies for 15 pathogens. Published studies from GEMS and MAL-ED were included. Ernest O. Asare & Virginia Pitzer (Yale University) conducted an analysis to examine heterogeneity in the CFR across pathogens, WHO regions, age groups and study settings, and to develop a model to estimate the overall CFR and the CFR for each pathogen, while controlling for predictors of heterogeneity.

Results: There is substantial heterogeneity in the estimated CFRs both within and between pathogens. For some pathogens, the CFR was higher in children under one year old, living in the AFRO region, or in higher mortality strata. For viral pathogens, the CFR was higher in community-based studies, whereas for bacterial pathogens, the CFR was higher in hospital-based studies. Table 2 summarises results of the CFR analysis.

Table 2. Summary of results from the systematic review and meta-analysis of case fatality rates for diarrheal pathogens (unpublished, confidential). Also shown are the odds ratios comparing the CFRs with that for Salmonella.

Pathogen	CFR	95% CI	Odds ratio	95% CI for OR
	<i>Fixed effects model</i>		<i>Multi-level mixed effects model[†]</i>	
Overall	0.0065	(0.0058, 0.0073)		
Salmonella	0.0028	(0.0026, 0.0030)	REF (1.0)	--
Shigella	0.0302	(0.0287, 0.0318)	1.18	0.67, 2.09
Campylobacter	0.0021	(0.0020, 0.0023)	0.44*	0.24, 0.82
Cholera	0.0107	(0.0106, 0.0108)	0.79	0.43, 1.44
ETEC	0.0304	(0.0470, 0.0195)	1.18	0.52, 2.69
EPEC	0.0637	(0.0546, 0.0741)	3.24*	1.68, 6.26
Rotavirus	0.0006	(0.0006, 0.0007)	0.22*	0.14, 0.36
Norovirus	0.0015	(0.0015, 0.0016)	0.72	0.40, 1.29
Sapovirus	0.0266	(0.0215, 0.0330)	1.25	0.34, 4.55
Astrovirus	0.0034	(0.0016, 0.0070)	2.38	0.84, 6.75
Adenovirus	0.0015	(0.0009, 0.0023)	0.80	0.36, 1.79
Giardia	0.0000	(0.0000, 0.0003)	0.46	0.12, 1.76
Cryptosporidium	0.0049	(0.0041, 0.0059)	1.24	0.59, 2.60
Entamoeba	0.0000	(0.0000, 0.0132)	0.60	0.09, 3.94
Aeromonas	0.0048	(0.0013, 0.0173)	1.71	0.48, 6.14
Other	0.0260	(0.0208, 0.0323)	1.26	0.34, 4.69
Covariates included in full multi-level model				
Age group (REF: Under 5 yrs)				
Under 1 yr			1.39	0.92, 2.10
Above 5 yrs			0.77	0.51, 1.14
Other			0.96	0.64, 1.45
Under-5 Mortality Strata (REF: very low)				
Low			1.83*	1.04, 3.21
High			5.50*	3.30, 9.16
Setting (REF: hospital)				
Community			0.80	0.47, 1.34
Other			0.76	0.36, 1.62

[†]Accounts for between-study (and within-study) heterogeneity using random effects

*Denotes $p < 0.05$

Next steps: Virginia and Ernest are finalizing models to calculate pathogen-specific CFRs while controlling for potential predictors of heterogeneity. Once finished, the analysis will be published together with other manuscripts as a series of publications related to this work. WHO together with Virginia Pitzer and Ernest O. Asare will work closely with IHME and MCEE to understand how the results of this analysis may be incorporated into future modelling estimates.

Discussion:

- Calculated CFRs are similar to the ones calculated using the data from the WHO Global Rotavirus surveillance network;

- Observed differences in CFRs between hospital and community studies might reflect the clinical course of a disease. Short-lasting viral infections would most likely present and cause deaths in a community, whereas longer-lasting bacterial infections would likely present and cause deaths in a hospital;
- Data on the proportion of dying children that have access to a hospital could help to adjust for variations in access to treatment and its impact on CFR;
- Studies conducted in communities introduce community interventions that change the underlying epidemiology of diseases and access to treatment in that population. They should be interpreted with caution.
- Hospital-based CFRs account for treatment access and could be used to inform future mortality estimates.

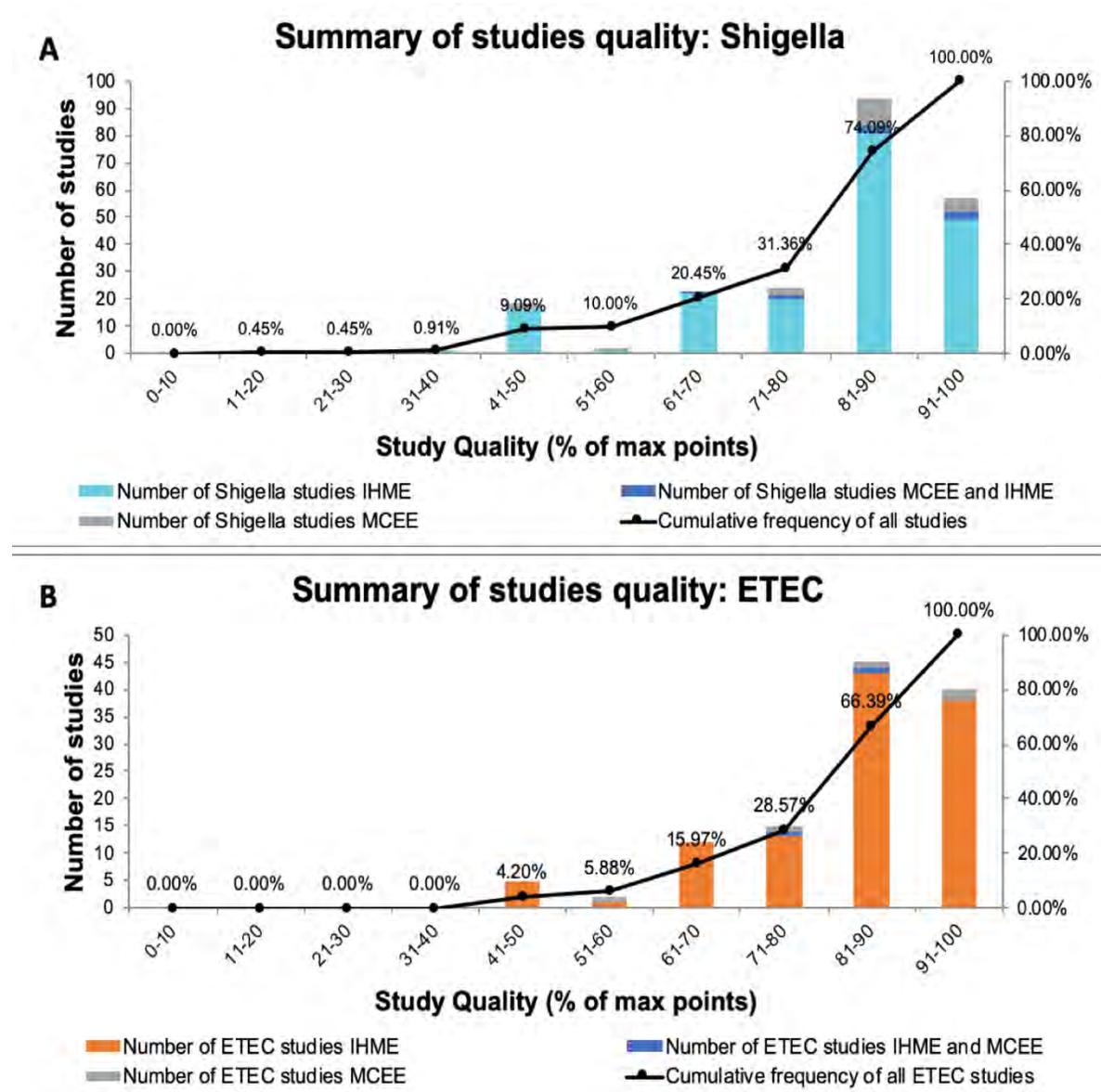
4. Workstream 2: Study Quality Exercise

Rationale: There is a limited understanding of the type and quality of studies that are used to calculate mortality estimates by both IHME and MCEE. The BoED WG suggested conducting a quality grading review of all ETEC and Shigella studies to determine the quality of the studies used by each of the groups.

Methodology: Egle Butkeviciute (LSHTM), together with the BoED WG, developed a modified Newcastle-Ottawa Scale (NOS) to assess the quality of IHME and MCEE studies. To determine the study quality, the NOS considers selection, comparability and outcome criteria. A total of 119 studies were graded for ETEC and 220 for Shigella.

Results: Out of 119 studies for ETEC, only two were used by both IHME and MCEE; and out of 220 studies for Shigella, only eight were used by IHME and MCEE. The limited overlap is a reflection of different inclusion criteria that are adopted by the groups. For Shigella, 20.45% of studies scored less than 70/100 quality score (figure 1A); for ETEC, 15.97% scored less than 70/100 quality score (figure 1B). Similar quality scores were observed for studies used by both groups, both for ETEC and Shigella.

Figure 1. Results of the quality grading analysis for ETEC and Shigella (unpublished, confidential).



Next steps: The grading analysis is finished and WHO is working closely with IHME to conduct a sensitivity analysis of low-quality studies and their impact on mortality estimates. The results of the grading and sensitivity analyses will be incorporated into a publication that articulates high-level recommendations for studies to be included in reports of mortality estimates.

Discussion:

- This analysis was focused on identifying study characteristics that could lead to bias in interpreting results;

- The sensitivity analysis of low-quality studies will focus on the IHME dataset as 1) a small number of studies included in the MCEE model would prevent informative analyses, and 2) MCEE's approach to calculating mortality estimates has evolved since 2013, data gaps were identified, and the estimates were not published.

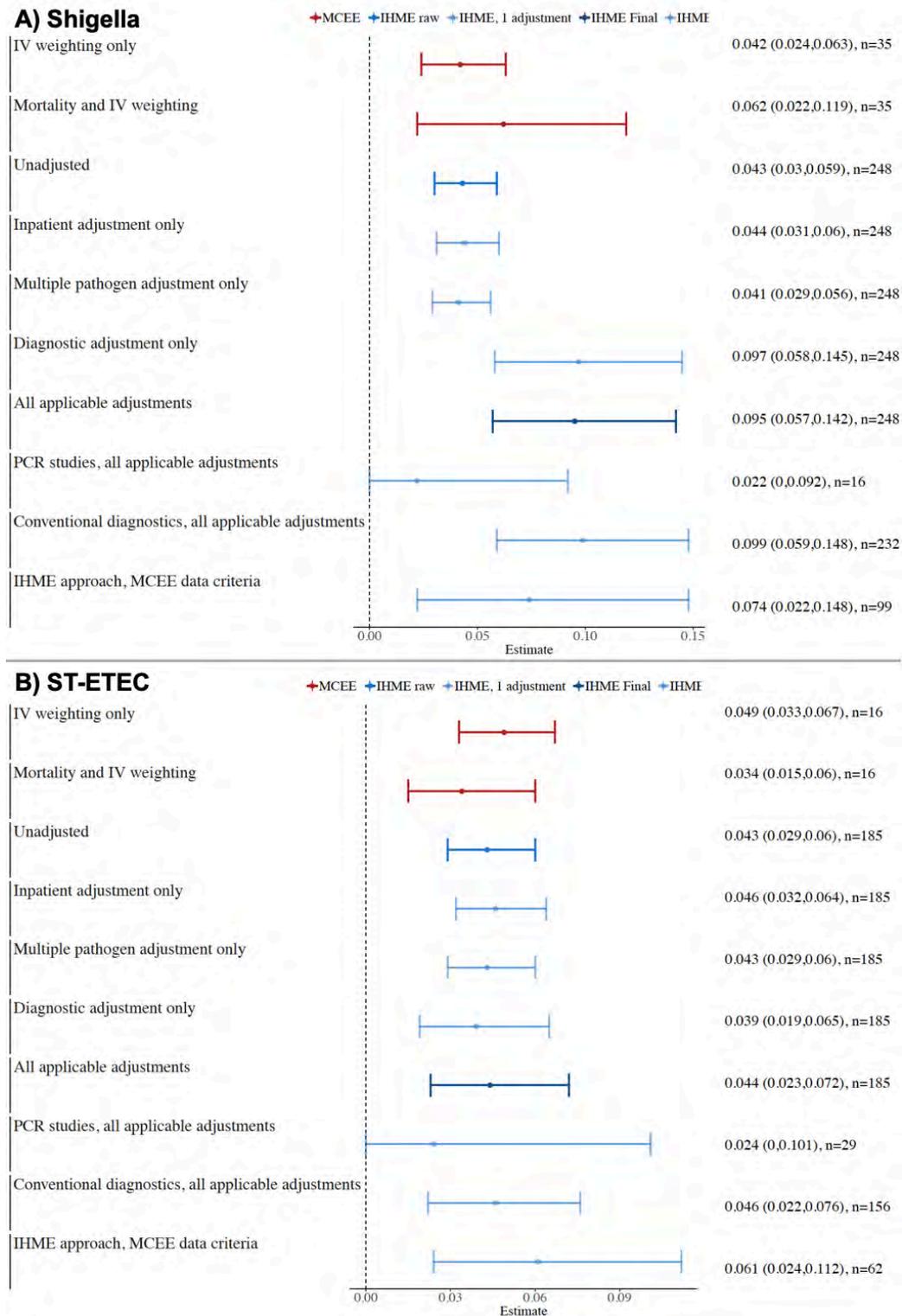
5. Workstream 3: Data Processing Exercise

Rationale: There is a limited understanding of how data used by IHME and MCEE compare, before and after applying model adjustments. The BoED WG recommended comparing the aetiological proportions between MCEE and IHME and investigating the impact of study adjustments on prevalence estimates.

Methodology: Pathogen prevalence data for ST-EPEC and Shigella were collected from both modelling groups. James Platts-Mills and Sarah Elwood (University of Virginia) conducted a high-level meta-analysis of both groups' age-adjusted data. They also applied IHME data adjustments and examined the impact on prevalence estimates.

Results: The IHME diagnostic test adjustments increase the Shigella mortality estimate by approximately twofold (figure 2A) but do not increase the ST-EPEC estimate (figure 2B); these increases are conservative when compared to the GEMS/MAL-ED re-analyses. The other IHME adjustments have a negligible impact on the estimates (and it is possible that, for example, restricting to studies of hospitalised diarrhoea would yield a different result). Alternative approaches to the diagnostic test adjustment are being considered, but if adopted, would likely further increase the gap between Shigella and EPEC burden for GBD. Differential application of the aetiology proportions to the mortality envelope (national/sub-national by IHME, regional by MCEE) may also lead to differences in the estimates.

Figure 2. Results of the meta-analysis of prevalence estimates and the impact of IHME adjustments for Shigella (A) and ST-EPEC (B), (unpublished, confidential).



Next steps: The analysis is finished and will be published together with other manuscripts as a series of publications related to this work. WHO together with James Platts-Mills and Sarah Elwood will work closely with IHME and MCEE to understand the impact of this analysis on future modelling estimates.

6. Perspectives on findings from IHME, MCEE, and BoED WG/PDVAC members

Hmwe Kyu (IHME) articulated that the analyses undertaken by the BoED are needed and will help to inform future mortality estimates. IHME will continue to work with WHO and modellers who conducted the analyses to understand if and how to incorporate the results into their future estimates. IHME proposed to:

- based on an earlier discussion with the modelling groups, a general consensus was that incorporating CFRs may not be very helpful in improving the estimates. Therefore, IHME won't be incorporating the CFRs but could compare estimated CFRs based on IHME results and the CFRs from the systematic review and investigate potential differences;
- consider incorporating ORs into the PAF calculation, determining a ratio of PCR to conventional detection methods;
- explore the possibility of predicting ORs by country as a function of sociodemographic development.

Robert Black (MCEE) highlighted his recent work with WHO to estimate causes of deaths due to diarrhoea in children and adolescents under 20 years old. MCEE did not publish previous aetiology estimates, as data to inform critical study adjustment such as for the difference in detection methods was missing. The results of the BoED analyses could inform such gaps and facilitate the publishing of future mortality estimates by MCEE. Results of the ORs analysis could be incorporated into future mortality estimates; however, inconsistent patterns of ORs across pathogens and mortality strata need to be fully investigated. MCEE continues to focus on studies in hospitalised patients and aims to calculate regional estimates. The results from the CFR analysis are unlikely to be used, as studies that measure CFRs include inpatient treatment and community interventions, and do not capture the true pathogen mortality.

PDVAC and BoED members (CL, GK, PS) highlighted that these extensive analyses provide more clarity on the data used by both models and improve our understanding of how models are conducted. The analyses help to explain the observed differences in mortality between the two modelling groups. The results should be interpreted with caution, together with wide confidence intervals and a caveat that research sites may not appropriately represent a country in which they are located. The BoED WG should be ready to assess new data that could inform future mortality estimates, such as from the CHAMPS minimally invasive autopsy studies. A set of publications with proposed recommendations for inclusion and exclusion criteria will be an important outcome of this group. Going forward, the group should focus on measuring the full value of vaccines assessment (FVVA), including the impact of enteric pathogens on morbidity, as well as healthcare utilisation.

7. Finalisation of analyses and future steps

The analysis of odds ratios of developing diarrhoea when a pathogen is detected in stool, the study quality analysis, and the meta-analysis of input studies and model adjustments are all completed. The analysis of pathogen-specific CFRs is near completion, and the sensitivity analysis of removing low-quality studies from the IHME analysis is pending but will hopefully be completed this summer.

The model comparison exercise (workstream 4), previously discussed, is on hold and the need for it will be revisited when results from workstreams 1-3 become available. The WHO team will work closely with IHME and MCEE to inform future iterations of U5 mortality estimates, and will share results and accompanying databases from the conducted analyses. Upon completion of workstreams 1-3, WHO proposes to disseminate results through a series of publications. Going forward, WHO and the BoED WG will continue to monitor for additional data to inform models that calculate mortality estimates. The work will also expand to measure the impact of enteric pathogens on morbidity.

8. Discussion and recommendations:

- The outcomes of the BoED WG lead to improved understanding of the data inputs and data processing that inform the U5 mortality estimates, and improve their robustness and credibility;
- Where possible, consider stratifying results to countries and WHO regions; however, as data are scarce, there are large confidence intervals when reporting country-level data;
- Results of all analyses should be represented visually on a map to highlight countries with no data or countries where data quality is low;
- The analyses show that pathogen biology varies between pathogens, and pathogen independent models should be developed to assess the pathogen burden;
- Both the pathogen impact on disease burden as well as a broader impact on diarrhoea should be considered when calculating mortality estimates;
- By the time a vaccine for ETEC or Shigella is developed and licenced, mortality might be a much smaller component of FVVA, and it should be considered together with other components such as morbidity and economic burden;
- Additional PCR, hospital-based, multi-pathogen studies, such as from GPDS, might further inform mortality estimates.

9. The proposed expansion of BoED WG scope to include morbidity assessment

Diarrheal diseases burden estimates have been dominated by childhood deaths, and as a result, public health policy decisions are mainly based on mortality estimates. In addition to mortality, diarrhoea episodes can lead to long-term effects such as wasting, stunting, cognitive impairment, decreased school performance and others. A comprehensive assessment of long-term effects of diarrhoea is challenging, estimates are limited, and methodologies to measure such impact are heterogeneous, often leading to incomparable results. The BoED WG proposes to expand its scope of work to measure the impact of enteric pathogens on morbidity through the following proposed workstreams:

- Conduct a landscape analysis of the available and forthcoming data, and methods used to measure morbidity (variables, metrics, types of tests performed, etc.)
- Examine the evidence for the pathologic pathway leading to long term sequelae of enteric infections and diarrhoea (inflammation biomarkers, EED, stunting, etc.)
- Collaborate with / track the ongoing efforts of the AMR vaccine value attribution framework to incorporate the contribution of AMR, when appropriate
- Identify critical data gaps and propose research studies that may improve understanding, including mining existing data sets from past studies.
- **Output 1:** Identification of data and research gaps to quantify morbidity, recommendations communicated through a publication
- **Output 2:** Assess whether the evidence collected on disease impact and the existing studies/methods to measure morbidity could inform the development of a standardised framework to quantify the burden

The proposed morbidity work would start in September 2020.

Discussion:

- PDVAC agrees with the proposed scope of morbidity work; however, the committee highlighted that the scope needs to inform strategic decisions around vaccine development investment, policy recommendation, and vaccine introduction and use.
- PDVAC recommended to engage early in the process with multiple stakeholders (NITAGs, RITAGs, SAGE, vaccine developers, GAVI) to ensure that results from the proposed workstreams will drive decision making;
- It might be challenging to incorporate estimates of morbidity into current IHME and MCEE models (as they report diarrhoea as a disease and pathogens as risk factors);
- Results of ABCD and CHAIN studies could potentially be used to inform some of the morbidity estimates;
- Consider utilisation of health services, as outpatients, emergency room use and hospitalizations, at a country or regional level, as part of the morbidity assessment;
- An important element of the proposed work is to develop consensus on methodologies to measure the impact of pathogens on morbidity;
- The morbidity caused by AMR pathogens is assumed to be greater than drug susceptible pathogens, the AMR component should be reflected in the morbidity assessment;
- Consider alignment with FVVA, identify elements that are specific to enteric pathogens and the ones that are applicable to a broader group of pathogens.

Start times:

06:00 Seattle; 8:00 Lima; 9:00 Washington DC; 14:00 London; 15:00 Johannesburg; 15:00 Geneva; 18:30 New Delhi, 21:00 Beijing; 22:00 Seoul

Time (Geneva CEST)	Topic	Duration	Detail	Moderators, speakers
15.00 – 15.10	Welcome and introductions			David Kaslow and Martin Friede
15.10 – 15.15	Introduction: session overview & objectives	5'	Summary the purpose of the session and highlight of PDVAC's 2018 recommendations related to this work	Birgitte Giersing
15.15 – 15.20	Summary of workstreams related to mortality of enteric pathogens	5'	High-level description of all workstreams that investigated the differences in the burden of U5 mortality for enteric pathogens.	Mateusz Hasso-Agopsowicz
15.20 – 15.35	Results of the study grading analysis	10' + 5'	For information: To describe findings of the study quality assessment of studies that were used to calculate mortality estimates	Mateusz Hasso-Agopsowicz
15.35 – 15.50	Analysis of the systematic review of odds ratios	10'+5'	For information and discussion: To describe results of the analysis of the systematic review of odds ratios of developing diarrhoea when a pathogen is detected in stool.	Benjamin Lopman
15.50 – 16.05	Analysis of the systematic review of case fatality rates	10'+5'	For information and discussion: To describe results of the analysis of the systematic review of pathogen specific case fatality rates.	Virginia Pitzer
16.05 – 16.20	Results from the meta analysis of input studies	10'+5'	For information and discussion: To inform about the results from the meta-analysis of studies used to calculate mortality estimates, and the impact of IHMEs model adjustments on mortality estimates.	James Platts-Mills

Time (Geneva CEST)	Topic	Duration	Detail	Moderators, speakers
16.20 – 16.30	Perspectives on findings from the mortality modelling groups	10'	For information: To highlight potential implications from the systematic reviews and meta-analysis on future mortality estimates	TBC
16.30 – 16.50	Discussion			Rob to moderate?
16.50 – 16.55	Anticipated outcomes, timelines, next steps	5'	For information: To inform on proposed outcome, their timelines, and next steps	Mateusz Hasso
16.55 – 16.15	Expansion of scope to morbidity	10'+10'	For decision and discussion: To inform, discuss and agree on the proposed scope of work to measure the impact of enteric infections on morbidity	Ibrahim Khalil
16.15 – 16.45	Closed session	30'		

WHO BoED OR Manuscript- Draft

Updated: July 19, 2020

Title: Association of enteropathogen detection with diarrhea across age and child mortality settings: A systematic review and meta-analysis

Authors: Julia M. Baker, Mateusz Hasso-Agopsowicz, Birgitte Giersing, Virginia E. Pitzer, James A. Platts-Mills, START Group, Benjamin A. Lopman

Introduction

Diarrheal disease is a leading cause of morbidity and mortality among children and adults worldwide.(1,2) The highest rates of diarrhea occur among children under 5 years of age with an estimated 1.1 billion episodes and 440-580 thousand deaths annually.(1,2) The development of vaccines against enteropathogens has been identified as a public health priority for further reducing the diarrheal disease burden.(3,4)

The success of such a strategy will depend on correctly identifying the enteropathogens that contribute most to diarrheal disease mortality. Rotavirus vaccines, the only globally-recommended immunization that targets diarrheal disease,(4) is demonstrative of this approach. Prior to vaccine introduction, rotavirus was the leading cause of diarrheal mortality in children (5) and, despite suboptimal vaccine effectiveness in high burden settings,(6) vaccine introduction was associated with a 36% reduction in acute gastroenteritis mortality.(7) Several other vaccines against enteropathogens are at various stages of development.(4,8,9) Burden of disease estimates and extrapolation of these estimates to predict vaccine impact are essential for guiding prioritization of vaccine development investments, financing introductions, and policy recommendations.(10,11)

A central challenge in accurately estimating the burden is determining the proportion of diarrheal disease attributable to a particular enteropathogen. The highly influential Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) uses a model that apportions diarrheal mortality based on a pathogen-specific population attributable fraction.(1) This attributable fraction is a function of the odds ratio (OR) quantifying the relationship between pathogen detection and the odds of developing diarrhea. The ORs used in GBD's calculations are derived from the Global Enteric Multicenter Study (GEMS).(1) This application requires a critical assumption: that the ORs from GEMS, a study among children under 5 years of age in seven low- and middle-income countries,(12) are generalizable across age groups, settings, and disease severities for which GBD produces burden estimates. Limiting ORs to those produced by a single study, even one as rigorously conducted as GEMS, may result in inaccurate attribution of pathogen-specific burden of disease estimates, risking misguided vaccine investment and public health intervention efforts.

In 2018, the World Health Organization (WHO) Product Development for Vaccines Advisory Committee (PDVAC) established the *Burden of Enteric Disease Working Group* tasked with

exploring differences between recent enteric disease burden estimates.(10) In support of this effort, our study aimed to examine the relationship between detection of an enteropathogen in stool and the occurrence of diarrhea. Specifically, we conducted a systematic review and meta-analysis to determine pathogen specific ORs for 15 enteropathogens stratified by age group and child mortality level.

Methods

Data source

The primary dataset for this analysis was generated through a systematic review of literature conducted by the University of Washington Strategic Analysis, Research & Training (START) Center. Adhering to the PRISMA guidelines, literature from January 1, 1990 through July 9, 2019 were compiled from EMBASE, Cochrane, Medline, and PubMed databases to identify studies that examined the association between enteropathogens and diarrhea. Studies were included if they were either case-control or cohort in design and examined at least one enteropathogen of interest and the outcome “diarrhea”. Articles were limited to those published in English, French, Spanish, Portuguese, Italian and Chinese. Studies were excluded if they 1) did not report on non-diarrheal controls, 2) included participants with a broad case definition of gastroenteritis (i.e. diarrhea or vomiting) and in which it was not possible to ascertain that all cases had diarrhea, 3) were limited to nosocomial infections, and 4) were conducted among patients with underlying chronic conditions (except Human Immunodeficiency Virus). Additional details on inclusion and exclusion criteria are provided in the supplemental material.

Information was extracted from each article using REDCap and included, but was not limited to, study design, number of cases/gastroenteritis samples, number of controls/non-gastroenteritis samples, pathogens screened, pathogens detected, pathogen detection method, and all provided measures of association between pathogen presence in stool and gastroenteritis. Fifteen pathogens were of interest including five viruses (adenovirus, astrovirus (40/41), norovirus, rotavirus and sapovirus), seven bacteria (*Aeromonas*, *Campylobacter*, *V. cholerae*, Enteropathogenic *E. coli* (EPEC), Enterotoxigenic *E. coli* (ETEC), *Salmonella enterica*, and *Shigella*), and three parasites (*Cryptosporidium*, *E. histolytica*, and *Giardia lamblia*). When available, strain-specific data were extracted (Supplemental Table 1) including for norovirus (GI and GII,) and ETEC (heat-stable type toxin (ST) and heat-labile type toxin (LT)). The data collection process is further detailed in the supplemental material.

Data from the START Center systematic review were supplemented with case-control and nested case-control data from GEMS and the Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) study, respectively. The available data included the proportion of stool samples positive by pathogen, stool type (case or control), age group, and study site, from which we calculated ORs. These data were included because measures of association from these studies were not available for extraction in the literature review and because of the studies’ size and influence on the field of childhood gastroenteritis.

Data structure

The dataset was structured to provide measures of association stratified by pathogen(s), pathogen strain, age group, study presentation, lab detection method, and country. Available measures of association included ORs (adjusted and unadjusted) and relative risk (RR, adjusted and unadjusted). For studies from which no measures of association were provided, unadjusted ORs were calculated when the number of cases/diarrhea samples, the number of controls/non-diarrhea samples, and the proportion of each that were positive for a particular pathogen were available. A hierarchy was set up to allow the best available measure of association for each stratum to be used in the final meta-analysis (from best to worst): adjusted OR, unadjusted OR, adjusted RR, unadjusted RR, unadjusted OR-calculated. For strata indicating coinfection, the reported effect estimate was used to represent the association between each individual pathogen detected and diarrhea. For example, if an OR of 1.8 was estimated for the association between rotavirus and giardia coinfection and diarrhea, two effect estimates were created and 1.8 was used to represent the association between rotavirus and diarrhea as well as giardia and diarrhea for that study.

Statistical analysis

Statistical analysis began with examination of forest plots and heterogeneity of effect estimates by fitting an unadjusted random effects model for each pathogen using the DerSimonian-Laird estimator for heterogeneity and examining the I^2 . Pathogen-specific heterogeneity was first examined using only OR effect estimates in the models and then again using both ORs and RRs to determine the impact of including the RRs. Including RRs had almost no impact on heterogeneity for each pathogen so ORs and RRs were used together for the subsequent analysis steps. Influential outliers were identified using Studentized Residual Plots and Cook's distances.

Five factors of interest were incorporated into the models: age group, child mortality level, pathogen detection method, and study design. Three age group categories were created including 0-5 years of age, over 5 years of age, and "mixed" which included strata that were unable to be assigned to the previous two age groups either because age data were unknown or because the ages spanned the 0-5 and over 5 age categories. Child mortality levels were assigned based on country-level UN Inter-agency Group for Child Mortality Estimation estimates of under 5 mortality rates for 2003 (the median study start year in the dataset).⁽¹³⁾ Using categorizations proposed by the World Health Organization,⁽¹⁴⁾ countries were divided into child mortality quintiles with the three lowest quintiles being categorized as "very low and low" child mortality and the two highest quintiles categorized as "high" child mortality. Pathogen detection method was categorized as conventional (enzyme-linked immunosorbent assay, culture, isolation, microscopy), polymerase chain reaction (PCR), and other/unspecified. Study design was categorized as case-control (standard or nested) and cohort (prospective, retrospective, cross-sectional, and randomized controlled trial).

The final models were specified with the goal of producing summary ORs specific to age groups and settings that could then be used in future burden of disease models. Random effects meta-analysis models, again using the DerSimonian-Laird estimator, were then fit incorporating five factors of interest. The models were stratified by age group and adjusted for pathogen detection method and study design. The 0-5 age group was further stratified by child mortality level; however, the over 5 years of age category was not further stratified due to small sample size. We

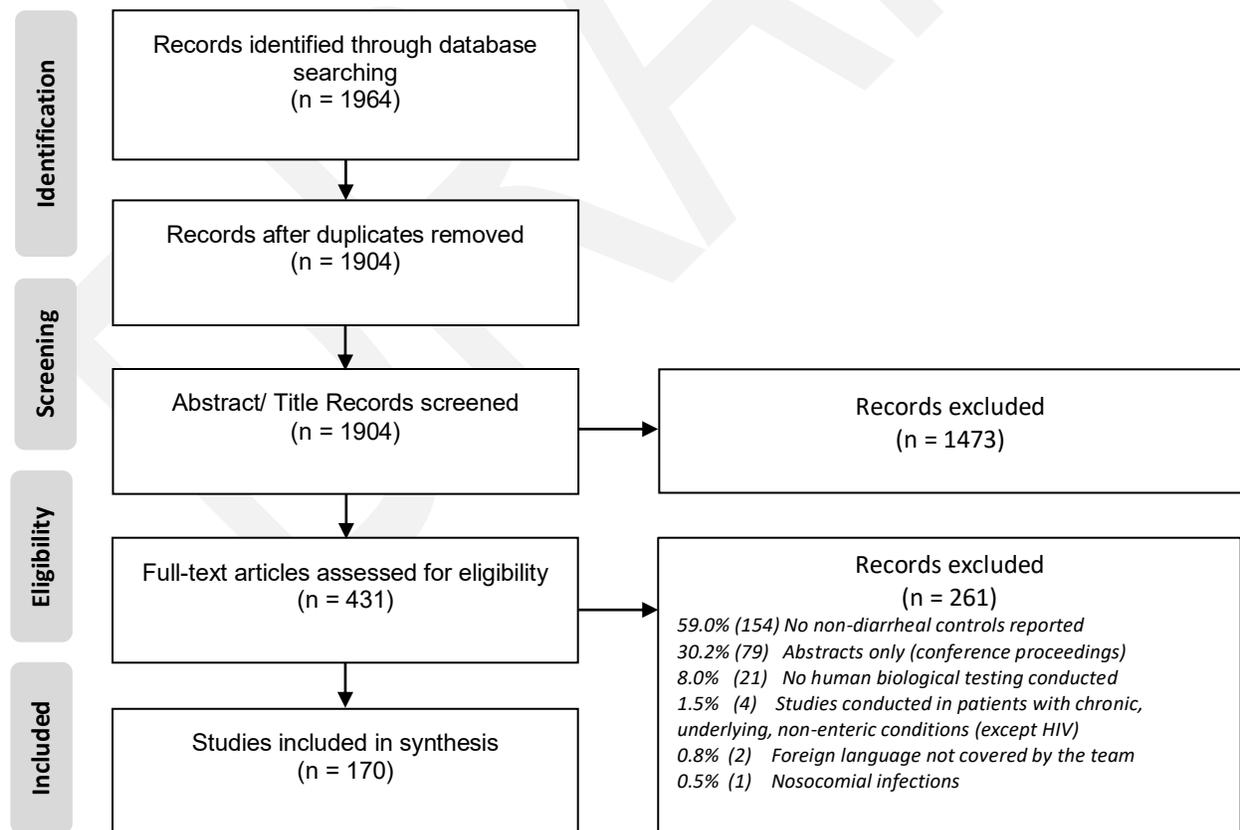
adjusted for pathogen detection method and study design as potential modifiers of the summary OR with conventional detection methods and case-controls study design as the reference groups. The final model was fit using the full dataset. Three sensitivity analyses examined results when the dataset excluded 1) outliers/influential observations, 2) RRs (i.e. used only ORs), and 3) observations that indicated coinfections. Analyses were run in R version 3.6.3 and using the *metafor* package. Data and model code are available at https://github.com/lopmanlab/enteropathogen_odds

Results

Systematic review

The systematic review identified 1,964 studies total and 1,904 unique studies after duplicates were removed. After title and abstract screening, 431 full text articles were further assessed for eligibility. Of these 431 full texts, over half (59.0%, n = 154) were excluded because no data on non-diarrheal controls were reported. 30.2% (n = 79) were excluded because only abstracts were available. Another 2.7% (n = 7) were excluded because the studies were conducted in patients with underlying, non-enteric conditions, were limited to nosocomial infections, or were published in a language not covered by the START team. The systematic review produced a final dataset of 1,951 observations from 185 studies (Figure 1).

Figure 1. Flowchart of the systematic review



Analytic dataset

In preparation for analysis, 594 observations were excluded because an effect estimate was unavailable from the publication and unable to be calculated. Another 32 observations were excluded because the pathogen was not specified or was not one of the 15 of interest. The final analytic dataset included 1,324 observations from 144 studies. Over 107,319 cases/diarrheal samples and 158,604 controls/non-diarrheal samples contributed to the dataset. Examination of outliers and influential observations identified 35 observations that were considered both outliers and influential.

The majority of effect estimates were ORs. Of the 1,324 observations, 181 (13.7%) were adjusted ORs, 181 (13.7%) unadjusted ORs extracted from the publications, 26 (2.0%) adjusted RRs, 28 (2.1%) unadjusted RRs, and 908 (68.6%) unadjusted ORs calculated from the data available in the publication. Heterogeneity by pathogen, assessed in unadjusted models, was considered “substantial” or “considerable” based on I^2 values (range: 52.4-99.3) when only ORs were considered (Supplemental Table 2).⁽¹⁵⁾ Only very small changes in I^2 values were observed when RRs were included in the models, so RRs were included in subsequent analyses.

The distribution of factors varied by pathogen (Table 1). Nearly three-quarters (n=973, 73%) of data were for children 0-5 years of age with a small proportion of data available among older children and adults (n=98, 7%). Over half of data were collected from studies in high child mortality settings (n=755, 57%). The most common method of pathogen detection was PCR (n=402, 30%), however, the distribution of detection methods varied substantially by pathogen. Over three-quarters (n=1,012, 76%) of observations were from case-control studies.

Model results

Forest plots from the unadjusted models showed a wide range of effect estimates for each pathogen (Supplement Figure 1-15). For all pathogens were associated with diarrhea except *Giardia lamblia*.

In adjusted models, ORs varied markedly by pathogen, many with wide confidence intervals (Table 2). Substantial differences in ORs were observed for some pathogens when comparing child mortality settings within the 0-5 age group. The OR for viral pathogens (except astrovirus) tended to be higher in very low/low child mortality settings when compared to high child mortality settings. The OR for adenovirus, for example, decreased from 3.6 (95% CI: 1.9, 6.8) to 1.3 (95% CI: 0.8, 2.1) in very low/low child mortality settings and high child mortality settings, respectively. This pattern was not consistent across bacterial or parasitic enteropathogens. For some pathogens, differences in ORs were apparent by age group. For rotavirus, for example, we found ORs of 7.1 (95% CI: 3.7, 13.3) and 5.9 (95% CI: 4.1, 8.4) among children 0-5 years of age, which decreased to 2.9 (95% CI: 1.3, 8.8) among older children and adults. The effect of PCR testing methods (versus conventional) varied by pathogen (Table 2).

When the adjusted models were run excluding influential outliers (n=35), the main results were largely unchanged (Supplemental Table 3) with three notable exceptions: 1) a decrease in the OR for norovirus among children in very low/low child mortality settings (OR = 3.2, 95% CI: 1.2,

84); 2) an increase in the OR for rotavirus among children in high child mortality settings (OR = 7.8, 95% CI: 5.2, 11.6); and 3) a decrease in the OR for adenovirus among children in high child mortality settings (OR = 0.5, 95% CI: 0.2, 1.1). Additional sensitivity analyses, including adjusted models excluding RRs (i.e. using only OR effect estimates, Supplemental Table 4) and excluding coinfections (Supplemental Table 5) did not substantially impact the results for most pathogens.

DRAFT

Table 1. Factor distributions by pathogen

	All Pathogens	Adenovirus	Astroviruses	Noroviruses	Rotavirus	Sapoviruses	<i>Aeromonas</i>	<i>Campylobacter</i>	<i>V. cholerae</i>	EPEC	ETEC	<i>Salmonella</i>
Total obs.	1324 (1.00)	64 (0.05)	50 (0.04)	85 (0.06)	119 (0.09)	44 (0.03)	16 (0.01)	148 (0.11)	6 (0.00)	97 (0.07)	222 (0.17)	65 (0.05)
Age group, n (%)												
0-5 years	973 (0.73)	55 (0.86)	44 (0.88)	59 (0.69)	87 (0.73)	42 (0.95)	12 (0.75)	105 (0.71)	5 (0.83)	78 (0.80)	184 (0.83)	43 (0.66)
Mixed	253 (0.19)	8 (0.13)	5 (0.10)	20 (0.24)	27 (0.23)	2 (0.05)	2 (0.13)	28 (0.19)	0 (0.00)	12 (0.12)	24 (0.11)	16 (0.25)
>5 years	98 (0.07)	1 (0.02)	1 (0.02)	6 (0.07)	5 (0.04)	0 (0.00)	2 (0.13)	15 (0.10)	1 (0.17)	7 (0.07)	14 (0.06)	6 (0.09)
Child mortality status, n (%)												
Very low	158 (0.12)	10 (0.16)	8 (0.16)	10 (0.12)	12 (0.10)	5 (0.11)	2 (0.13)	13 (0.09)	0 (0.00)	14 (0.14)	20 (0.09)	9 (0.14)
Low	411 (0.31)	12 (0.19)	7 (0.14)	32 (0.38)	38 (0.32)	10 (0.23)	5 (0.31)	41 (0.28)	3 (0.50)	67 (0.69)	89 (0.40)	19 (0.29)
High	755 (0.57)	42 (0.66)	35 (0.70)	43 (0.51)	69 (0.58)	29 (0.66)	9 (0.56)	94 (0.64)	3 (0.50)	16 (0.16)	113 (0.51)	37 (0.57)
Pathogen detection method, n (%)												
EIA	229 (0.17)	19 (0.30)	12 (0.24)	9 (0.11)	67 (0.56)	0 (0.00)	0 (0.00)	2 (0.01)	0 (0.00)	3 (0.03)	41 (0.18)	0 (0.00)
Culture	181 (0.14)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	5 (0.31)	70 (0.47)	3 (0.50)	3 (0.03)	3 (0.01)	31 (0.48)
Microscopy	81 (0.06)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.06)	6 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)	6 (0.09)
PCR	402 (0.30)	11 (0.17)	13 (0.26)	55 (0.65)	23 (0.19)	16 (0.36)	2 (0.13)	37 (0.25)	1 (0.17)	72 (0.74)	86 (0.39)	16 (0.25)
Other/Unsp ec	201 (0.15)	5 (0.08)	1 (0.02)	1 (0.01)	8 (0.07)	1 (0.02)	8 (0.50)	7 (0.05)	2 (0.33)	19 (0.20)	62 (0.28)	12 (0.18)
Missing	230 (0.17)	29 (0.45)	24 (0.48)	20 (0.24)	21 (0.18)	27 (0.61)	0 (0.00)	26 (0.18)	0 (0.00)	0 (0.00)	30 (0.14)	0 (0.00)
Study design, n (%)												
Cohort	312 (0.24)	4 (0.06)	4 (0.08)	13 (0.15)	33 (0.28)	4 (0.09)	3 (0.19)	39 (0.26)	1 (0.17)	21 (0.22)	99 (0.45)	12 (0.18)
Case-control	1012 (0.76)	60 (0.94)	46 (0.92)	72 (0.85)	86 (0.72)	40 (0.91)	13 (0.81)	109 (0.74)	5 (0.83)	76 (0.78)	123 (0.55)	53 (0.82)

EPEC, Enteropathogenic *E. coli*, ETEC, Enterotoxigenic *E. coli*

Table 2. Unadjusted and final random effects meta-analysis model results by pathogen

	Unadjusted and unstratified OR (95% CI)	0-5 years of age				> 5 years of age	
		Very low/low child mortality		High child mortality		All child mortality levels	
		OR (95% CI)	PCR OR (95% CI)	OR (95% CI)	PCR OR (95% CI)	OR (95% CI)	PCR OR (95% CI)
Adenovirus	2.1 (1.8, 2.6)	3.6 (1.9, 6.8)	1.5 (0.7, 3.1)	1.3 (0.8, 2.1)	2.6 (1.0, 7.3)		
Astrovirus	1.9 (1.6, 2.3)	0.8 (0.3, 2.1)	2.3 (0.9, 6.2)	1.7 (0.9, 3.1)	1.4 (0.6, 3.1)		
Norovirus	1.7 (1.4, 2.0)	7.7 (1.3, 44.8)	0.4 (0.1, 2.0)	2.9 (1.4, 6.0)	0.4 (0.2, 0.8)	3.2 (1.3, 7.6)	
Norovirus GI	1.4 (0.7, 3.0)	1.6 (0.5, 5.2)		0.8 (0.5, 1.2)		1.4 (0.4, 4.4)	
Norovirus GII	2.1 (1.6, 2.9)	1.8 (0.6, 5.1)	2.5 (0.8, 8.2)	1.7 (1.2, 2.4)	0.6 (0.2, 1.7)	3.4 (1.3, 8.8)	
Rotavirus	6.4 (5.6, 7.3)	7.1 (3.7, 13.3)	1.7 (0.6, 4.7)	5.9 (4.1, 8.4)	1.4 (0.9, 2.2)	2.9 (1.3, 6.5)	
Sapovirus	1.8 (1.5, 2.1)	3.5 (2.5, 4.8)	0.6 (0.4, 1.0)	1.5 (1.2, 1.9)	0.6 (0.3, 1.2)		
<i>Aeromonas</i>	2.4 (1.7, 3.3)	0.6 (0.1, 6.6)	2.2 (0.1, 60)	3.7 (3.2, 4.2)	0.6 (0.3, 1.2)		
<i>Campylobacter</i>	1.7 (1.5, 1.9)	2.4 (1.3, 4.6)	0.9 (0.3, 2.8)	1.7 (1.3, 2.2)	0.9 (0.6, 1.3)	5.1 (2.6, 10.0)	0.8 (0.3, 1.8)
<i>V. cholerae</i>	5.3 (1.6, 17.1)						
EPEC	1.4 (1.2, 1.6)	2.4 (0.5, 10.7)	0.6 (0.1, 2.7)	1.4 (0.9, 2.0)		2.0 (1.2, 3.4)	0.6 (0.3, 1.1)
ETEC	1.8 (1.6, 1.9)	0.5 (0.3, 0.9)	2.6 (1.5, 4.3)	1.5 (1.2, 1.9)	1.0 (0.7, 1.4)	1.4 (0.1, 24.7)	2.4 (0.1, 51.1)
ST ETEC	2.2 (1.9, 2.6)	1.3 (0.9, 1.7)	0.7 (0.4, 1.1)	1.6 (1.1, 2.5)	1.2 (0.7, 2.3)	4.8 (1.7, 14.2)	
LT ETEC	1.1 (1, 1.3.0)	0.4 (0.2, 1.0)	2.7 (1.2, 6.1)	1.0 (0.7, 1.4)	0.7 (0.5, 1.1)	1.2 (0.2, 6.3)	
<i>Salmonella</i>	1.9 (1.4, 2.5)	1.5 (1.0, 2.2)	0.7 (0.4, 1.1)	1.4 (0.8, 2.5)	1.4 (0.5, 4.0)	0.9 (0.6, 1.3)	10.2 (1.3, 82.7)
<i>Shigella</i>	5.5 (4.3, 7.1)	4.6 (2.2, 9.8)	0.3 (0.1, 0.9)	4.2 (2.4, 7.3)	0.5 (0.1, 2.3)	2.8 (1.5, 5.5)	
<i>Cryptosporidium</i>	2.2 (1.9, 2.4)	1.4 (0.8, 2.5)	0.9 (0.4, 2.0)	1.9 (1.7, 2.2)	1.8 (1.2, 2.5)	3.4 (1.2, 9.6)	0.5 (0.1, 2.2)
<i>E. histolytica</i>	1.3 (1.1, 1.6)	0.6 (0.2, 1.9)	1.1 (0.2, 5.2)	1.7 (1.1, 2.7)	0.8 (0.4, 1.7)	1.2 (0.6, 2.3)	
<i>Giardia lamblia</i>	1.0 (0.9, 1.1)	2.0 (1.3, 3.1)	0.8 (0.4, 1.8)	0.8 (0.6, 1.1)	1.0 (0.7, 1.4)	1.2 (0.6, 2.3)	2.6 (0.5, 13.6)

CI, confidence interval; EPEC, Enteropathogenic *E. coli*, ETEC, Enterotoxigenic *E. coli*; OR, odds ratio
Reference for adjusted models: conventional pathogen detection method, case-control study design

Discussion

In this systematic review and meta-analysis we have estimated ORs quantifying the association of pathogen detection in stool and diarrhea for 15 pathogens stratified by age group and child mortality setting. The association with diarrheal disease varied substantially by pathogen though all except *Giardia lamblia* showed an association with disease in unstratified and unadjusted analyses. In spite of the large dataset that included over 265,923 individuals/samples from 144 studies, summary ORs were generally accompanied by wide confidence intervals reflecting the considerable heterogeneity between studies. Summary ORs typically differed by age, child mortality status, or both, though not in a systematic way that is consistent with an overarching explanation.

The summary ORs produced in this analysis highlight an important limitation of models that use only one effect estimate to produce burden of disease estimates across diverse populations. The ORs estimated by age and setting in this meta-analysis may relate to epidemiologic and natural history/immunity characteristics unique to each pathogen such as frequency of exposure, asymptomatic infection, and development of immunity. For example, the lower OR for rotavirus in high child mortality settings compared to low child mortality settings may be reflective of high frequency of exposure and asymptomatic infection in settings with poorer sanitation and health infrastructure.(16,17) The strong immunity that develops with repeated rotavirus infections and age (16,17) is consistent with a substantially lower OR among older children and adults when compared to children 5 years of age and younger. Applying one OR across settings and age groups is likely not appropriate for several enteropathogens.

In comparison to the GEMS study, we found several similarities but also notable difference in the association between pathogen presence and diarrhea. We found adenovirus, norovirus, rotavirus, sapovirus, and *Shigella* to have the strongest associations with diarrhea among children 0-5 years of age. GEMS similarly found adenovirus, rotavirus and *Shigella* to be strongly associated with diarrhea, however, they also found strong associations with *Cryptosporidium* and ST ETEC. Astrovirus, ETEC, *Salmonella*, and *E. histolytica* showed very modest associations with diarrhea in our meta-analysis and were associated with diarrhea in GEMS. Similar to GEMS, we found *Aeromonas* to be associated with diarrhea only in certain settings.(18) The differences we found may be a result of different place/populations, time of study and study protocol including diagnostics.

These results should be considered in the context of important limitations. First, for all pathogens, our ORs are accompanied by wide CIs. These confidence intervals reflect both the limited sample size available for some groups (e.g. *V. cholerae*, *Aeromonas*, older children and adults) but also the wide range of effect estimates from the individual studies identified in the literature review. These wide CIs may be an appropriate reflection of the wide range effect estimates that should contribute to burden of disease models. Second, pathogen detection methods vary by study and may contribute to heterogeneity in effect estimates. The number of pathogens tested for and differences within these methods (e.g. different sensitivities or differences in PCR cycle threshold cut-offs used to define infection (18,19)) are not captured in this analysis. Relatedly, we collapsed the pathogen detection methods into categories in an effort to create reasonable sample sizes. This categorization may not be applicable across pathogens as

what is considered conventional detection may differ. Third, including results from cohort studies may be contributing to an age bias in our analysis. Cohort studies that do not control for age (i.e. are not age matched) may inappropriately reduce the effect estimate because carriage of pathogens generally increases with age.(18) We did not take into account differences in what factors were controlled for in studies that provided adjusted effect estimates. Interpretation of these results should take into account additional important factors. The ORs produced by this analysis are only part of the attributable fraction calculations and do not take into account prevalence of disease. Additionally, ORs may not accurately reflect association with disease.(20–22)

This meta-analysis demonstrates the variability in the association between pathogen detection and diarrheal disease by population, setting and study methodology, emphasizing the importance of building burden of disease estimates upon diverse data sources.(23) This analysis provides stratified ORs that can be integrated into or adapted for burden of disease models to strengthen their ability to capture a range of etiology estimates. More representative and accurate burden of disease estimates can then be used to inform decisions and prioritization of public health measures such as vaccine investment and policy.

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Supplemental Material

Systematic review methods

Search string for identifying literature in PubMed:

(diarrh*[tiab] OR gastroenteritis[tiab] OR enteric infection*[tiab])
AND
(aeromonas[tiab] OR entamoeba[tiab] OR cryptosporidium[tiab] OR giardia lamblia[tiab] OR adenovir*[tiab] OR astrovir*[tiab] OR sapovirus[tiab] OR norovirus[tiab] OR rotavirus[tiab] OR Escherichia coli[tiab] OR etec[tiab] OR epec[tiab] OR E. coli[tiab] OR cholera*[tiab] OR campylobacter[tiab] OR shigell*[tiab] OR salmonell*[tiab])
AND
(Case Control[tiab] OR Cohort[tiab])
AND
1990:3000[pdat]
NOT
(animals[mh] NOT humans[mh])

Inclusion criteria:

- Studies published between Jan 1, 1990 and July 9, 2019
- Studies performed in humans
- Studies with at least one of the pathogens of interest
- Either a case-control or a cohort study with a disease outcome of “diarrhea”
- Published in English, French, Spanish, Portuguese, Italian, or Chinese

Exclusion criteria:

- Studies in which non-diarrheal controls were not reported
- Studies which included participants with a broad case definition of gastroenteritis (i.e. diarrhea *or* vomiting) in which it was not possible to ascertain that all cases had diarrhea
- Studies limited to inclusion of participants with nosocomial infections
- Studies conducted in patients with chronic, underlying, non-enteric conditions (except participants a Human Immunodeficiency Virus diagnosis)
- Studies evaluating inflammatory bowel diseases
- Abstracts and conference proceedings
- Studies in which no human biological testing was conducted
- Publication was a systematic review

Supplemental Table 1. Pathogens of interest, relevant strains, and detection methods

Pathogen	Strains measured	Acceptable detection methods
<i>Salmonella (enterica) spp.</i> Or Salmonellosis	All <i>Salmonella</i> (enterica) spp. except <i>Salmonella typhi</i>	Isolation in salmonella agar, xylose-lysine-deoxycholate agar, Hektoen enteric agar, selenite enrichment for salmonella, or PCR
<i>Shigella spp.</i> Or Shigellosis	All	Isolation in shigella agar, xylose-lysine-deoxycholate agar, and Hektoen enteric agar, or PCR
<i>Campylobacter spp.</i> Or Campylobacter enteritis	All	Isolation by use of transport media with antibiotics (Skirrow's supplement or similar) and inoculation into 5% sheep blood with antibiotics (Butzlers supplement or similar), cultivated at 42C in micro-aerobic atmosphere, or PCR
<i>Vibrio cholerae</i> Or Cholera	O1 O139	Isolation by alkaline peptone water enrichment and subculture at 8 hrs into thiosulfate-citrate-bile salts -sucrose agar (TCBS), or PCR
Enterotoxigenic <i>Escherichia coli</i> (ETEC)	LT-ETEC ST-ETEC	Isolation from MacConkey agar and identification of ETEC by DNA probes or polymerase chain reaction (PCR) for heat-labile (LT) or heat stable (ST) toxins, cell cultures (Y1, CHO cells), ileal loop or mouse models
Enteropathogenic <i>Escherichia coli</i> (EPEC) Or Typical enteropathogenic <i>Escherichia coli</i> (tEPEC)	All	Isolation by the use of Hep 2 cell cultures or the presence of the plasmid for adherence (BFP) and the intimin gene (eae) identify in DNA probes or by PCR
Rotavirus Or Rotavirus gastroenteritis (RVGE)	All	Identification with enzyme-linked immunoassay (ELISA) or enzyme immune assay (EIA), electronic microscopy, or PCR
Calicivirus (Norovirus)	Group I Group II	Identification with enzyme immune assay (EIA) (including enzyme-linked immunoassay ELISA), or electronic microscopy, or PCR
Calicivirus (Sapovirus)	All	Identification with enzyme immune assay (EIA) (including enzyme-linked immunoassay ELISA), or electronic microscopy, or PCR
Astrovirus	All	Identification with enzyme immune assay (EIA) (including enzyme-linked

		immunoassay ELISA), or electronic microscopy, or PCR
Enteric adenovirus	40 41	Identification with enzyme immune assay (EIA) (including enzyme-linked immunoassay ELISA), or electronic microscopy, or PCR
<i>Giardia lamblia</i>	All	Identification by direct microscopic examination, or zinc-sulfate concentration from direct stools or by EIA/ELISA, or PCR
<i>Cryptosporidium spp.</i>	All	Identification by EIA/ELISA, or the modified Ziehl-Neelsen stain for microscopy, or PCR
<i>Entamoeba histolytica</i> (amoebiasis)	All	Identification by direct microscopic examination, or PCR
<i>Aeromonas spp</i>		

Data collection process:

Titles and abstracts were screened according to the inclusion and exclusion criteria by two independent reviewers. Any conflict between reviewers were resolved by reaching an agreement through discussion; if the difference persisted, the study was passed through to full-text review. At the full-text review stage, two independent reviewers also conducted screening, and conflicts were once again resolved through discussion. If a conflict persisted, the decision of inclusion was made by the senior faculty member. The abstract and full-text review was completed in *Covidence* Software (available at <https://www.covidence.org>).

Data extraction was done by a single reviewer per study using *REDCap* (available at <https://www.project-redcap.org/>). A random sample of 20 manuscripts targeted for data extraction were also extracted by a second reviewer to assess for errors. All questions relevant to data extraction were discussed during a weekly team meeting.

Quality control review:

Following the data extraction process, we completed a quality control review of 10% of all studies extracted (n=17). The quality control process assessed 1) the accuracy of data entered into the REDCap database and 2) whether any data entry errors contributed to risk measure calculations. Researchers reviewed studies originally extracted by team members other than themselves. Following quality control review, the team determined data entry errors were below the predetermined established threshold of 5%.

Insert unadjusted/unstratified forest plots here (supplemental figures 1-15)

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Supplemental Table 2. Heterogeneity (I^2) by pathogen and effect estimate type

	OR only	OR and RR
Adenovirus	60.0	59.7
Astrovirus	58.8	58.3
Norovirus	85.3	85.2
Rotavirus	94.5	94.7
Sapovirus	52.4	51.6
<i>Aeromonas</i>	63.7	69.1
<i>Campylobacter</i>	95.3	95.2
<i>V cholerae</i>	62.6	62.6
EPEC	67.1	65.0
ETEC	96.6	96.4
<i>Salmonella ent.</i>	98.9	98.9
<i>Shigella</i>	99.3	99.3
<i>Cryptosporidium</i>	69.6	69.6
<i>E. histolytica</i>	83.8	83.8
<i>Giardia lamblia</i>	87.2	87.2

EPEC, Enteropathogenic *E. coli*, ETEC, Enterotoxigenic *E. coli*, OR, odds ratio; RR, relative risk

Supplemental Table 3. Unadjusted and final random effects meta-analysis model results by pathogen, excluding influential outliers

	Unadjusted OR (95% CI)	0-5 years of age				> 5 years of age	
		Very low/low child mortality		High child mortality		All child mortality levels	
		OR (95% CI)	PCR OR (95% CI)	OR (95% CI)	PCR OR (95% CI)	OR (95% CI)	PCR OR (95% CI)
Adenovirus	2.0 (1.7, 2.4)	3.6 (1.9, 6.8)	1.5 (0.7, 3.1)	1.3 (0.9, 1.9)	0.5 (0.2, 1.1)		
Astrovirus	1.8 (1.5, 2.1)	0.8 (0.3, 2.1)	2.3 (0.9, 6.2)	1.7 (1.0, 2.8)	0.8 (0.4, 1.7)		
Norovirus	1.8 (1.6, 2.1)	3.2 (1.2, 8.4)	0.8 (0.3, 2.0)	2.9 (1.4, 6.0)	0.4 (0.2, 0.8)	3.2 (1.3, 7.6)	
Norovirus GI	1.4 (0.7, 3.0)	1.6 (0.5, 5.2)		0.8 (0.5, 1.2)		1.4 (0.4, 4.4)	
Norovirus GII	2.0 (1.5, 2.6)	1.8 (1.2, 2.7)	1.7 (1.1, 2.7)	1.7 (1.2, 2.4)	0.6 (0.2, 1.7)	3.4 (1.3, 8.8)	
Rotavirus	6.9 (6.0, 7.9)	6.5 (3.7, 11.2)	1.0 (0.4, 2.8)	7.8 (5.2, 11.6)	1.1 (0.7, 1.8)	2.9 (1.3, 6.5)	
Sapovirus	1.9 (1.6, 2.2)	3.5 (2.5, 4.8)	0.6 (0.4, 1.0)	1.7 (1.4, 2.0)	0.6 (0.4, 1.1)		
<i>Aeromonas</i>	2.4 (1.7, 3.3)	0.6 (0.1, 6.6)	2.2 (0.1, 60)	3.7 (3.2, 4.2)	0.6 (0.3, 1.2)		
<i>Campylobacter</i>	1.7 (1.6, 1.9)	2.5 (1.6, 3.8)	0.8 (0.4, 1.8)	1.5 (1.3, 1.8)	0.9 (0.7, 1.2)	5.1 (2.6, 10.0)	0.8 (0.3, 1.8)
<i>V. cholerae</i>	3.4 (1.3, 9.0)						
EPEC	1.4 (1.2, 1.6)	2.2 (0.5, 9.4)	0.6 (0.1, 2.6)	1.4 (0.9, 2.0)		2.0 (1.2, 3.4)	0.6 (0.3, 1.1)
ETEC	1.7 (1.6, 1.9)	0.5 (0.3, 0.9)	2.6 (1.5, 4.3)	1.5 (1.3, 1.9)	1.0 (0.7, 1.3)	1.4 (0.1, 24.7)	2.4 (0.1, 51.1)
ST ETEC	2.1 (1.9, 2.4)	1.3 (0.9, 1.7)	0.7 (0.4, 1.1)	1.7 (1.2, 2.4)	1.3 (0.8, 2.0)	4.8 (1.7, 14.2)	
LT ETEC	1.1 (1.0, 1.3)	0.4 (0.2, 1.0)	2.7 (1.2, 6.1)	1.0 (0.7, 1.4)	0.7 (0.5, 1.1)	1.2 (0.2, 6.3)	
<i>Salmonella</i>	1.8 (1.4, 2.3)	1.5 (1.0, 2.2)	0.7 (0.4, 1.1)	1.4 (0.8, 2.3)	1.4 (0.6, 3.5)	0.9 (0.6, 1.3)	10.2 (1.3, 82.7)
<i>Shigella</i>	4.9 (3.7, 6.4)	4.6 (2.2, 9.8)	0.3 (0.1, 0.9)	4.2 (2.3, 7.6)	0.5 (0.1, 2.6)	2.8 (1.5, 5.5)	
<i>Cryptosporidium</i>	2.2 (2.0, 2.4)	1.4 (0.8, 2.5)	0.9 (0.4, 2.0)	2.0 (1.7, 2.3)	1.7 (1.2, 2.3)	3.4 (1.2, 9.6)	0.5 (0.1, 2.2)
<i>E. histolytica</i>	1.4 (1.2, 1.7)	0.6 (0.2, 1.9)	1.1 (0.2, 5.2)	1.7 (1.1, 2.7)	0.8 (0.4, 1.7)	1.2 (0.6, 2.3)	
<i>Giardia lamblia</i>	1.0 (0.9, 1.1)	1.3 (0.8, 2.1)	1.2 (0.6, 2.6)	1.1 (0.8, 1.4)	0.9 (0.6, 1.3)	1.4 (0.7, 2.8)	2.2 (0.4, 11.2)

CI, confidence interval; EPEC, Enteropathogenic *E. coli*; ETEC, Enterotoxigenic *E. coli*; OR, odds ratio

Reference for adjusted models: conventional pathogen detection method, case-control study design

Supplemental Table 4. Unadjusted and final random effects meta-analysis model results by pathogen, excluding risk ratio effect estimates

	Unadjusted OR (95% CI)	0-5 years of age				> 5 years of age	
		Very low/low child mortality OR (95% CI)	PCR OR (95% CI)	High child mortality OR (95% CI)	PCR OR (95% CI)	All child mortality levels OR (95% CI)	PCR OR (95% CI)
Adenovirus	2.1 (1.7, 2.6)	4.3 (2.1, 8.9)	1.1 (0.5, 2.6)	1.3 (0.8, 2.1)	2.6 (1.0, 7.3)		
Astrovirus	1.9 (1.6, 2.3)	0.6 (0.1, 2.4)	3.3 (0.7, 15.9)	1.7 (0.9, 3.1)	1.4 (0.6, 3.1)		
Norovirus	1.7 (1.4, 2)	10.0 (1.7, 57.6)	0.3 (0.1, 1.5)	2.9 (1.4, 6.0)	0.4 (0.2, 0.8)	3.2 (1.3, 7.6)	
Norovirus GI	1.4 (0.7, 3)	1.6 (0.5, 5.2)		0.8 (0.5, 1.2)		1.4 (0.4, 4.4)	
Norovirus GII	2.1 (1.6, 2.9)	1.8 (0.6, 5.1)	2.5 (0.8, 8.2)	1.7 (1.2, 2.4)	0.6 (0.2, 1.7)	3.4 (1.3, 8.8)	
Rotavirus	7.1 (6.2, 8.2)	6.8 (3.4, 13.6)	2 (0.5, 8.0)	5.9 (4.1, 8.4)	1.4 (0.9, 2.2)	2.9 (1.3, 6.5)	
Sapovirus	1.7 (1.4, 2.1)	3.5 (2.5, 4.8)	0.6 (0.4, 1)	1.5 (1.2, 1.9)	0.6 (0.3, 1.2)		
<i>Aeromonas</i>	2.2 (1.5, 3.3)	0.6 (0.1, 6.6)	2.2 (0.1, 60)	2.8 (1.9, 4.1)	0.8 (0.3, 1.7)		
<i>Campylobacter</i>	1.7 (1.5, 1.9)	2.4 (1.3, 4.6)	0.9 (0.3, 2.8)	1.7 (1.3, 2.2)	0.9 (0.6, 1.3)	5.1 (2.6, 10.0)	0.8 (0.3, 1.8)
<i>V. cholerae</i>	5.3 (1.6, 17.1)						
EPEC	1.4 (1.2, 1.7)	2.2 (0.5, 10.1)	0.6 (0.1, 3.0)	1.4 (0.9, 2.0)		2.0 (1.2, 3.4)	0.6 (0.3, 1.1)
ETEC	1.8 (1.7, 2.0)	0.5 (0.3, 0.9)	2.6 (1.5, 4.4)	1.6 (1.3, 2.1)	0.9 (0.6, 1.3)	1.4 (0.1, 24.7)	2.4 (0.1, 51.1)
ST ETEC	2.4 (2.0, 2.8)	1.3 (0.9, 1.7)	0.6 (0.3, 1.2)	2.0 (1.3, 3.3)	0.9 (0.5, 1.8)	4.8 (1.7, 14.2)	
LT ETEC	1.1 (1.0, 1.2)	0.4 (0.2, 1.1)	2.7 (1.2, 6.1)	1.0 (0.7, 1.4)	0.7 (0.5, 1.1)	1.2 (0.2, 6.3)	
<i>Salmonella</i>	1.9 (1.4, 2.5)	1.5 (1.0, 2.2)	0.7 (0.4, 1.1)	1.4 (0.8, 2.5)	1.4 (0.5, 4.0)	0.9 (0.6, 1.3)	10.2 (1.3, 82.7)
<i>Shigella</i>	5.5 (4.3, 7.1)	4.6 (2.2, 9.8)	0.3 (0.1, 0.9)	4.2 (2.4, 7.3)	0.5 (0.1, 2.3)	2.8 (1.5, 5.5)	
<i>Cryptosporidium</i>	2.2 (1.9, 2.4)	1.4 (0.8, 2.5)	0.9 (0.4, 2.0)	1.9 (1.7, 2.2)	1.8 (1.2, 2.5)	3.4 (1.2, 9.6)	0.5 (0.1, 2.2)
<i>E. histolytica</i>	1.3 (1.1, 1.7)	0.6 (0.2, 1.9)	1.1 (0.2, 5.2)	1.7 (1.1, 2.7)	0.8 (0.4, 1.7)	1.2 (0.6, 2.3)	
<i>Giardia lamblia</i>	1.0 (0.9, 1.1)	2.0 (1.3, 3.0)	0.8 (0.4, 1.8)	0.8 (0.6, 1.1)	1.0 (0.7, 1.4)	1.2 (0.6, 2.3)	2.6 (0.5, 13.6)

CI, confidence interval; EPEC, Enteropathogenic *E. coli*; ETEC, Enterotoxigenic *E. coli*; OR, odds ratio
Reference for adjusted models: conventional pathogen detection method, case-control study design

Supplemental Table 5. Unadjusted and final random effects meta-analysis model results by pathogen, excluding coinfections indicated by authors

	Unadjusted OR (95% CI)	0-5 years of age				> 5 years of age	
		Very low/low child mortality OR (95% CI)	PCR OR (95% CI)	High child mortality OR (95% CI)	PCR OR (95% CI)	All child mortality levels OR (95% CI)	PCR OR (95% CI)
Adenovirus	2.4 (1.7, 3.4)	3.6 (1.9, 6.8)	1.5 (0.7-3.1)	1.2 (0.5, 2.8)	2.5 (0.4-13.9)		
Astrovirus	1.9 (1.5, 2.5)	0.8 (0.3, 2.1)	2.3 (0.9-6.2)	1.6 (0.7, 4.0)	1.3 (0.4-4.3)		
Norovirus	1.7 (1.4, 2.1)	7.7 (1.3, 44.9)	0.4 (0.1-2.0)	2.9 (1.5, 5.7)	0.4 (0.2-0.7)	3.2 (1.3, 7.6)	
Norovirus GI	1.4 (0.7, 3.0)	1.6 (0.5, 5.2)		0.8 (0.5, 1.2)		1.4 (0.4, 4.4)	
Norovirus GII	3.0 (1.8, 5.1)	4.6 (2.6, 7.9)		0.9 (0.7, 1.2)		3.4 (1.3, 8.8)	
Rotavirus	6.7 (5.7, 7.8)	7.1 (3.7, 13.4)	1.7 (0.6-4.8)	5.7 (4.0, 8.1)	1.4 (0.9-2.2)	2.9 (1.3, 6.5)	
Sapovirus	2.1 (1.5, 2.9)	2.1 (1.5, 2.9)		0.9 (0.5, 1.9)			
<i>Aeromonas</i>	2.5 (1.8, 3.5)			3.7 (3.2, 4.2)	0.6 (0.3-1.2)		
<i>Campylobacter</i>	1.7 (1.5, 2.0)	2.5 (1.3, 5.0)	0.8 (0.2-2.8)	1.6 (1.2, 2.1)	0.8 (0.6-1.3)	5.1 (2.6, 10.0)	0.8 (0.3-1.8)
<i>V. cholerae</i>	7.3 (2.1, 25.3)						
EPEC	1.4 (1.2, 1.7)	2.4 (0.5, 11.0)	0.6 (0.1-2.8)	1.4 (0.9, 2.0)		2.0 (1.2, 3.4)	0.6 (0.3-1.1)
ETEC	1.7 (1.5, 1.9)	0.5 (0.3, 0.9)	2.6 (1.5-4.3)	1.4 (1.1, 1.8)	1.1 (0.8-1.5)	1.4 (0.1, 24.7)	2.4 (0.1-51.1)
ST ETEC	1.9 (1.6, 2.4)	1.0 (0.6, 1.9)	0.7 (0.4-1.1)	1.9 (1.1, 3.3)	1.2 (0.6-2.3)	4.8 (1.7, 14.2)	
LT ETEC	1.1 (1.0, 1.3)	0.4 (0.2, 1.0)	2.7 (1.2-6.1)	1.0 (0.7, 1.4)	0.7 (0.5-1.1)	1.2 (0.2, 6.3)	
<i>Salmonella</i>	1.9 (1.4, 2.5)	1.5 (1.0, 2.2)	0.7 (0.4-1.1)	1.2 (0.7, 2.3)	1.6 (0.5-4.5)	0.9 (0.6, 1.3)	10.2 (1.3-82.7)
<i>Shigella</i>	6.0 (4.4, 8.1)	4.6 (2.2, 9.8)	0.3 (0.1-0.9)	4.2 (2.4, 7.5)	0.5 (0.1-2.3)	2.8 (1.5, 5.5)	
<i>Cryptosporidium</i>	2.1 (1.9, 2.4)	1.5 (0.8, 2.8)	0.9 (0.4-1.8)	1.9 (1.7, 2.2)	1.8 (1.3-2.5)	3.4 (1.2, 9.6)	0.5 (0.1-2.2)
<i>E. histolytica</i>	1.3 (1.0, 1.7)	0.6 (0.2, 1.9)	1.1 (0.2-5.2)	1.7 (1.1, 2.7)	0.8 (0.4-1.7)	1.2 (0.6, 2.3)	
<i>Giardia lamblia</i>	1.0 (0.9, 1.1)	2.0 (1.3, 3.0)	0.8 (0.4-1.9)	0.8 (0.6, 1.1)	1.0 (0.7-1.4)	1.2 (0.6, 2.3)	2.6 (0.5-13.6)

CI, confidence interval; EPEC, Enteropathogenic *E. coli*; ETEC, Enterotoxigenic *E. coli*; OR, odds ratio
Reference for adjusted models: conventional pathogen detection method, case-control study design



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The impoverished gut—a triple burden of diarrhoea, stunting and chronic disease

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Abstract

More than one-fifth of the world's population live in extreme poverty, where a lack of safe water and adequate sanitation enables high rates of enteric infections and diarrhoea to continue unabated. Although oral rehydration therapy has greatly reduced diarrhoea-associated mortality, enteric infections still persist, disrupting intestinal absorptive and barrier functions and resulting in up to 43% of stunted growth, affecting one-fifth of children worldwide and one-third of children in developing countries. Diarrhoea in children from impoverished areas during their first 2 years might cause, on average, an 8 cm growth shortfall and 10 IQ point decrement by the time they are 7–9 years old. A child's height at their second birthday is therefore the best predictor of cognitive development or 'human capital'. To this 'double burden' of diarrhoea and malnutrition, data now suggest that children with stunted growth and repeated gut infections are also at increased risk of developing obesity and its associated comorbidities, resulting in a 'triple burden' of the impoverished gut. Here, we Review the growing evidence for this triple burden and potential mechanisms and interventions that must be understood and applied to prevent the loss of human potential and unaffordable societal costs caused by these vicious cycles of poverty.

Introduction

The fact that children who live in poverty have disproportionately high levels of hunger and disease is an unacceptable reality. The World Bank estimates that 1.3 billion people (>20% of the world's population) live in extreme poverty, most of whom are women and children who survive on less than US\$1.25 per day.^{1,2} The gut, as the single largest interface of humans with their external environment, is unique among organ systems in its role in, and responses to, the challenges of diseases caused by poverty, undernutrition and their combinations. Highlighting this importance, the application of basic discoveries in intestinal sodium–glucose cotransport to oral rehydration therapy (ORT) has prevented millions of deaths from diarrhoea in the past four decades. However, the persistence of poor sanitation

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and crowded living conditions in developing countries continues to contribute to high rates of enteric infections, particularly among young children.³

When enteric infections lead to overt diarrhoea, they can cause a high mortality rate. Indeed, this rate exceeded 13.6 per 1,000 children <5 years (>23 per 1,000 children <1 year of age) in studies reviewed from 1955 to 1979, although it has improved to <5 per 1,000 children <5 years (<8 per 1,000 <1 year of age) since 1990, largely as a result of ORT.³ However, high morbidity rates of diarrhoeal illnesses continue unabated,³ and children living in developing areas continue to experience ongoing enteric infections, which contribute to long-term effects of stunted growth and impaired cognitive development. This interaction between infections and malnutrition has been recognized as a vicious cycle since classic work conducted by Scrimshaw *et al.*⁴ and Mata⁵ during the 1960s and 1970s. These studies showed that repeated diarrhoeal illnesses as well as other common childhood infections progressively altered the normal growth trajectories of children. Ultimately, poor growth and impaired cognitive development have been linked to societal effects on both productivity and ‘human capital’—a term used by Victora *et al.*⁶ to reflect long-term morbidity from impaired cognition and reduced productivity. Although the term ‘double burden’ has been applied to the two problems of malnutrition and obesity occurring in developing areas, we suggest that these problems are both related to early childhood enteric infections. Hence, we propose that the link between enteric infections and child growth and development is a double burden of enteric infections and malnutrition, and the potential link of both of these factors to obesity in later life is an interrelated ‘triple burden’ (Figure 1).⁷

Mounting evidence now indicates that further links exist between enteric infections and poverty. Indeed, infections and stunting in early childhood might predispose to greater risk of obesity, type 2 diabetes, metabolic syndrome or cardio vascular disease (CVD) later in life, which are usually considered as major noncommunicable diseases. Therefore, potential, as yet not well defined, ‘thrift’ genes, which have a role in promoting fat storage to protect against starvation and signalling pathways responsible for catch-up growth—a term used to describe accelerated child growth after resolution of infections or under nutrition providing that diarrhoea burdens do not continue—(Figure 2) might increase an individual’s, and potentially their children’s risk, of obesity and associated comorbidities.^{8,9}

Here, we Review the epidemiology, intestinal pathophysiology and interventions for the double burden of infection and malnutrition, in which enteric infections and undernutrition follow each other in a vicious cycle to result in adverse acute and chronic health and developmental outcomes in children. We highlight emerging evidence for the triple burden of disease in survivors of the vicious enteric infection–malnutrition cycle.

The double burden

The concept of an impoverished gut provides compelling targets for potential interventions to break the infection–malnutrition cycle. Evidence for enteropathy (such as blunted small intestinal villi with lamina propria inflammation), functional impairment with increased intestinal permeability leading to bacterial or lipopolysaccharide translocation from the gut to the blood, as well as chronic systemic immune activation, has arisen from clinical and animal model studies of undernutrition and enteric infections. Lindenbaum and colleagues¹⁰⁻¹² described malabsorption, weight loss and jejunitis in Peace Corps volunteers under going intestinal biopsies in the 1960s. This phenotype has come to be known as ‘environmental enteropathy’ or the ‘impoverished gut’ because of clear relationships between the setting itself (that is, tropical, developing areas with endemic enteric infections), the histological findings and the effects on gut function.

A review of work by Lunn and co-workers¹³⁻¹⁶ in Gambian children showed that mucosal enteropathy, as assessed by the lactulose:mannitol urinary excretion ratio—an indicator of intestinal permeability per available surface area—explained up to 43% of observed growth faltering.^{15,17} Furthermore, this increased intestinal permeability was a chronic condition, far exceeding the 7.3% of days over their first 2 years of life that these children spent with diarrhoea. Indeed, their lactulose:mannitol excretion ratios were associated with growth suppression on 76% of days during this period. In a follow-up study, total IgG antibody and anti-endotoxin core antibody (EndoCAB) were assessed as a marker of intestinal bacterial endotoxin translocation across a disrupted intestinal barrier.¹⁸ The weight-for-age z-score (WAZ) and height-for-age z-score (HAZ) anthropometry, lactulose:mannitol ratio and plasma EndoCAB levels were all similar in Gambian and UK infants at 2 months of age.¹⁸ By 15 months of age, however, the Gambian children's HAZ and WAZ had fallen from mean values of -0.6 to -1.8 , and -0.4 to -2.4 , respectively; their lactulose:mannitol ratio almost tripled (by contrast, this ratio declined in UK children); and mean IgG and EndoCAB concentrations were twofold and fivefold higher in Gambian children than UK children. Lactulose:mannitol ratios, total IgG and EndoCAB concentrations were all correlated with each other and were negatively correlated with linear and ponderal growth, accounting for 51–56% of linear growth shortfalls.^{17,18}

The causal relationships between infection and mal nutrition have been confirmed in mouse models in which enteric infections with *Cryptosporidium* or enteroaggregative *E. coli* species caused enteropathy and growth impairment.¹⁹⁻²¹ In addition, as infected mice showed heavy pathogen burdens and worsened intestinal damage and weight loss when malnourished (that is, milk deprived or protein deprived), these findings support causal relationships in the vicious cycle of enteric infection and malnutrition (Figure 1).¹⁹⁻²¹ Furthermore, weaning undernutrition itself perturbed small intestinal morphology and barrier function in a mouse model.²² Thus, although overt diarrhoea could account for ~25% of stunted growth,²³ this vicious cycle of enteric infection and malnutrition often 'smoulders' as enteropathy for extended periods of time without overt diarrhoea in young children exposed to multiple enteric pathogens when adequate water and sanitation are lacking. Enteric infections in these children could therefore account for around half of all stunting, as well as the lasting effects on development.

This double burden stunts not only a child's growth, but also cognitive development and full human potential, as well as the economic productivity and progress of the community. Christopher Eppig²⁴ suggests that recognized improvements in national IQ seen with development of nations (the so-called Flynn effect) are a result of reductions in the burden of infectious diseases even when controlling for gross domestic product per capita and for malnutrition. Clearly a link exists between common, potentially preventable, infectious diseases (especially in early childhood), undernutrition and impaired cognitive development (Figure 1). Whether early childhood enteric infections have a direct effect on cognitive development that is independent of the effects through malnutrition (most notably HAZ at 2 years, HAZ-2) remains unclear. In either case, the importance of interventions that interrupt the vicious diarrhoea–malnutrition cycle and its double burden remains paramount.

Vicious cycles of poverty

Malnutrition, which can occur following famines and food shortages, illustrates the potential relevance of infections of poverty as the impoverished gut becomes impaired in its absorptive capacity by multiple and repeated enteric infections from contaminated water and inadequate sanitation. Indeed, Eppig²⁴ suggests that infections themselves blunt human development. We suggest that the disrupted intestinal barrier and blunted absorptive function and common mucosal or even systemic inflammation that are seen with repeated

enteric infections are pivotal points in the increasingly appreciated vicious cycles of poverty. In addition to mortality from acute enteric infections, early childhood infections are also linked with more than half of the 7.6 million deaths in children <5 years of age, caused in part by malnutrition and the life-long consequences of the moderate–severe stunting that occurs in 178 million children worldwide (20% of children worldwide; 32% of children in developing countries)²⁵⁻³² (Box 1). From early childhood, diarrhoea accounts for substantial amounts of stunting observed worldwide. Indeed, a 20-year multicountry analysis revealed that five or more diarrhoeal infections in the first 2 years of life accounted for 25% of all stunting observed; moreover, every five diarrhoeal episodes increased stunting risk by 13%.²³ These data indicate that diarrhoea and stunting combine to dramatically increase the global mortality, often seen with diseases such as pneumonia and malaria, as well as hinder human capital.⁶ The potential added burden of obesity, type 2 diabetes, and CVD (the triple burden) further compounds individual and societal costs (Figure 3).

Stunting and cognitive impairment

Evidence for role of enteric infections

The effects of enteric infections on stunting and cognitive impairment have been extensively reviewed elsewhere.^{6,7} Below, we summarize the key points of evidence in support of these relationships.

Stunting

Evidence for the effect of diarrhoea or enteric infections on growth failure stems from the classic studies in Guatemala, which showed that impoverished children often start off on a fairly good growth trajectory, similar to healthy children, only to be reduced after repeated diarrhoeal episodes and other infections (including respiratory as well as enteric infections) during the first 2 years of life.^{4,5,33,34} This pattern has also been observed in multiple studies over several decades in populations throughout Asia, Africa and Latin America.^{35,36} Early childhood diarrhoea was shown to have a specific effect on subsequent growth impairment in prospective studies in Northeast Brazil, Peru, Bangladesh, Guinea-Bissau and Ghana.^{23,37-41} Indeed, it is the crucial catch-up growth that is linearly ablated by progressively heavier diarrhoeal burdens (Figure 2) and malnourished children are at greater risk of both increased diarrhoea frequency and duration than better nourished children.^{5,8,37,42-44} As noted above, findings from mouse models have further confirmed the vicious infection–malnutrition cycle with specific pathogens.^{20,21,45}

Stunting and cognition

The cognitive impairment associated with stunting at 2 years of age is clear from studies in the Philippines, Brazil, Peru, Jamaica, Thailand, Bangladesh and Guatemala.⁴⁶⁻⁵⁹ Not only does stunting delay schooling (with progressive delays of age at starting school by 1 year to 3 years in children with mild-severe stunting), but the cognitive (IQ) benefit of schooling is also reduced >25% by 11 years by stunting in early life (that is, HAZ-2 <2).⁵² Furthermore, a follow-up study was conducted in 1,448 individuals 25–35 years after feeding studies were carried out in four villages in Guatemala. The original feeding studies were conducted from 1969 to 1977 when the children were 0–7 years; children were randomly assigned to receive a calorie-protein supplement (91 kcal and 6.4 g protein per 100 ml) versus 33 kcal and no protein supplement in age-matched controls. Supplementation improved IQ (10%), wages (46%) and reading and schooling (8–20%) when compared with controls when assessed by Raven testing and follow-up visits, but only if the supplement was given in the first 2–3 years of life.^{60,61}

Cognition

Whether enteric infections have an independent effect on cognitive development, through such mechanisms as chronic inflammation,^{46,53,54,62-66} in addition to their unambiguous indirect effects through growth impairment remains somewhat controversial. Fischer and colleagues have reviewed this evidence from careful studies done over time in Brazil, Philippines, Guatemala and Peru.⁶⁷ Similar to Eppig's suggestion that infections associate with impaired IQ independently of gross domestic product and education as well as malnutrition,²⁴ we find that associations of early childhood diarrhoea with later cognitive impairment might include both stunting-dependent as well as stunting-independent correlations (R. L. Guerrant, A. A. M. Lima and R. C. Pinkerton, personal communication). However, many of the cognitive outcomes in studies of early childhood illness reflect the multifactorial origin of developmental delay that includes such factors as birthweight, household stimulation, and maternal behaviour. More studies are needed to clarify potential direct, as well as indirect effects, and mechanisms by which early childhood enteric infections might impair cognitive development.

The triple burden

Chronic, noncommunicable diseases, such as CVD and type 2 diabetes, have increased in incidence in the developing and the developed world, resulting in a growing need for resources.^{68,69} An emerging line of research links poor growth in foetal and early life to an increased risk of adult chronic disease. This research—often referred to as the developmental origins of health and disease⁶⁹—had its beginnings in the findings of David Barker, who demonstrated that children born small for gestational age had increased risk of cardiovascular mortality, as well as multiple risk factors for CVD and type 2 diabetes.⁷¹⁻⁷⁶ Nutrient deprivation is believed to have a role in these processes, as supported by data from the Dutch Hunger Winter of 1944–1945, when individuals, including pregnant women, had to survive on minimal food rations imposed by the government owing to food scarcity.⁷⁷ Children born from these pregnancies were more likely than those conceived after the famine to become obese and hypertensive as adults.⁷⁸ Although the mechanism behind these findings is under continued investigation, multiple researchers have hypothesized that nutrient deprivation in particular, as well as other potential insults including maternal stress⁷⁸ and inflammation,⁷⁹ during gestation result in epigenetic changes such as DNA methylation and histone acetylation, modifying expression of genes related to metabolism⁸⁰ and growth, particularly insulin growth factor-2 (IGF-2)⁷⁴ to prepare the individual for potential future caloric deficiencies. In contrast to the thrifty genotype, in which individuals inherit specific alleles contributing to early life metabolic advantage, the alteration in gene expression as a result of these epigenetic changes are hypothesized to produce a thrifty phenotype.⁹

Adult chronic disease risk Stunting

Research over the past 10 years has expanded the concept of the developmental origins of health and disease to investigate whether caloric deprivation, protein or micronutrient deficiencies, infection or other challenges in young children might affect long-term risk of future adult disease. Currently, the majority of published data on this topic relate to poor weight gain in early childhood and are centred on data from large retrospective evaluations of childhood weight patterns among individuals diagnosed in adulthood with prediabetes (glucose intolerance) or CVD. In these studies, individuals who developed these diseases had on average poor weight gain in early childhood (up to 2–3 years old), followed by rapid weight gain in later childhood starting around age 6 years.⁸¹⁻⁸³ These studies followed long-term associations of low BMI in early life, without assessment of the aetiology behind the poor weight gain.⁸³ One of the studies was performed in New Delhi, India, which, during

the 1960s (when the study was conducted), had a high prevalence of enteric infections; whether enteric disease contributed to the children's poor weight gain, however, remains unclear.⁸² Overall, these data provide inferential evidence of a causal link between poor early weight gain and later disease, although genetic factors could also have influenced both poor early childhood weight gain and later adult disease.

Further links between poor early weight gain and later disease are suggested by findings from cross-sectional studies, which demonstrate that stunting (as assessed by HAZ <2 for children or adults from regions with high rates of enteric infection) is associated with central obesity, high body fat, insulin resistance, hypertension, and low HDL cholesterol in adults.⁸⁴⁻⁸⁷ Changes related to stunting in blood pressure levels in both sexes⁸⁸ and body habitus in girls⁸⁹ were already noted in later childhood, whereas, among adults, most of the findings (with the exception of central obesity)⁸⁷ were only noted among women^{84,85} and not men,⁸⁶ suggesting that stunting-related alterations can be apparent early in life and might be affected by gender. The studies cited here were all performed in developing areas with a high prevalence of enteric infections, raising the potential that poor early weight gain was related to underlying enteropathy. Nevertheless, these studies are based on the evaluation of growth alone (and not enteric disease) and their cross-sectional nature has considerable drawbacks. There might have been confounding issues, such as differences in family environments, which influence both early growth and adult metabolic disease. Other studies performed during childhood—both using longitudinal and cross-sectional approaches—have not noted links between childhood stunting and later obesity^{90,91} and insulin resistance⁹² during childhood, emphasizing that before manifestation many of these effects might require additional metabolic challenge such as that seen during puberty and with lifestyle changes in early adulthood.

Perhaps the most notable evidence for the link between childhood growth and adult disease risk comes from long-term studies in developing countries evaluating future risk factors among children who exhibited poor growth in childhood. One such study from New Delhi, India, found negative correlations between BMI at age 2 years and glucose intolerance (a strong risk factor for future diabetes) at age 30 years.⁹³ After adjustment for adult BMI, low BMI at age 2 years was strongly linked with insulin resistance, high triglyceride levels, hypertension, glucose intolerance and metabolic syndrome (a cluster of risk factors for CVD that frequently precede type 2 diabetes).⁹³ Similarly, following adjustment for adult BMI, a multicountry analysis of long-term cohorts from five developing countries in four continents revealed links between low BMI at 2 years and high levels of fasting glucose and blood pressure at a mean age of 23 years of follow-up.⁶

Overall, the evidence of poor early weight gain among individuals who go on to develop CVD and glucose intolerance, associations between stunting and risk factors for CVD, and the association of low BMI at 2 years with CVD risk factors provides a basis for relationships between stunting or low BMI in childhood and risk of adult obesity and CVD (Figure 3). However, the causative mechanisms explaining these relationships remain uncertain, although the potential exists that nutrient deprivation in early life is associated with epigenetic changes in a manner similar to what has been postulated to link low birth weight and future CVD risk. Although this nutrient deprivation contributing to poor childhood growth could theoretically be a result of food scarcity among affected children, the strong link between childhood enteric disease and stunting discussed above is also likely to contribute.

Early infections

Additional data move beyond evaluating the risk of adult chronic diseases based on poor gains in weight or height in childhood to instead investigate potential links of childhood

disease with the increase in adult risk factors. Follow-up of children in the Nutrition Institute of Central America and Panama (INCAP) revealed links between early childhood diarrhoea and low HDL cholesterol levels, elevated fasting glucose levels, and abdominal obesity in adulthood (aged 25–37 years).^{94,95} Febrile illness in early childhood was also associated with an increased risk of low HDL cholesterol levels, high levels of tri glycerides and metabolic syndrome in adulthood at ages 25–42 years.⁹⁵ The association of diarrhoea frequency with adult CVD risk factors provides early evidence that childhood enteric infections have a direct link with adult CVD risk. As such, the previously mentioned links between adult CVD risk factors and low BMI at age 2 years could be related to upstream events such as childhood enteric disease (Figure 3). The association with febrile illnesses raises the possibility that inflammatory cytokines have a role in epigenetic changes, as has been demonstrated in the regulation of blood pressure.⁷⁹ Nevertheless, further research is clearly needed to solidify these associations and clarify potential mechanisms, including whether aetiologic roots, including calorie deprivation, deficiencies in protein or micronutrients, inflammation or some other aetiology, are related to long-term risk of CVD.

Controlling vicious cycles

Biomarkers of the impoverished gut

Effective biomarkers of the impoverished gut are essential for our understanding of the causes, pathogenesis and patient responses to interventions. These bio markers need to be applicable in resource-limited community settings in which the impoverished gut develops, and where any effective interventions must ultimately apply. Simple noninvasive markers are therefore key, be they in faecal, urine, or blood specimens^{96,97} or in the medical histories or measurements of childrens' clinical course and growth.⁹⁸ Although several reports noted below and in Table 1 suggest that biomarkers hold promise,¹³⁻¹⁸ considerably further study is required to critically assess how specific infections and interventions alter selected biomarkers, in contrast to those altered by growth or particular nutrient deficiencies (Table 1).

Established and experimental laboratory studies have shown the potential biomarkers in urine, stool, blood and potentially saliva to assess intestinal barrier function or damage, impaired absorptive function, intestinal or systemic inflammation or intestinal injury repair (Table 1). Thus far, the best established biomarkers from human clinical studies are urine lactulose:mannitol ratios,^{13,99,100} serum EndoCAB, faecal lactoferrin (if the child has not been breastfed), α -1-antitrypsin (A1AT) and Reg1.^{18,39,66,101-104} In addition, plasma bacterial DNA (16S rRNA gene) levels and/or plasma soluble CD14 or fatty-acid binding protein, intestinal (I-FABP) levels^{96,97,105} and urine metabolomics^{106,107} could provide alternative (or additional) markers for microbial translocation as a consequence of increased gut permeability.^{96,97} Other markers of inflammation or immune activation include faecal myeloperoxidase, neopterin, calprotectin or serum C-reactive protein or serum amyloid A protein;¹⁰⁸⁻¹¹¹ zonulin is being explored as a potential marker of inflammation.^{112,113} A lactulose breath test has also been used to assess small bowel bacterial overgrowth.^{114,115}

Finally, plasma citrulline might be a quantitative biomarker of small bowel mass integrity that correlates with crypt depth and xylose absorption in HIV-associated villous atrophy in a tropical entero pathy population in Zambia.¹¹⁶ An example of the clinical utility of these biomarkers is provided by the substantial improvement in urinary lactulose excretion after 10 days of alanyl-glutamine therapy in undernourished children whose weight recovery improved up to 4 months after therapy.¹¹⁷ In addition, the simple assessment of any child experiencing a diarrhoeal illness extending beyond 7 or 14 days in duration (termed prolonged or persistent diarrhoea, respectively), who is at risk of heavy diarrhoeal burdens and growth shortfalls, thus warrants special attention. Provision of nutritional

supplementation and potential targeted antimicrobial therapy should be considered, depending on the local predominant pathogens or specific test results, perhaps targeting protozoa or predominant bacterial pathogens, analogous to single dose albendazole therapy for the geohelminths.^{64,118} Zinc supplementation is currently recommended by the WHO for all episodes of childhood diarrhoea in developing countries.¹¹⁹ Some clinicians recommend a trial of nitazoxanide for persistent diarrhoea. Yogurt-based or amino-acid-based diets could also accelerate recovery from persistent diarrhoea in children¹²⁰

Advances in interventions

Discovery of biomarker signatures that capture complex interactions of host factors, including nutritional status, intestinal barrier function, microbiome and inflammation in coordination with specific enteropathogens, will lead to novel understanding of microbial pathogenesis. We and others have described the effects of undernutrition, alone or in combination with enteric infections, on growth intestinal mucosal architecture, barrier function and tight junctions in mouse models.^{19-22,45,121,122} These models should be also examined for susceptibility to chronic diseases such as metabolic syndrome. Multiplex PCR assays¹²³⁻¹²⁵ have shown that children acquire an increasing array of enteropathogens in the first years of life; however, the presence of these pathogens is not always clearly associated with overt diarrhoea or growth failure, emphasizing a fundamental question: when is a gut microorganism a gut pathogen? We propose that a systems biology approach incorporating information about host and microbial genetics, nutrition and growth, epithelial homeostasis, inflammation and metabolomics is needed to untangle this web and point the way to novel interventions.

Novel interventions

Prevention—Preventive and therapeutic interventions were the focus of a 2009 WHO Report “Diarrhoea: Why are children still dying and what can be done”.¹¹⁹ These interventions included several measures that had a clear evidence base: prompt and adequate ORT; promotion of breast feeding; use of rotavirus vaccine and potentially other vaccines such as cholera vaccine; zinc and other nutritional therapies; and improved water and sanitation. Long-term investments in sanitation and hygiene represent the largest challenges, along with strengthening nutrition programmes, education and primary care in low-income and middle-income settings around the world. Thus, we should consider the importance of water, sanitation, micronutrients and vaccines as preventing not just diarrhoea, but also malnutrition, its developmental consequences and perhaps obesity in later life.

Therapy—Stopgap measures include improving the availability and efficacy of ORT, defining the optimal dosing and timing of micronutrient supplementation (such as zinc and vitamin A) and repair nutrient supplementation (such as glutamine or alanylglutamine) that have been shown to improve intestinal barrier function or weight gain in undernourished children.^{100,117} Probiotics deserve further study, although data from developing countries are limited. Extensive reviews of 16 randomized controlled trials in the Cochrane database showed a mean reduction in duration of diarrhoea by 29 h, approximate 4-day reductions in persistent diarrhoea and 13–14% reductions in diarrhoea incidence, as well as variably improved growth and vaccine-induced antibody production with probiotic treatment.¹²⁶⁻¹²⁸ In addition, an updated meta-analysis of 34 studies including >4,000 patients suggests nearly a 50% reduction in antibiotic-associated diarrhoea after probiotics.¹²⁹ Certain infections involve anorexia and malabsorption compounded with faecal protein loss and febrile caloric consumption making its effect on malnutrition even worse. *Helicobacter pylori* has been variably associated with increased risk of diarrhoea, including shigellosis, perhaps via hypochlorhydria,^{130,131} but this association has been debated.¹³² Carefully targeted single-dose antimicrobial therapy (analogous to or including single-dose albendazole) might also

warrant further study.^{64,118} Interventions to improve the efficacy of oral rotavirus and other enteric vaccines in low-income countries are needed.¹³³ These potential approaches include novel adjuvants or mucosal repair nutrients that might improve intestinal mucosal function and help to optimize vaccine immunogenicity and protection.

Conclusions

Multiple preventive and therapeutic measures, including improved water and sanitation, ORT and micronutrient delivery, existing and new vaccines, hygiene education and innovative therapies such as probiotics, prebiotics, key nutrients and carefully targeted single-dose antimicrobial therapy will be needed to break the vicious cycles of poverty. The continued lack of adequate water and sanitation can now be seen to have increasingly costly consequences for the health of an individual and for societal budgets: a triple burden that compounds the costs of poverty through enteric infections, malnutrition and noncommunicable diseases. These costs thus become increasingly unaffordable, not to mention unconscionable. Indeed, we predict that multiple synergistic approaches to interrupt the vicious cycles of enteric infections, malnutrition and noncommunicable diseases will be required to reduce the human and societal costs.

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Box 1**The global burden of infections and malnutrition**

- Disability Adjusted Life Years incorporate both mortality (years of potential life lost) and morbidity (years lost to disability)
- Global mortality of children <5 years is most commonly caused by respiratory diseases, diarrhoea, malaria and other illnesses, but over half of all deaths in young children are also associated with malnutrition
- Although diarrhoea morbidity has declined over the past four decades, morbidity has not declined
- The full, potential lifelong effect of enteric infections (that is, diarrhoea and stunting) on human development, productivity and chronic diseases is not adequately appreciated

Key points

- High diarrhoea rates continue unabated in developing countries, despite benefits from oral rehydration therapy in reducing mortality
- One-fifth (178 million) children worldwide have stunted growth; early childhood enteric infections, with or without overt diarrhoea, are predicted to account for 25–43% of this burden
- Malnutrition severe enough to cause stunting contributes to more than half of global mortality in children >5 years old, as well as to impaired cognitive development
- Enteric infections and undernutrition each increase the risk of the other in a vicious cycle
- Increasing data show that early childhood infections and stunting are associated with obesity and its comorbidities in later life, forming a triple burden of poverty
- Enteric infections, malnutrition and noncommunicable diseases form vicious cycles with poverty that are best reduced using multiple approaches including improved water purity and availability, sanitation, vaccines and supplementary nutrients

Review criteria

A search for original articles published between 1960 and 2012 and focusing on the effect of diarrhoea or enteric infections on long-term growth, cognition and chronic diseases was performed using the MEDLINE and PubMed databases. The search terms used were “diarrhoea”, “enteric disease”, “environmental enteropathy”, “tropical enteropathy”, “stunting”, “wasting”, “development”, “cognitive function”, “early childhood”, “obesity”, “metabolic syndrome” and “cardiovascular disease”, alone and in combination. All articles identified were English-language, full-text papers. We also searched the reference lists of identified articles for further relevant papers.

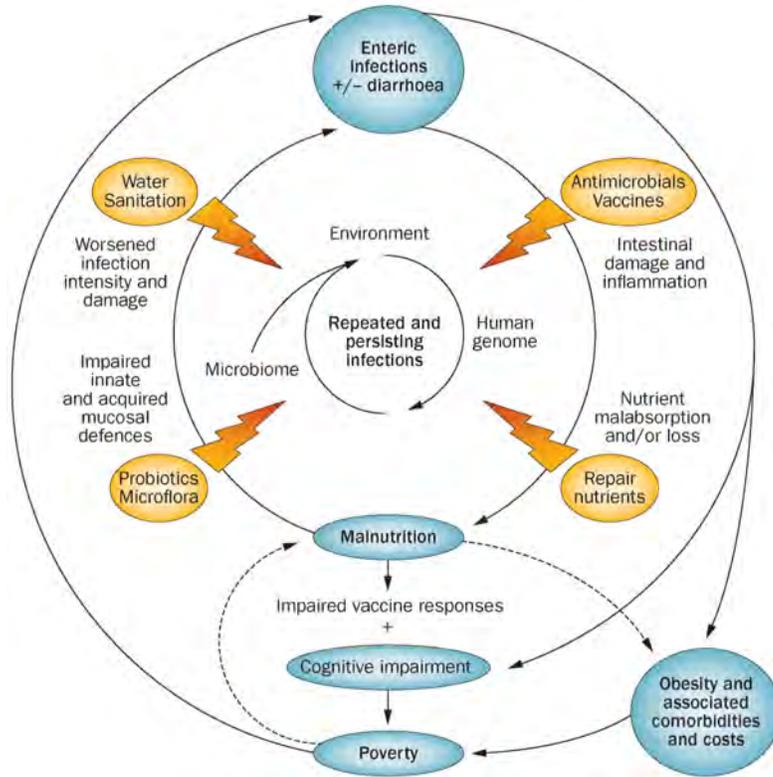


Figure 1. The vicious cycles of diseases of poverty. Enteric infections, especially in the first 2–3 years of life, with or without overt diarrhoea, can predispose an individual to malnutrition and stunted growth through multiple mechanisms. Stunting by 2 years of age, in turn, is associated with impaired cognitive development that extends into later childhood and even adulthood and adult productivity. In addition, malnourished children experience both greater frequency and duration of diarrhoeal illnesses, and, documented in animal models, heavier infections. The latter is documented with *Cryptosporidium* and with enteroaggregative *E. coli*. Finally, enteric infections or stunting can predispose to obesity and its comorbidities of diabetes, hypertension, cardiovascular disease, metabolic syndrome and burgeoning health-care expenditures, contributing to individual and societal poverty in vicious cycles.

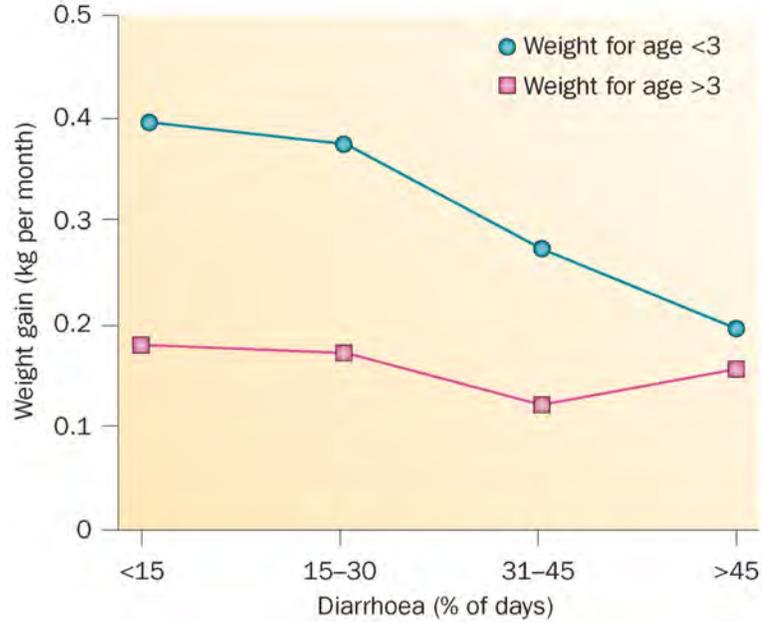


Figure 2.

Catch-up growth in malnourished children and its eradication by recurring diarrhoea. Malnourished children (that is, with weight-for-age <3 z-scores, less than three standard deviations below normal weight for age) tend to catch up with a doubling of weight gains, if they do not experience heavy diarrhoeal burdens (that is, <15% of their days are spent with diarrhoea in this observation period in the first 2 years of life). However, heavy diarrhoeal burdens are associated with a progressive ablation of this crucial catch-up growth. Permission obtained from Elsevier © Schorling, J. B. & Guerrant, R. L. *Lancet* 335, 599–600 (1990).

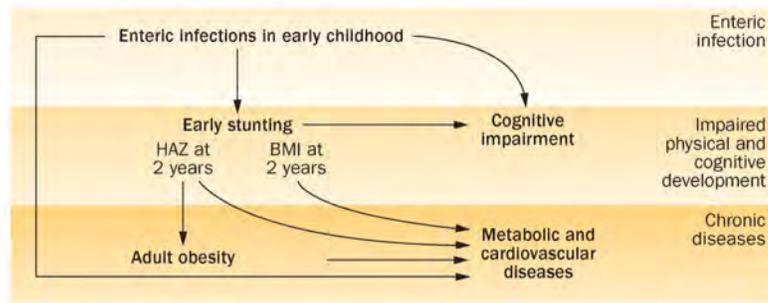


Figure 3.

Chronic consequences of early childhood enteric infections and stunting. The triple burden of enteric infections, impaired physical development (including low HAZ-2, or stunting and BMI-2) and cognitive development, and later life risk of obesity and its comorbidities are shown. Abbreviation: HAZ-2, height-for-age z-score at age 2 years.

Table 1

Known and potential biomarkers of the impoverished gut or environmental enteropathy

Assessing	Urine	Stool	Blood	Study
Damage to intestinal barrier and absorptive function	Lactulose: mannitol ratio *	α -1-antitrypsin	EndoCAB *, lipopolysaccharide or soluble CD14	Goto; ¹³ Camilleri; ⁹⁹ Lima; ¹⁰⁰ Campbell; ¹⁸ Lima; ³⁹ Petri; ⁶⁶ Barbosa; ¹⁰¹ Rahaman; ¹⁰² Brenchley; ⁹⁶ Sandler ¹⁰⁵
	ND	ND	Bacterial 16S rRNA	Jiang ⁹⁷
	Creatinine	Zonulin	Zonulin	Fasano; ¹¹² Tripathi ¹¹³
	I-FABP	I-FABP	I-FABP	Sandler ¹⁰⁵
Intestinal inflammation	ND	Methylene blue stain detects faecal leukocytes using microscopy	ND	Steiner; ¹⁰³ Masoodi; ¹⁰⁸ Langhorst; ¹¹⁰ Campbell ¹⁰⁹
	ND	(Hemocult)	ND	
	ND	Lactoferrin (nonbreastfed infants) *	ND	
	ND	Myeloperoxidase	ND	
	Nitric oxide	IL-8 and other proinflammatory cytokines IL-8 mRNA	ND	
	ND	Calprotectin Calprotectin mRNA	ND	
	ND	Neopterin	ND	
	ND	SAA3	ND	Reigstad ¹¹¹
Intestinal barrier repair	Citrulline	ND	Citrulline	Papadia ¹¹⁶
	ND	RegI	ND	Peterson ¹⁰⁴
Small bowel overgrowth	ND	Lactulose breath test	ND	George; ¹¹⁴ Esposito ¹¹⁵
Tissue biopsy to assess intestinal barrier disruption and inflammation	ND	+ Quantitative culture	ND	Lindenbaum; ¹¹ Gerson ¹⁰
	Metabonome	ND	ND	Swan; ¹⁰⁶ Saric ¹⁰⁷
Field history	ND	Any prolonged or persistent diarrhoeal illness (>7 days) *	ND	Lima; ³⁹ Moore ⁹⁸

Abbreviations: EndoCAB, anti-endotoxin core antibody; I-FABP, fatty-acid binding protein, intestinal; ND, not determined; SAA3, serum amyloid A3 protein.

* Recognized biomarkers in published reports.