Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC)

Virtual Meeting Report 21-25 September 2020
# TABLE OF CONTENTS

ABBREVIATIONS..........................................................................................................................3

INTRODUCTION........................................................................................................................................5

SESSION 1: Risk of SARS-CoV-2 transmission with different immunization services........6

SESSION 2: Frameworks and methods to guide COVID-19 vaccine development.............11

SESSION 3: The WHO/UNICEF Estimates of National Immunization Coverage (WUENIC 2.0) .................................................................................................................................................14

SESSION 4: MR-MAPs (Measles-Rubella Microarray Patches)........................................18

SESSION 5: RTS,S Malaria Vaccine ..........................................................................................22

SESSION 6: Vaccine Delivery Costing Consensus Statement..............................................25

SESSION 7: Vaccine Estimates for Immunization Agenda 2030 (IA2030).......................27

SESSION 8: Country-led Assessment for Prioritisation on Immunisation (CAPACITI).......31

SESSION 9: Burden of Enteric Diseases (BoED) ........................................................................36

ANNEX ..............................................................................................................................................41

   ANNEX 1 - IVIR-AC Meeting Agenda .......................................................................................41

   ANNEX 2 - List of Participants ....................................................................................................54

   ANNEX 3 - COVID-19 Special Session 2, Request for Information (RFI).........................60

   ANNEX 4 - WUENIC 2.0 use cases .........................................................................................68

   ANNEX 5 - RTS,S Vaccine Technical Questions addressed by presenters ......................69
ABBREVIATIONS

ABCD  Antibiotics for children with severe diarrhea
ACER  Average Cost-Effectiveness Ratio
BMGF  Bill & Melinda Gates Foundation
BoED  Burden of Enteric Disease
C4P   Cervical Cancer Prevention and Costing Control Tool
CAPACITI  Country-led Assessment for Prioritization on Immunization
CEA   Cost-Effectiveness Analysis
CFR   Case-fatality rate
CHAINs  Childhood Acute Illness and Nutrition
CHOICE  The WHO Choosing Interventions that are Cost-Effective
CHW   Community Health Worker
COGS  Cost of Goods Sold
CI    Confidence Interval
COVID-19  Coronavirus Disease 2019
DCVMN  Developing Country Vaccine Manufacturers Network
DTP3  Diphtheria-tetanus-pertussis
EPI   Expanded Programme on Immunization
ETEC  Enterotoxigenic Escherichia coli
GAVI  The Vaccine Alliance (Global Alliance on Vaccines and Immunizations)
GBD   Global Burden of Disease
GCEA  Generalized Cost-Effectiveness Analysis
GEMS  Global Enteric Multicenter Study
GoC   Grade of Confidence
GVAP  Global Vaccine Action Plan
HIC   High-Income Country
HW    Health Worker
IA2030 Immunization Agenda 2030
IDM   Institute for Disease Modelling
IHME  Institute for Health Metrics Evaluation
IVI   International Vaccine Institute
IVIR-AC Immunization and Vaccine-related Implementation Research Advisory Committee
IVB   Immunization, Vaccines and Biologicals
IVR   Initiative for Vaccine Research
IPC   Infection-prevention control
LMIC  Low and middle income country
LSHTM  London School of Hygiene and Tropical Medicine
MAPs  Micro-Array Patches
MAL-ED Malnutrition and Enteric Disease Study
MCDA  Multiple-Criteria Decision Analysis
MCEE  Maternal Child Epidemiology Estimation
MCV-1 Measles-containing-vaccine first-dose
MCV-2 Measles-containing-vaccine second-dose
MMGH  MM Global Health Consulting
MMRV  Mumps-Measles-Rubella Vaccine
MR    Measles-Rubella
MVIP  Malaria Vaccine Implementation Programme
NIP   National Immunization Programme
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>NITAG</td>
<td>National Immunization Technical Advisory Group</td>
</tr>
<tr>
<td>NPI</td>
<td>Non-pharmaceutical intervention</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PATH</td>
<td>Program for Appropriate Technology in Health</td>
</tr>
<tr>
<td>PCV</td>
<td>Pneumococcal Conjugate Vaccine</td>
</tr>
<tr>
<td>PDVAC</td>
<td>Product Development Vaccine Advisory Committee</td>
</tr>
<tr>
<td>PPC</td>
<td>Personal Protective Clothing</td>
</tr>
<tr>
<td>PPE</td>
<td>Personal Protective Equipment</td>
</tr>
<tr>
<td>PHVP</td>
<td>Public Health Value Proposition</td>
</tr>
<tr>
<td>RATR</td>
<td>Relative acquisition/transmission rate</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and Development</td>
</tr>
<tr>
<td>RFI</td>
<td>Request for Information</td>
</tr>
<tr>
<td>RFP</td>
<td>Request for Proposals</td>
</tr>
<tr>
<td>RI</td>
<td>Routine Immunization</td>
</tr>
<tr>
<td>RTS,S</td>
<td>RTS,S/AS01 Malaria Vaccine</td>
</tr>
<tr>
<td>SAGE</td>
<td>Strategic Advisory Group of Experts</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Severe acute respiratory syndrome Coronavirus #2</td>
</tr>
<tr>
<td>SIA</td>
<td>Supplementary Immunization Activities</td>
</tr>
<tr>
<td>TPP</td>
<td>Target Product Profile</td>
</tr>
<tr>
<td>TSE</td>
<td>Total System Effectiveness</td>
</tr>
<tr>
<td>UHC</td>
<td>Universal Health Coverage</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
</tr>
<tr>
<td>UNPD</td>
<td>United Nations Population Division</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VPD</td>
<td>Vaccine-preventable disease</td>
</tr>
<tr>
<td>VIMC</td>
<td>Vaccine Impact Modelling Consortium</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WUENIC</td>
<td>The WHO/UNICEF Estimates of National Immunization Coverage</td>
</tr>
</tbody>
</table>
INTRODUCTION

Kate O’Brien, the Director of the Immunization, Vaccines and Biologicals (IVB) Department of World Health Organization, welcomed attending members of the Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC), presenters, WHO Staff, and guests. She thanked IVIR-AC for their vital contribution to shaping vaccine implementation policy and stressed the important role they will play in the new global immunization strategies. Global immunization approaches and strategies of the coming decades will rely and depend on good quality data to establish baselines, refine practices, redirect resources, and to ultimately determine the overall success of projects or programmes. The WHO Immunization Agenda 2030 (IA2030) and the new IVB 5-year strategy rely on good quality data. The data generated from IVIR-AC’s multiple programmatic and modelling-related projects will be essential to successful implementation of these two strategies.

Immunization coverage and equity are at the center of IVB’s new strategy and will require new ways to identify populations and communities. This year, due to COVID-19, the immunization programme will require support to aid in its recovery. Data are critical to these tasks and a vital part of decision making for policy makers at all levels, when choosing to adopt or to introduce a new vaccine. The process to assess and compare vaccine options, or to introduce a regional vaccine, such as a malaria vaccine, rely on data. Data are used for determining coverage, which is then used to plan interventions. IVIR-AC has an important role to play in this next stage of immunization strategy. Their ongoing contribution to strengthening and broadening the evidence-base used to support and advise the Strategic Advisory Group of Experts (SAGE), illustrates the crucial role that IVIR-AC has played and will continue to play in informing and shaping global immunization policy.

Raymond Hutubessy provided an introduction on the focus and function of IVIR-AC. IVIR-AC has no executive, regulatory or decision-making function. Its role is to provide advice and recommendations to SAGE and the IVB Director of WHO.

The key objectives of IVIR-AC are:

- To appraise methods to estimate disease burden and resolve differences in disease burden estimates.
- To appraise guidance documents including methods to estimate disease and economic impact of vaccines.
- To advance techniques to assess cost-effectiveness of vaccines.
- To develop behavioral research to facilitate optimal and timely acceptance of vaccines.
- To define how disease and post-marketing surveillance should be conducted.
SESSION 1: Risk of SARS-CoV-2 transmission with different immunization services

Background

The global COVID-19 pandemic has disrupted immunization activities in nearly all countries. In low and middle-income countries (LMICs), many supplementary immunization activities (SIAs) have been delayed, due to concerns over transmission risk and/or the reprioritization of health personnel and resources toward the COVID response. When decisions were made to delay SIAs and reduce services, they were appropriate, given the high level of uncertainty around COVID-19 and how it may evolve. However, immunization services are essential, and the risk of increased morbidity and mortality due to reduced routine coverage or delayed SIAs is well characterized (Abbas et al.; Roberton et al.).

In March 2020, WHO identified immunization as an essential health service to be prioritized and safeguarded for continuity during the COVID-19 pandemic. At the same time, WHO emphasized the need to adapt vaccine delivery strategies in order to conduct them under safe conditions without undue risk of SARS-CoV-2 transmission to health workers and the community. In order to properly advise WHO SAGE on safe immunization scenarios that mitigate transmission risk to health workers and the community, a better understanding of transmission dynamics and the risk-benefit of proceeding with immunization services was needed. Although prior modelling by the London School of Hygiene and Tropical Medicine (LSHTM) (Procter et al., unpublished) and the Institute for Disease Modelling (Frey et al., unpublished) looked at COVID-19 transmission risk, transmission dynamics of health workers is also a function of varying levels of infection and prevention control (IPC).

IPC includes both personal protective equipment (PPE), such as masks and gloves, and structural and behavioural interventions, such as hand-washing, frequent cleaning of high-touch surfaces, open-air settings, etc. During the Spring 2020, there was limited understanding of IPC, and disagreement on the role of masks and aerosol transmission. Clarifying IPC standards for health service delivery scenarios has required ongoing incorporation of emerging evidence and problem-solving.

To better understand the risks of SARS-CoV-2 transmission to health workers and the community and to inform strategies for safe vaccination, WHO requested a modelling study from the Institute for Disease Modelling (IDM) to address the following question:

**Key question for analysis:** What is the risk of COVID-19 transmission to communities and to health workers for settings with 1) various levels of COVID-19 transmission (including the WHO transmission categories), 2) under different health service delivery conditions (e.g., fixed-site, outreach, 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?

Modelling

IDM executed a modelling study of vaccination events-related SARS-CoV-2 transmission among/between health workers and the community involved in vaccination events. This included secondary transmission (e.g. a care-giver acquired COVID-19 during an SIA and later transmitted the virus to a household contact). The model focused solely on COVID-19 transmission burden, and not on any benefit deemed from vaccination.

---

1. [https://doi.org/10.1016/S2214-109X(20)30308-9](https://doi.org/10.1016/S2214-109X(20)30308-9)
2. [https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30229-1/fulltext](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30229-1/fulltext)
3. [https://apps.who.int/iris/handle/10665/331590](https://apps.who.int/iris/handle/10665/331590)
That was out of the scope the study. Vaccine benefit would be cumulative, and not immediate, and depend on the age-group being vaccinated and the disease being prevented.

SARS-COV-2 transmission among/between health workers and the community involved in vaccination events was modelled under different transmission scenarios, using in-facility routine immunization programs as a baseline.

Variations included:

- Immunization service delivery types (fixed site campaigns, house-to-house campaigns, routine outreach).
- Health worker Relative acquisition/transmission rate (RATR), a parameter describing the infection rate (both acquisition and transmission) of HWs relative to the community. RATR varied from 20X RATR to 1X RATR (20X, 15X, 10X, 5X, 1X), with 20X RATR indicating the highest infection rate of HWs relative to the community and 1X indicating an equivalent infection rate of HWs and the community. RATR served as a proxy for hypothetical variations in circumstances which may impact HWs’ susceptibility or protection against both acquisition and transmission of COVID-19.
- Country characteristics (age pyramid, income levels, urban/rural).
- Country setting (6 countries-Angola, Ecuador, Laos, Nepal, Pakistan, Ukraine).

Main Results Summary

- 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%.
- The effect of different delivery scenarios 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. Total infections are elevated by around 60 [0, 230] per 1000 vaccinations in scenarios where HWs have 10X RATR, but outcomes are very sensitive to prevalence of infection in health workers and SIA timing. These scenarios highlight the possibility for infected HWs to import COVID-19 into populations who are not experiencing local circulation.
- Structural differences of 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 populations.
- 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 (through the use of IPC), will reduce the risk of excess infections.

Questions Posed 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?
  o Are assumptions about roles of children in transmission justified and sufficiently conservative?
  o How can we extrapolate the results from the six analyzed settings to other countries?
  o 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?

**Discussions/Considerations leading to IVIR-AC Recommendations**

Overall, the committee found the modelling approach to be robust, as it explores multiple scenarios and uses parameters defined by the best available evidence at the time of model initiation. However, the committee discussed ways to improve communication of the results, the age assumption and its impact on the modelling results, ways to extrapolate the results, and the limitations and objective of the modelling with respect to IPC.

**Communicating Results**

The committee indicated the importance of communicating the results in the larger context of the COVID-19 outbreak in each country. Rather than only reporting additional COVID-19 infections/1000 vaccinees, this should also be presented as a % of the total infections occurring in the outbreak at that time. This helps to evaluate the impact of any one immunization activity in the context of the larger outbreak. For example, the result, 26 COVID-19 infections/1000 vaccinees does not say as much as ‘the immunization activity contributes less than 2% of the total COVID-19 infections due to the outbreak’. How the results are communicated influences interpretation of the results, which is critical to policy making. The committee highlighted that the models’ parameters should be fully disclosed and transparent to policy makers and programme managers; however, results should not be used as a projection of real cases, but rather as means to guide and inform policy within the context of the resurgence of vaccine preventable diseases.

**Age Assumption**

The committee found that the age assumption (children <15 years of age acquire COVID-19 55% less than persons >15 years of age and transmit 15% less) was not conservative, but it was based on the best available evidence. However, it would be important to cite all references finding a transmission reduction in younger people and any counter evidence, if there is any. There was some concern about the extent to which the age assumption drives the results and that maybe an additional model could explore the implications of that assumption. Additionally, the committee sought clarification on the application of the reduced acquisition and transmission (RATR) assumption of younger persons across countries. It was clarified that the model used point estimates from a contact tracing study in Israel, and that the model assumes a child in Angola has the same immunological profile as a child in any other country.

The model used synthetic contact matrices from Prems et al⁴. The committee informed the modellers of a more recent publication under peer review by Prems et al⁵, which expands the contact matrices. The committee suggested the possibility of running the model using the new contact matrices, to stay up to date with the latest literature (see footnote⁶).

**Extrapolating Results**

---

⁴ https://journals.plos.org/ploscombbiol/article?id=10.1371/journal.pcbi.1005697
⁵ https://cmuid.github.io/topics/covid19/synthetic-contact-matrices.html
⁶ Preliminary work suggests that the updated matrices do not change model outcomes, but this was not known at the time of the IVIR-AC meeting.
The committee used the results summary as a starting point to discuss ways to extrapolate from the 6 modelled countries to any and all additional countries. To help with the extrapolation, different country contexts could be explored with respect to age and urban and rural divide to better understand how those two aspects drive results. All countries could then be organized by these two aspects.

Additional Clarifications

There was some concern around source data used for HW $RATR$ and whether the data came from hospital-based health workers. Although that question was not answered, it was clarified that variations in HW $RATR$ (1X, 5X, 10X, 15X, 20X) serve as a proxy for a range of IPC (maximum IPC examined in this study would be HW $RATR$ 1X, meaning the $RATR$ of a HW is the same as a gender/age match in the community). The impact on health worker attack rates and the epidemic curve illustrates the impact of IPC in general.

The committee also asked which IPC is recommended as a way to minimize risk to health workers, and it was further clarified that the model was not specific to the implementation of any one IPC. IPC and implementation of its specific components (masking, distancing, hand-washing, surface cleaning, etc.) is beyond what IDM was looking at in the model. However, full coverage of IPC would be critical to reduce seeding new infections in house to house vaccine campaigns using health personnel from outside the community.

Conclusions

The committee summarized:

- Any incremental activity which increases contact rates and transmission of SARS-CoV-2 has an impact on the total number of community infections.
  - Effect size in all model scenarios (except for SIAs occurring at peak prevalence of an outbreak with overall attack rates > 50%) was < 100 community infections/1000 vaccination
  - Safer to have SIAs outside peak prevalence period of an outbreak and when overall attack rates are <50%.
  - Risk of additional COVID-19 infections associated with routine immunization/SIAs varied with context and setting and COVID burden and attack rate. In all modelling scenarios (except SIAs as noted above), <2% increase in incidence of total COVID-19 infections were due to immunization events. However, this result is only an illustration as the model did not look at cases, only transmission. This result cannot be applied in a real world circumstance.
- Bringing health workers from outside of a community for house to house SIAs could have more of an adverse impact than using people from within the community, although this impact is sensitive to prevalence of infection in health workers.
- The model does not address or define specific elements of IPC due to limitations in available evidence and data; however, this is within the context of the modelling.

IVIR-AC Recommendations

- IVIR-AC concludes that the model partially answers the key analytical question on COVID-19 transmission, within the scope of its design, however, there are knowledge and information gaps due to limited empirical evidence and understanding of COVID-19 transmission (e.g. the effectiveness of different IPC measures in practice and the relative risk of transmission to HWs). Both empirical and modelling evidence are still needed to determine the necessary considerations for delivering vaccines thorough SIAs and routine immunization programs. Some of these issues are being addressed by other work.
The risk of transmission to and by health workers depends on their relative exposure to COVID-19 cases (the input parameter Relative acquisition/transmission rate (RATR) in the model). The study is not designed to estimate the likely values of RATR. As such, location-specific empirical evidence on the relative risk of SARS-Cov-2 transmission to health workers is needed in order to assess the corresponding absolute risk.

The main conclusions on community impact are robust (i.e. that the risk of additional COVID-19 infections associated with routine immunization/SIAs is small, <2% increase in incidence of total COVID-19 infections). Yet, this result will vary with context and setting.

Conclusions regarding HWs should be interpreted as policy guidance rather than precise projections, due to uncertainty in the RATR. RATRs should also be considered as an important input variable in various scenarios.

The objective of the modelling work was to assess transmission risk related to resumption of immunization activities. However, the results of the modelling work should be viewed within the context of increases in vaccine preventable diseases (VPD)s, which would occur if these immunization activities were not commenced; an important next or concurrent step would be to compare the burden of (VPD)s with and without these immunization activities.

SIAs in areas with zero or very low COVID-19 prevalence need particular caution – PPE for HWs should be maximized (subject to the local resource constraints) in order to avoid viral introduction.

Children are assumed to be 55% less susceptible to infection and 15% less infectious than adults, based on published estimates. These assumptions are reasonable (i.e. based on the best, currently-available evidence), but not necessarily conservative. Depending on the % of children in the population, the primary outcome (cumulative no. of infections per 1,000 vaccinated) could increase by up to 2-3 times if age had no effect on susceptibility and infectiousness (i.e., children were as susceptible and contagious as older persons).

There needs to be an overall improvement to the communication of results and existing uncertainties, including the range of outcomes and corresponding parameters.

The primary results could be more clearly presented and communicated, e.g. the community impact should be presented as the % increase in the cumulative no. of infections (in addition to the no. of cases per 1,000 vaccinations).

To facilitate extrapolating to other countries, results from the 6 countries should be plotted and organized in terms of % rural/urban and % <15 yrs. old, and the addition of useful characteristics not included in the model.
SESSION 2: Frameworks and methods to guide COVID-19 vaccine development

**Background:**

The *SAGE Working Group on COVID-19-Vaccines* was established in June 2020 to anticipate a licensed COVID-19 vaccine, to ensure a coordinated approach with the Research and Development (R&D) community, and to maximize global efforts to make evidence-informed policy decisions on the best use of the vaccine.

The working group aims to:

- 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.

The working group includes four sub-groups, including two that work in conjunction to propose priority populations for vaccination, the *Public Health Objectives and Prioritization* and the *Impact Modelling* sub-groups. The *Public Health Objectives and Prioritization* sub-group provides the broader social, anthropological, and ethical framework to support vaccine prioritization, while the *Impact Modelling* sub-group provides guidance in the development and interpretation of high-quality prediction and impact modelling to inform policy recommendations for vaccine prioritization.

The population in need of COVID-19 vaccine is already larger than the assumed (supply assumed <10% of population) vaccine availability or supply in 2021. In order to advise SAGE on the use of initial vaccine products assuming a supply constraint, the *Impact Modelling Subgroup* invited modelers and economists to provide information about their work on COVID-19 vaccination through a *Request for Information (RFI)* (see ANNEX 3). Recognizing the evolving landscape of evidence on SARS-CoV-2, COVID-19, and vaccine candidates, the *RFI* included 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 prioritization of modelling questions in the *RFI* reflected the Working Groups’ 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).

More than 20 modelling groups responded that could potentially address several different hypothetical scenarios. The groups’ responses to the modelling questions revealed several challenges that the sub-group and the larger SAGE working group will face when developing strategies to allocate a COVID-19 vaccine. There are limited modelling results currently available across the prioritized questions, and available evidence is skewed towards analyses of individual countries, high-income countries, vaccine prioritization by age group, and on health outcomes, not economic or other outcomes. There are a number of modelling gaps including prioritization of essential workers, other than HWs, and vaccination scenarios on delivery of essential services, other than healthcare (education, public safety, etc.). There are also many uncertainties around SARS-CoV-2 epidemiology and any vaccine performance which may remain, even when a decision on prioritization is made.
To inform upcoming deliberations on policy-relevant use case scenarios and modelling needs to the *SAGE Working Group for COVID-19 Vaccines*, the committee was asked to identify any additional criteria to prioritize target groups using models, ways to address outstanding knowledge gaps that remained following the completion of the RFI, and the potential role and involvement of the IVIR-AC committee with the *Impact Modelling Group*, now and in the future.

**Questions Posed to IVIR-AC**

- In reference to the SAGE Working Group deliberations on policy-relevant use case scenarios and modelling needs:
  - 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?

**Discussions/Considerations leading to IVIR-AC Recommendations**

The committee commended the presenters and acknowledged that their work is extremely important. They acknowledged the immense uncertainties at this moment and brought up several questions or points to consider for the model, which were discussed and/or explained by the *Impact Modelling* Sub-group:

- Connectivity (geographic and individual) as a determinant of disease dynamics and the importance of targeting or prioritizing vaccine to the most connected places (i.e. high-density cities) or people (i.e. police officers or motorbike/truck drivers).
  - There are a couple of problems with this approach, including biased surveillance (limited reporting in rural areas) and equity (unfair to not allocate vaccine to rural areas or places with effective lockdowns and fewer cases).
  - Can consider prioritizing those who transmission is occurring to, by prioritizing those who have contact with groups where the consequences of infection are most severe (such as care home staff).
- Interaction substitution and identifying and substituting immune for susceptible individuals (e.g. a bit like immunity passports).
  - There is very little knowledge about immunity and protective immunity\(^7\) or for how long it may last, so this is a challenging concept.

The committee agreed that the uncertainties about SARS CoV-2 epidemiology and the vaccine to come require any model to be robust to this uncertainty. The committee suggested that all models be systematically graded and that the working group consider developing a process to systematically grade models. The model’s structure should be validated, and checks performed to ensure the model reliably reproduces observed epidemiological dynamics (such as the acquisition of herd immunity) and the impact of non-pharmaceutical interventions (NPI)s, if relevant. Further to this, it was suggested to quantify model inadequacy using a Bayesian approach, although this may likely be something that specific models would need to address, rather than the synthesis of the models.

The committee highlighted the importance of examining the role of children in more detail and the interaction that any COVID-19 vaccine might have on other interventions (i.e. Test and Trace).

They also presented several factors to consider:

- Country-specific vaccine delivery constraints (immunization programs only targeting children and how to reach adults and/or logistical barriers) and the possibility of including realistic constraints.

---

\(^7\) https://doi.org/10.1016/S1473-3099(20)30630-7
• Vaccine demand/acceptance and behavior (to be explored with behavior and social drivers sub-group).
• Political or communication issues around vaccination.
• Use of modelling work to motivate data collection in clinical trials and epi studies.

An important knowledge gap identified through the RFI related to equity. The committee highlighted its inclusion in the values framework released by WHO SAGE on Sept. 14 and the limited coverage of this topic by modelling groups so far. They suggested several ways to fill these knowledge gaps, including direct model requests through RFPs or by requesting specific modelling from identified groups in order to fill these gaps.

**IVIR-AC Recommendations**

• Both within and between country equity considerations warrant more attention from the modelers. It is important to consider people disproportionately affected by COVID-19, both directly (because of increased susceptibility to infection and/or severe disease) and indirectly (because of reduced access to healthcare, lockdowns, income loss and other impacts). National and global equity are noted as being values in the *WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination*.

• Utilize an objective approach to grading, when synthesizing outputs from different models. One example would be approaches that assign posterior probabilities to models given some observations, which then use these probabilities in a weighting scheme when synthesizing model outputs.

• Confirm that model structures sufficiently reproduce any relevant epidemiological dynamics (such as the increase in herd immunity) or the effects of non-pharmaceutical interventions (if used as counter-factuals).

• Encourage modelers to quantify and report the uncertainty (and general limitations) of their models whenever possible.

• The committee recommends that models consider the impact outcome measures of interest when vaccines are preferentially targeted to the most connected places within countries (e.g. commercial hubs vs. rural areas) and/or the most connected individuals (potential super-spreaders).

• Take a proactive approach with the modelers identified in the *Request for Information* and request models that fill the knowledge gaps needed for decision making.

• The committee can support any future review processes and assessments of the quality of modelling by providing:
  o Input into coordination of efforts by different groups.
  o Ongoing review as the work progresses.
  o Participation in a working group which could be established as needed.
  o Ad hoc advice from individuals.
  o Support with ongoing grading exercises.
  o Guidance on mathematical approaches for synthesizing outputs from different models to inform policy recommendations by SAGE.
SESSION 3: The WHO/UNICEF Estimates of National Immunization Coverage (WUENIC 2.0)

**Background**

Since 2000, WHO and UNICEF have produced the WHO/UNICEF *Estimates of National Immunization Coverage* (WUENIC) using a rule-based methodology first developed in 1999 and improved over time. However, since inception of the WUENIC methodology, the use-cases for WUENIC have expanded beyond traditional monitoring of coverage trends of National Immunization Programmes (NIPs); the immunization programme, schedules, data availability, coverage levels, and estimation tools/techniques have also changed. WUENIC is now challenged to produce credible estimates for diverse use cases.

A plan to identify complementary or replacement methodologies to WUENIC was previously presented to IVIR-AC and included a Request for Proposals (RFP) on *Modelling Approaches to Produce Estimates of National Immunization Coverage*. Three institutions responded to the RFP, and Imperial College London and WorldPop at the University of Southampton were chosen for further consideration.

IVIR-AC previously advised the WUENIC project team on ways to critically assess and compare the different methodologies proposed by the various groups. Further to these initial methodological assessments, a comparison of the models from Imperial, Southampton, and The Institute for Health Metrics and Evaluation (IHME), which produces yearly coverage estimates in the context of IHME’s *Global Burden of Disease* (GBD), were systematically compared to WUENIC. This comparison revealed differences in model approaches, input data, uncertainty measures, including quantitative (confidence intervals (CI)) vs qualitative (grade of confidence (GoC)) uncertainty measures, among other differences. A more comprehensive model comparison across vaccine/doses illustrated modest divergence of each model’s coverage estimates from the WUENIC estimates, but not necessarily in the same pattern (see figure 1).

*Figure 1: Comprehensive Model Comparison of Diphtheria-tetanus-pertussis (DTP3) immunization coverage estimates from Imperial, Southampton, and IHME relative to WUENIC’s estimates.*

In the absence of a “gold standard” for vaccine coverage, a simulation-based approach was also explored, to better understand observed differences; however, to produce a dataset that resembled what real coverage...
might be was complex, would make simulations very work intensive, and could inherently favor one approach over another. The simulations were presented as a way to improve the individual methodologies by evaluating and understanding selected aspects, such as borrowing data across countries and the use of covariates (which only the IHME model does at this time).

The results of the comparison demonstrated that the current WUENIC rule-based approach has desirable elements, including its understandability and the use of reported country coverage when not challenged by other reliable sources. However, the models open up new possibilities. The Imperial model provides a framework to use subnational data, includes hyperparameters for recall and administrative bias, and could be adapted to include additional input data sources. Southampton’s model can incorporate relevant input data sources, produces interpretable uncertainty intervals, and may be extended to subnational estimates. On the other hand, IHME is an established coverage estimation methodology with a different objective but provides estimates which are similar to WUENIC. All three modeling approaches from Imperial, Southampton, and IHME provide quantitative measures of uncertainty in the form of confidence intervals (CIs), while WUENIC uses a qualitative measure of uncertainty, i.e. grade of confidence (GoC).

The next generation WUENIC, WUENIC 2.0, could be an improved rule-based approach, a hybrid approach utilizing some or all of the above models to complement the rule-based approach, or a purely model-based approach. IVIR-AC considered the pros and cons of each methodology and stressed how coverage estimates generated from different methodologies could be used to strengthen the final estimate, most importantly strengthen the input data, or be used, as appropriate, for specific use cases (see ANNEX 4).

Questions to IVIR-AC

- Considering the use cases for WUENIC and observations from doing simulations, what does IVIR-AC see as the main pros and cons of a modelling approach vis-à-vis the current rule-based method?
- What model to estimate national immunization coverage for Member States would IVIR-AC recommend to WHO and UNICEF replace and or/complement WUENIC?

Discussions/Considerations leading to IVIR-AC Recommendations

IVIR-AC greatly appreciated the depth of the analysis that went into comparison of all the methodologies. The committee considered the different aspects of each approach, and stressed the difficulty in choosing one model over another at this time for several reasons:

- Each approach has strengths and weaknesses and no approach is the answer, especially when the quality of the approach highly depends on the availability and quality of data inputs.
- It is difficult for one approach to satisfy all use cases.
- Having multiple approaches is valuable for several reasons:
  - in line with the GATHER Guidelines⁸, which suggest comparing models head-to-head.
  - could be used to better identify data issues and strengthen existing data.
  - could be used to investigate trends in data quality (if different data sources).
  - WUENIC has the advantage that it is well-known at the local level and easier to understand compared to model-based approaches.
- A modelling approach provides quantitative measures of uncertainty, such as credible or confidence intervals, standard errors, etc.
- IHME, as an independent and parallel exercise, could provide a good reference for comparison.

---

⁸ www.gather-statement.org
- A hybrid approach, where modeled data are used for some scenarios, could include an algorithm that also involves several human checks (e.g. to define inputs, account for stock outs, etc.).

The committee stressed the pressing issue of poor data quality. There is an immediate need to develop capacity at the country level to encourage sustainable data collection, data analysis, and reliability of the data. This is in line with 2019 SAGE findings and recommendations⁹. IVIR-AC suggested that in order to facilitate capacity building at the local level and to cultivate understanding on the importance of good data, any chosen WUENIC 2.0 methodologies should be easily accessible and transparent at the local level. This will improve local understanding of how estimates are calculated and foster enthusiasm and engagement with local data. If trainings could use these existing methodologies to facilitate local familiarity of the justifications for chosen methodologies, their inputs, the processes involved, and the intricacies of the methodologies used, this would in turn create more awareness of the importance of strong and reliable data. The committee felt that any improvement to the current WUENIC methodology must involve an improvement in the data.

The committee mostly agreed with the pros and cons presented for each model. However, they stressed that models should not be judged based on the width of the confidence intervals, as these are not always an honest representation of the uncertainty in coverage. They also noted that it would be worthwhile to further investigate instances in which the Imperial and Southampton models provided estimates that were considerably higher or lower than WUENIC to determine what might be driving the differences.

IVIR-AC agreed with the challenges posed by performing a simulation study and noted that it would require different inputs for each model, which is work intensive and may ultimately bias the simulation in favor of one approach over another. They stressed the necessary precautions when using covariates, as they can drive results and affect outcome variables at different time points. Overall the committee felt that each model had distinct pros and cons which complement WUENIC.

**IVIR-AC Recommendations**

- The committee does not recommend one model or approach over another.
- Each approach, including WUENIC, which is rule-based, has strengths and weaknesses. There is not one single approach which is ideal for meeting all the intended use cases.
  - The new models have the advantage, over the current approach, of allowing formal quantification of uncertainty.
  - Confidence intervals should provide an honest representation of uncertainty and be sensitive enough to detect possible changes in coverage over time (e.g. due to stock outs).
- There are pros and cons of both the Imperial and Southampton models:
  - The *Imperial model* incorporates subnational data, which is desirable going forward, but also relies more heavily on survey data, which may lead to over-smoothing and an inability to capture year-to-year changes in coverage.
  - The *Southampton model* relies more on administrative data (with bias adjustments, including use of denominators from the United Nations Population Data (UNPD)) provided the differences with survey data are <10%, similar to the WUENIC rule; and the autoregressive process used by the model also allows for prediction of coverage in the near term.
- Efforts should be made to improve and promote country-level (should not exclude country drug administration or private industry if possible) data collection, quality assurance, analytical capacity, utilization, and buy-in, including developing interfaces to visualize country-level data and the way they are used in model results.

⁹ [https://www.who.int/immunization/sage/meetings/2019/october/presentations_background_docs/en/](https://www.who.int/immunization/sage/meetings/2019/october/presentations_background_docs/en/)
• Efforts should be made to ensure transparency and understandability across all approaches, including the current WUENIC approach and the proposed modeling approaches.
• Data inputs should be clear and presented alongside model estimates.
• Having multiple models may be desirable, although efforts to force model convergence should be avoided while also avoiding multiple estimates, which may cause confusion at the country level.
• IHME, as an external and ongoing effort to produce coverage estimates in the context of the Global Burden of Disease initiative, can serve as a good comparator.
• The potential for a “hybrid approach” (rule-based complemented by modeling) should be further explored.
SESSION 4: MR-MAPs (Measles-Rubella Microarray Patches)

Background
The typical measles-containing vaccine presentation is a 10-dose, lyophilized vial, which requires cold-chain storage. The vaccine has to be reconstituted and administered within six hours by a trained health worker. These complex handling requirements put undue strain on LMICs, potentially impacting their ability to reach measles and rubella (MR) vaccination targets, especially in hard to reach locations.

Microarray patches (MAPs), the innovative, needle-free, vaccine presentation and administration technology, utilize 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 within seconds to a few minutes. MAPs are sharps-free devices which can be applied without an applicator, by applying pressure with fingers, or by using an integrated applicator.

Clinical testing using MAP technology for influenza vaccines has advanced through Phase I clinical trials, and dose sparing has been demonstrated. Preclinical development is underway with several other vaccines, and two types of measles-rubella vaccine micro-array patches (MR-MAPs) are expected to begin Phase I studies in early 2021. A MR-MAP could potentially ease logistical challenges faced by LMICs by enabling easier delivery and administration to hard-to-reach populations (single dose presentation, potentially thermostable, no reconstitution required, potential administration by community healthcare workers). As such, MR-MAPs could significantly contribute to expanding equitable MR vaccination coverage.

Despite the clear advantages over the current vaccine presentation and the potential impact that MR-MAPs may have on measles-rubella vaccination coverage in LMICs, they have been slow to advance into the clinic. For this reason, in 2016, SAGE recommended that the most expeditious pathway to clinical development and licensure be determined and any barriers to development, licensure, and use be identified and addressed. One major bottleneck to the advancement of MR-MAPs has long been the investment in a pilot manufacturing facility that will be needed to produce materials for pivotal licensure clinical studies. The high cost and risk associated with this means it will likely not be initiated before clinical proof of concept data is available in the target population, which delays the timeline to availability and access to MR-MAPs. However, in consultations with developers, WHO learned that the high risk of investment may be offset by a proven and documented user demand by countries, and commitment to procurement.

To address the SAGE recommendations and incentivize MR-MAP developers, WHO and MMGH Consulting developed an analytical framework to identify, evaluate and validate use case scenarios to deliver MR-MAPs. They are working to determine the potential demand size of each of the use cases. The analytical framework was presented which included a landscaping analysis to identify six use cases to deliver MR-MAPs. The use cases were refined and validated through stakeholder consultations (surveys and interviews) in several countries. Having a clear understanding of priority use cases can inform critical product design attributes and estimating their size within the immunization programmes can provide an indication of potential demand. Both factors are critical to informing the investment case for MR-MAPs.

Surveys and interviews found that outreach-type immunization services (house-to-house or outreach campaigns) were very relevant and important use case scenarios for MR-MAPs. The use of MR-MAPs in routine immunization was found to be somewhat relevant as MR-MAPs could disrupt the immunization infrastructure established to deliver needle and syringe vaccines. There was less consensus on the use of MR-MAPs for self-administration (by a parent to a child with and without community health worker supervision). Overall, the stakeholders felt that MR-MAPs would be a positive innovation for their community. The last
stage of the analytical framework is to estimate the maximum potential size of the use cases as an estimate of the number of potential doses used, which will be globally extrapolated toward 2030.

IVIR-AC was asked to evaluate the use case findings and endorse the proposed approach to identify, verify, and size 6 MR-MAPs’ use cases.

Questions to IVIR-AC

- Does IVIR-AC agree that the approach to identify and verify the MR-MAPs use cases is appropriate, systematic and scientific? Does it make sense?
- Does IVIR-AC have suggestions to improve the methodologies to calculate the size of each of the use cases?

Discussions/Considerations leading to IVIR-AC Recommendations

Overall, the methodology to assess possible use cases for MR-MAPs through surveys and interviews was viewed favorably by IVIR-AC; however, IVIR-AC brought up several additional investigations to consider in the future. These included, cost-effectiveness analyses, value assessments, feasibility studies of use cases, health worker or caregiver demand studies, willingness to pay, exploration into new use cases that are beyond current thinking, and several vaccine development investigations into the usability of MR-MAPs by untrained individuals.

The presenters clarified that initial investigations were intended to provide reassurance to developers by demonstrating countries’ interest in MR-MAPs and examples of how MR-MAPs could be used in those countries. The analytical framework was designed to capture use case scenarios for delivery of MR-MAPs. The next steps of the analytical framework are to estimate the size of the use cases (as a measure of the number of doses). The presenters reiterated that the initial studies did not evaluate demand, administration, or usability of MR-MAPs within the different use cases and highlighted how multiple unknowns about any final MR-MAP product, including its cost, limit to what extent usability or demand can be assessed at this stage.

Previous acceptability studies of a prototype MAP showed positive feedback and openness from HWs on the use of an MR-MAP. Different stakeholders also expressed interest in seeing MR-MAPs administered by HWs, especially community HWs. The presenters felt that good communication with HWs would be a critical part of implementation to ensure high levels of demand as well as a slow inclusion of the new technology into the community.

The presenters shared their plans to include a Total Systems Effectiveness (TSE) evaluation of MR-MAPs, including cost-effectiveness studies, to further incentivize developers and inform product development. They shared the anticipated cost for an MR-MAP, 1$/dose (although price not guaranteed at this moment), which is the value they will use in future TSE evaluations.

As things move forward in the development pipeline, the presenters explained that implementation research would need to run in parallel to product development and that the learnings would be absorbed into and drive product development – which this is their long-term vision and strategy. These studies may include, demand, usability, feasibility and/or expansion of use cases into new areas (a lot of the studies which IVIR-AC proposed). This strategic approach is to ensure that countries’ needs and preferences are fundamental to product development, which will encourage future use of MR-MAPs, raise demands, and ensure a better market for developers.

IVIR-AC shared concern over the analytical approach’s long projection timeframe (8-10 years). Use case data gathered now, including any estimates of use (in number of doses), would potentially be very different in 2030. They stressed the need to adopt an analytical model which remains dynamic in light of possible changes by 2030, with respect to:
• Measles incidence and eradication efforts.
• Changes to assumptions (such as price $1 US/dose), etc.
• Supplementary data points (cost-effectiveness studies and the TSE results).
• Confidence in patch technology and awareness in the community.
• Potential for use with other vaccines (COVID-19, influenza).

IVIR-AC highlighted that generating demand and enticing developers will be difficult since countries would need price information 1st (from manufacturers), while developers would need demand information 1st. They suggested to consider identifying, categorizing, and sizing each use case in terms of its intended application (i.e. using MR-MAPs for vaccine hesitant patients in routine settings, needle phobia, during outbreaks, using drones for hard to reach places, and in high-income countries vs. LMICs, etc.) This may allow projection of the use case size and doses needed into settings not first evaluated. It might be helpful for developers and users to communicate how the MR patch and production could be applied to other vaccines, as it may be more relevant with other vaccines in certain settings (e.g., the US would need an MMR patch, rather than an MR patch).

IVIR-AC suggested to consider the use cases in high-income countries. The HIC market could use a MAP technology to contain outbreaks, reach populations quickly, and maintain elimination goals. This potential market may provide further incentive to developers and offset any risk. However, HICs would require a different formulation, which includes the mumps vaccine.

Recommendations

• The committee agrees that the use cases for MR-MAPs (Use Case 1: Delivery by HW or CHW in Fixed Post, Use Case 2: Outreach delivery by HW, Use Case 3: Outreach delivery by CHW, Use Case 4: Delivery by CHW in their “home” community, Use Case 5: Self-administration with HW or CHW assistance, Use Case 6: Self-administration without assistance) are appropriate, and the approach systematic and scientific.
  o Consider inclusion of adults in the definition and potential sizing of use cases that describe the use of MR-MAPs through self-administration (use cases five and six).

• The methodology of the survey should describe the demographics and role of the respondents in more detail and give numbers, possibly some quantitative validation of how representative the respondents are and hence the findings.

• The assessment of use cases, and their relative importance is dynamic and should be revisited between now and 2030, when there are shifts in the MR-MAP environment, such as:
  o additional end user acceptability and feasibility of self-administration studies that may bring new perspective.
  o changes in measles incidence and progress towards elimination efforts.
  o data that informs underlying assumptions (such as cost of goods sold (COGS) of $1 US/dose, thermostability, efficacy, wastage), etc.
  o supplementary analysis (cost-effectiveness studies, Total Systems Effectiveness and CAPACITI, etc.).
  o confidence in patch technology and awareness in/demand from the community.
  o Updated data on the conditions of practical use of these vaccines (duration of application, whether or not it is necessary to observe a skin reaction to ensure efficacy, etc., see product profile).
  o The possible interest from HICs in the technology (e.g. with MMR, MMRV) due to its unique benefits (to overcome hesitancy; reach special populations; eliminate cold-chain; other logistics), which may offset the lower procurement costs expected in LMICs and offer a return in investment.
• IVIR-AC provides insights and suggestions on the overall methodology to calculate the size of each use case:
  o The choice of individual countries and proposed groupings is possibly appropriate and focuses on the greatest public health need (one recommendation may be to focus on countries with larger numbers of unimmunized subjects - MCV1 or MCV2, some countries with a smaller population, but with the highest percentage of unimmunized patients).
  o Consider the shift from needle-syringe vaccination to MR-MAPs application as it evolves over time, rather than incrementally, to assess accessing previously unreachable populations with standard technologies.
  o Evaluate the feasibility of establishing novel financing/procurement mechanisms for MR-MAPs to incentivize MR-MAP product development. In particular, consider the implications of globally or regionally coordinated switch to MR-MAPs (as was done in the switch from oral to inactivated polio vaccine), which may release further financing and enable economies of scale.
  o Consider future market research to validate key assumptions developed through use case/demand sizing exercise (e.g. SIA vs. Routine Immunisation (RI) / outreach vs. fixed post).

• General comment:
  o Total systems effectiveness needs to be considered (decreased wastage, ease of use, delivery cost savings vs willingness to pay, etc.) to fully assess the economic trade-offs in where and how MR-MAPs are used. This will be crucial to move from a directional demand sizing exercise that proposes potential ranges, to a demand forecast model.
  o It will be important to incentivize potential manufacturers with supplementary data to encourage investment in the development of MAPs as many are currently profiting from traditional delivery systems (e.g. needle and syringe).
SESSION 5: RTS,S Malaria Vaccine

**Background**

Multiple partially-effective interventions are available for malaria prevention in children. The WHO Global Malaria Programme recommends packages of interventions to optimize malaria prevention and control. RTS,S/AS01 (RTS,S) malaria vaccine has demonstrated efficacy to reduce episodes of clinical and severe malaria; however, outstanding implementation questions remain on feasibility, impact, and safety in routine use. Pilot implementation studies were designed to address these critical questions, including the cost-effectiveness (value for money) of RTS,S in relation to other malaria control interventions. IVIR-AC previously recommended that an economic analysis using a sequential approach to introducing individual malaria control interventions until a coverage threshold would be reached was not a real-world scenario to inform policy.

In this *for information only* session, and in preparation for The RTS,S Malaria Vaccine Pilot Evaluation which will likely be reviewed for policy considerations in late 2021, the presenters requested feedback from IVIR-AC on their new proposed economic analysis approach. They presented The WHO Choosing Interventions that are Cost-Effective (CHOICE) approach, which uses a specific form of cost-effectiveness analysis, Generalized Cost-Effectiveness (GCEA). GCEA uses a “do nothing” comparator and expresses the result as an average cost-effectiveness ratio (ACER). This approach allows comparison of multiple interventions across disease areas, in terms of value for money, and the efficiency of the existing package of interventions. When applied to malaria, a retrospective CHOICE approach can inform allocative efficiency and policy decision making by illustrating the cost-effectiveness of RTS,S vaccine as an intervention within a package of malaria interventions (which will include currently recommended interventions). The WHO CHOICE analytical method identifies the most efficient package of health interventions at different stages of the health maximising pathway, regardless of past (potentially inefficient) decisions of interventions roll-out.

A retrospective CHOICE evaluation of interventions recommended by WHO between 2000 and 2010 was conducted. This analysis evaluated the efficiency of existing packages of interventions over the study period and looked for possible health gains through different combinations of interventions (considering increased coverage level of the same interventions, or different combinations of the same interventions, or new interventions). The malaria application within this methodology was an assessment of possible health gains from the addition of RTS,S vaccine to the existing interventions recommended during the study period (2000-2010). This approach would illustrate the possible impact and added value for money with the addition of RTS,S. The malaria interventions evaluated for the initial evaluations were limited to case management (with and without diagnosis), bed nets and RTS,S vaccine. The analysis could be expanded to include the whole array of malaria interventions currently recommended by WHO (e.g. chemoprevention in children and infants not studied) with the addition of RTS,S.

The committee was asked, in the context of the forthcoming policy review, for feedback on their proposed methodology. Although this session was for information only, they sought technical insight into the use of WHO Choosing Interventions that are Cost-Effective (CHOICE)/Generalised Cost-Effectiveness Analyses (GCEA) to inform future economic analysis of the RTS,S vaccine as part of a package of malaria interventions.

**Questions to IVIR-AC**

- Please provide feedback on the CHOICE approach to inform policy on the RTS,S vaccine.
• Please provide feedback on the different methods for decision-making at different levels.

**Discussions/Considerations leading to IVIR-AC Recommendations**

IVIR-AC agreed on the overall approach of GCEA for assessing RTS,S vaccine in the broader package of malaria interventions, but requested detailed answers to the following technical implementation questions:

- How to apply GCEA to infectious diseases, where the interaction of interventions may be non-linear?
- How to calculate incidence under the “null scenario” (i.e. no intervention, when some interventions are currently in place)?
- How to implement/look for evidence of synergistic effects of interventions?
- How to change existing interventions for the optimal package of interventions, and factor in transaction costs, political opposition etc.?
- How does CHOICE deal with uncertainty?
  - IVIR-AC highlighted a paper on incorporating uncertainty analyses into GCEA\(^\text{10}\)
- Is the CHOICE model available in the public domain for review?
- Can the broader societal perspective be included in the model by incorporating households OOP expenditures and productivity losses?
- Can vaccine impact indicators, like number of deaths prevented and number of cases prevented, also be considered in addition to healthy life years\(^\text{11}\)?

The presenters provided detailed technical information (ANNEX 5) addressing IVIR-AC’s concerns and questions about their chosen methodology. Further to this, IVIR-AC highlighted the importance of framing the results by looking at the wider impact of RTS,S. By capturing the societal impact and benefit of RTS,S and other malaria interventions, with productivity costs or losses for example, the wider perspective would illustrate additional benefits. The presenters clarified that although economic burden was not evaluated, household costs were included and EPIC\(^\text{12}\) was also utilized, which isn’t typically used for health decision making.

To inform policy considerations for RTS,S, IVIR-AC suggested that thought be put into the importance of how results are framed and what results are presented which provide the most useful story for policy makers. They indicated that deaths and lives averted should be captured and interventions should be compared and considered with respect to their impact on elimination goals or other public health goals. It would be useful and relevant to capture how RTS,S could strengthen services or contribute to the Extended Programme on Immunization goals (EPI) and a reduction in <5 deaths. In this way, the wider societal perspective is considered and at the center. IVIR-AC mentioned the possibility of complementing the CHOICE approach and looking at the synergy of RTS,S with other control measures. This could also expand the analysis to include outcomes which are more relevant in the context of malaria control programmes in the country.

**Recommendations**

- GCEA should be considered alongside other approaches, e.g. incremental CEA and probabilistic uncertainty analysis, as well as other considerations in the decision-making process (e.g. equity, budget impact analysis, acceptability etc.).
- Stand-alone incremental CEA with probabilistic uncertainty analysis and societal perspective may also be required to assess the full value of vaccine.

---


\(^\text{11}\) Healthy-life years (HLY) also called disability-free life expectancy (DFLE), is defined as the number of years that a person is expected to continue to live in a healthy condition.

• Human capital approach-based assessment may be adopted to measure RTS,S impact on broader outcomes like school attendance, labor supply and others.

• Considerations on the budget impact need careful consideration, as in many LMICs immunization programmes are funded from different national and/or international financing streams compared to other malaria interventions.

• Careful attention is needed to account for non-linear interactions of interventions (using dynamic models) to estimate incidence under the "null scenario" and evaluate the iterative effects of adding interventions.

•Generic malaria control interventions generally impact all vector borne diseases and have broader outcomes.

• Details of the dynamic model used to predict the impact of interventions should be included and explained. Multiple models might be considered (i.e. sensitivity analysis to the dynamic structure).

• Model transparency and reproducibility of results should be given preference over complexity.

• Communication of the results to decision-makers and other stakeholder will require careful consideration, given the GCEA perspective.

• In line with previous recommendations, IVIR-AC restates that additional models using a sequential design are unhelpful for public health decision making, as they do not reflect real world implementation.
SESSION 6: Vaccine Delivery Costing Consensus Statement

**Background:**

Vaccination costing studies assist countries in estimating the cost of introducing and delivering new vaccines. The methods used in vaccine delivery costing are currently not standardized, which limits the clarity and reliability of the results, leading to misinterpretation. IVIR-AC previously reviewed costing and planning tools supported by WHO, including the WHO Cervical Cancer Prevention and Control Costing Tool (C4P), the Seasonal Influenza Immunization Costing Tool, the Malaria Vaccine Introduction Costing Tool, the Typhoid Conjugate Vaccine Costing Tool, and the Oral Cholera Vaccine Costing Tool. Costing tools for vaccine delivery have been developed for a variety of diseases and by different groups and the methods need to be standardized.

In March 2018, IVIR-AC concluded that standardization of costing tools would be useful and necessary for comparing the costs of delivery within and across countries and by product or delivery strategy. As a starting point and in preparation for the development of a WHO Guide on Vaccine Delivery Costs, WHO put together a working group that included representatives of organizations working on vaccination costing, including the Bill and Melinda Gates Foundation (BGMF), Centers for Disease Control and Prevention (CDC), UNICEF, WHO, ThinkWell, Harvard T.H. Chan School of Public Health, Johns Hopkins University, and the International Vaccine Institute. The group determined that several different workstreams were conducting vaccination costing and should be consulted in the standardization of definitions, principles, and methods. They presented these findings in the IVIR-AC meeting in March 2019 and IVIR-AC recommended that a workshop be conducted with groups working on the different types of vaccine costing.

Following IVIR-AC’s recommendation, in July 2019, eleven experts from different organizations and institutions in immunization economics gathered in Basel, Switzerland, at the International Health Economics Association. They agreed to develop a consensus statement that presents the differing purposes of the different workstreams on vaccine costing, a review of existing vaccine delivery costing guidance documents and tools and agreed-upon costing terms and principles. As part of this process, they analyzed multiple guidance documents and tools and identified four workstreams for costing guidelines – retrospective routine immunization cross-sectional costs, retrospective single-vaccine costs, projection of new vaccine introduction cost, and projection of national immunization program. They also identified a gap in guidance documents – i.e., that there is no guidance document for vaccine-specific costing that explains the underlying principles for incremental costing assumptions, how to estimate retrospectively as well as for cost projections, and instructions on data collection, sampling, and uncertainty.

WHO will consolidate the information culminated in this review and consensus statement and develop a web page with links to all tools and guidelines. The webpage will present all the different tools and guidelines, their different purposes, and how they relate to each other. They will also develop a vaccine-specific guidance document.

**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?

**Discussions/Considerations leading to IVIR-AC Recommendations**
IVIR-AC was asked to review the multilateral consensus process, to recommend on the next steps, and highlight any lessons learned. They first congratulated the presenters and stressed that this was a tremendous achievement and a beneficial process of bringing together complex organizations that typically don’t work together. IVIR-AC felt that this process strengthened partnerships across organizations and that the outcomes will be very useful.

IVIR-AC stressed that this should be just the first step. Efforts moving forward should consider developing standardized results and results reporting. For now, it would be useful and important for organizations to refer back to the consensus statement. IVIR-AC felt that this process was very important and should be documented (both the process and lessons learned) and published in order to facilitate its use in other applications. IVIR-AC also noted that the approach would be useful for other groups who had presented to IVIR-AC during this meeting, including the burden of disease and immunization coverage estimations. People and organizations would benefit from coming together and looking at how they assess or measure the thing in question and develop consensus statements. This practice would be very useful in many applications. IVIR-AC stressed the importance of maintaining this practice and passing it on to other groups.

IVIR-AC suggested that the new terms and principles be used in a costing example to further refine the consensus definitions and principles and to identify issues on usability or needed refinements.

**Recommendations**

- This is a beneficial and valuable process with constructive and useful outputs, which strengthens the community of practice.
- Continuing collaboration among different organizations and institutions is encouraged to keep the momentum for the next steps.
- Future work harmonizing the definitions and recommendations in different guidelines is recommended.
- A WHO webpage should be set up for summarizing this effort; new work on vaccine delivery costing should refer back to the webpage and consensus statement.
- This is a good model for funders and stakeholders: the process and lessons learned should be written up so that other groups (not necessarily in the immunization area) can learn from it.
**SESSION 7: Vaccine Estimates for Immunization Agenda 2030 (IA2030)**

**Background**

Immunization is a global health success story, saving millions of lives every year. There are now vaccines to 20 life-threatening diseases, helping people live longer, healthier lives. Immunization is a human right and the foundation of the primary health care system. However, nearly 20 million infants a year have insufficient access to vaccines.

WHO is leading the co-creation of a new global vision and strategy to address these challenges over the next decade, to be endorsed by the World Health Assembly in May 2021. The *Immunization Agenda 2030* (IA2030) envisions a world where everyone, everywhere, at every age, fully benefits from vaccines to improve health and well-being. IA2030 includes three impact goals, which will serve as the basis for monitoring and evaluating the success of the program over the next decade. Monitoring and evaluation relies on measurable outcomes to track progress and guide strategic priorities.

The widely quoted estimate ‘vaccines save 2.5 million lives every year’ was generated a decade or more ago. Since that time, countries have expanded their vaccination portfolios to include more pathogens and overall vaccination coverage has increased, rendering the estimate possibly outdated. There is little understanding, documentation, or transparency of the methodology used to generate this estimate and global vaccine program assessments, monitoring and evaluation, global health investment, and strategy development depend on reliable quantitative evidence of vaccine impact.

To this end, WHO’s IVB and DDI – the Data Analytics and Delivery Department in collaboration with the Bill and Melinda Gates Foundation (BMGF), Gavi, the Vaccine Alliance (Gavi), Vaccine Impact Modelling Consortium (VIMC), Centers for Disease Control and Prevention (CDC), the Institute for Health Metrics and Evaluation (IHME), and other partners will establish an updated methodology, to be documented in a transparent manner, and generate updated global and regional vaccine impact estimates, for presentation at the 74th World Health Assembly 2021.

Due to the strategic priority of IA2030, there is an increased need to estimate the number of deaths averted due to vaccination, which can provide the baseline for Impact Goal #1 of IA2030— to reduce mortality and morbidity from vaccine-preventable diseases from across the life course. The scope of work, project objectives, timelines, analytical framework, and methodology to estimate future deaths averted were presented to IVIR-AC, including the current list of 17 pathogens being considered as the basis for the estimations in the 194 WHO Member States.

The project objectives include:

- Update the modeled vaccine impact estimates (for future deaths averted to start).
- 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*

The presenters shared the pathogen and vaccine-specific data availability and needs, the methodology for extrapolation and projection of global, regional, and country-specific estimates, and an overview of future plans to incorporate additional indicators to future deaths averted. More specifically, the approach to estimate antigen-specific future deaths averted due to vaccination involves use of an integrated demographic model.
and the Cohort Component Method of Population Projection (CCMPP)\textsuperscript{13}, which projects the population for each year, country, age and sex combination, and includes the number of antigen-specific deaths occurring under the observed ‘business as usual’ scenario versus the ‘with vaccination’ scenario. The expected output is the difference between these numbers the business as usual vaccine-preventable deaths (VPD) and the VPDs with vaccination, estimated for each country and aggregated to give a global number.

IVIR-AC was requested to provide guidance and methodological feedback on several technical questions to improve the modeling approach, including ways to address double counting of deaths averted when a child has been vaccinated for multiple diseases, the inclusion of different sources of uncertainty, and approaches for comparing health outcomes with short versus long-term impacts.

**Questions to IVIR-AC**

- How to best include a structure of competing risk (to avoid double counting deaths)?
- 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?

**Discussions/Considerations leading to IVIR-AC Recommendations**

IVIR-AC acknowledged the complexity inherent to addressing the questions posed by the presenters, appreciated their efforts, and congratulated them with this undertaking. Overall, IVIR-AC found that the methodology - the integrated demographic model - was an appropriate start for the objectives presented, especially to address the challenges associated with double counting deaths. Utilizing the demographic model, with its mortality envelopes, includes an overall constraint, which will reduce double counting.

IVIR-AC indicated that the dynamic demographic model applied to the inputs and outputs of the time-series disease model outputs from VIMC is a good start. However, IVIR-AC stressed the need to consider several points with respect to the estimation procedure:

- Describe the inputs and outputs pertaining to VIMC time-series data: where those data (e.g. for coverage, prevalence, mortality) are coming from, and be sure to look for any overlap or duplication across data sources.
- Detail the types of structural modeling employed: what is the prioritized strategy, what are possible alternative strategies.
- How to encompass several sources of uncertainty.

IVIR-AC went into the several aspects of model uncertainty to consider: (i) input uncertainty, including time-series of vaccine-preventable disease cases and deaths, and demographic uncertainty (e.g. from the United Nations World Population Prospects); and (ii) structural uncertainty, associated with the choice of the model itself (e.g. type of statistical model used).

IVIR-AC highlighted the strength of the demographic model to generate several outputs useful to policymakers, especially tangible outcomes such as deaths by age group, under-five deaths averted, adult deaths averted, and years of life lost.

Beyond the methodological considerations underlying the modeling approach, IVIR-AC stressed the importance of communicating the results, which was echoed by the presenters, who requested assistance with this. Each output and result generated by the model carries a different meaning and it is necessary to address

the appropriate use cases for each output. Use cases need to be well defined and explicitly communicated. Limitations also need to be explicitly communicated. IVIR-AC felt it could be beneficial to communicate results in terms of ranges. In this way, the inherent uncertainty underlying an estimate is more explicitly captured.

IVIR-AC highlighted that the methodology is still underdeveloped in several areas and could benefit from a more thorough technical consultation outside the scope of the meeting. They understand the presenters’ choice to use a complex statistical model but noted that the full estimation strategy and its specific analytical steps, including functional forms, remain to be fully described.

IVIR-AC found the scope of work ambitious considering the aggressive timeline. The project team shared their next steps and priorities based on several factors, and IVIR-AC suggested to look at data availability, data quality, and extent of disease burden impact when prioritizing next steps.

IVIR-AC recognized the presenters’ concerns with respect to short and long-term outcomes, as this question arises regularly when addressing vaccination. It will be important to consider the broader time horizon (e.g. deaths averted over lifetime of vaccines) when capturing the long-term outcomes from certain vaccines (e.g. HPV to protect against cervical cancer over a long-time period), whose mortality impact is not observed until decades after vaccination.

**Recommendations**

- The demographic model proposed is a good start to provide a reasonable overall framework to avoid double counting deaths, due to its explicit inclusion of mortality envelopes.
- IVIR-AC recommends the team elaborates on how to assimilate the impact estimates for individual vaccines (e.g. from VIMC and other sources) into the demographic modeling approach to avoid double counting, especially for areas where the burden of vaccine preventable diseases (VPD) is large. For instance, at the country level, technical advice will be needed on how the summation of all VPD-related deaths are constrained by specific age-group mortality envelopes.
- The full estimation strategy and its specific analytical steps remain to be fully described. Thorough thinking will be required to develop the statistical estimation (e.g. use of functional forms, calibration methods) of the currently proposed static regression model, which draws from the assembling of multiple independent and dependent variables that emerge from heterogeneous sources of modeled estimates (e.g. time series of incidence and mortality from mechanistic dynamic disease models of transmission; population and fertility assumptions; burden of disease; vaccine coverage). There are also concerns about out-of-sample extrapolation (e.g. extrapolating vaccine impact from Gavi countries to high-income countries).
- In order to include different sources of uncertainty, you need to fully reflect the incorporation of both:
  - *input uncertainty*; e.g. uncertainty ranges from modeled VPD incidence and mortality; uncertainty in vaccine coverage forecasts.
  - *structural modeling uncertainty*; e.g. from the estimation (‘regression coefficients’) strategy selected as described above.
- Given that the work agenda is complex, and the proposed timeline is aggressive, prioritization should be exercised with respect to the level of uncertainties anticipated in the many different impact estimates. A suggestion was made to focus first on mortality estimation and vaccines with higher anticipated impact and more reliable data available.
- In order to best compare health outcomes with a short-term versus long term impact (e.g. immediate mortality reduction conferred from measles versus long term mortality reductions from HPV vaccines), IVIR-AC recommends reporting of both cohort- and period-specific impact.
- For example, report health benefits:
  - among 2021-2030 cohorts of vaccinees over their lifetime (which goes beyond 2030).
- within the time-period (2021-2030).
  - This will provide a clear and transparent stepping-stone from which further analyses can be undertaken by analysts and policymakers.
  - Use cases of the estimates need to be carefully defined to ensure the results are not misused. For example, possibly minimize the availability and use of estimates at the country level and prioritize the use of estimates at the global and regional level.
  - The project team should consider connecting with suitable members of IVIR-AC who could conduct a more detailed review of methodology and provide advice.
SESSION 8: Country-led Assessment for Prioritization on Immunization (CAPACITI)

Background

The Country-led Assessment for Prioritization on Immunization (CAPACITI), previously known as Total Systems Effectiveness (TSE), was first introduced to IVIR-AC in March 2018 as a pilot project funded by the Bill and Melinda Gates Foundation (BMGF) and led by the Immunization Vaccines and Biologicals (IVB) programme of WHO, in partnership with UNICEF, GAVI, PATH and others. The primary aim of the pilot project was to test “multi-criteria decision analysis” (MCDA) to facilitate product selection and prioritization of vaccine products at the country-level and promote decision-making from a holistic systems perspective, with consideration of coverage and equity.

Through piloting TSE from the country perspective, WHO developed CAPACITI, which still echoes the original ethos and intention of TSE, with an expanded aim to bridge the gap between vaccine users and vaccine developers and strengthen decision making at the country level. The latest iteration of CAPACITI reflects the insights gained from multiple pilot studies in Africa, Asia and the Americas, and the incorporation of several rounds of refinements incited by recommendations from IVIR-AC during CAPACITI’s multiple stages of development.

CAPACITI’s goal is to strengthen low and middle-income countries (LMIC)s’ ability to evaluate immunization choices – products, services, and/or strategies – according to their own country priorities and programme context, for immunization programme decision making and to inform vaccine supply, research, and development.

Countries’ ability to evaluate multiple vaccine products and services is essential to achieving the Immunization Agenda 2030 (IA2030) goals. However, WHO’s current guidance for priority-setting within national immunization programmes does not currently include a framework and process to compare and assess the trade-offs between multiple immunization options. CAPACITI’s fundamental strength is its focus on contextually-driven prioritization across options, to benefit the country and its vaccine users, and to possibly drive research and development toward contextually-relevant vaccine products or services.

CAPACITI is composed of three frameworks:

- The Decision Support Framework is the most advanced of the three frameworks. The framework documents and structures decision-making to select or prioritise between multiple immunisation products, services, or strategies. The EXCEL-based Decision-Support Tool, the main application of the Decision Support Framework, is now ready for public release in December 2020.
- The Country Context Framework aims to ensure that programme considerations and national strategic priorities are considered during decision-making.
- The Innovation Framework is a set of processes to get country and regional input on vaccine research and development.

Considering IVIR-AC’s historic involvement and engagement in both TSE and CAPACITI, as well as their most recent recommendations to improve the Decision Support Tool in September 2019, IVIR-AC was asked to assess the readiness of the Decision-Support Tool for release in December 2020 and provide feedback on the Country Context and Innovation Frameworks.

Questions to IVIR-AC
• 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?

Discussions/Considerations leading to IVIR-AC Recommendations

IVIR-AC praised the whole CAPACITI team for their hard work and persistence to keep CAPACITI moving forward. They highlighted the team’s efforts to address all of IVIR-AC’s previous comments and suggestions, to make improvements, and to pilot and test the tool in multiple settings. IVIR-AC acknowledged that the new name, CAPACITI, was informative and meaningful and an improvement from the previous TSE. They confirmed that the Decision Support Tool would be ready for release in December 2020 and recognized the significant changes which have led to its current iteration. They pointed out several positive elements to the current tool:

• It has additional flexibility and added constraints; has been tested in multiple countries; is of high quality and rigorous; has an elegant and user-friendly interface; has a strong value proposition and embeds the value of respect by delivering guidance rather than direction; it supports and prioritizes country ownership, sustainability and integration; it was clearly designed for specific need and a clear purpose; it is more relevant than ever, with trade-offs from the current and ongoing COVID-19 crisis; it addresses the need to enhance citizen engagement in the new “participation” tab, which looks at voices of different stakeholders, asks countries to consider those systematically, and to address how to engage with them.

IVIR-AC provided guidance on ways to improve the tool moving forward, in the medium term, following the tool’s release in December 2020.

• The caregiver element could be improved with added cues, as it is currently drowned out by the prompt for expert voices. Since caregivers are unequivocally impacted by the introduction of a new intervention and fulfilling its requirements for implementation, it is important not to forget their perspective.
• Qualitative methods may be a better choice than surveys for stakeholder participation, as survey developers tend to frame the issues toward the expected answer.
• The tool may benefit from more pilot testing to confirm its utility to evaluate strategies to improve uptake, before promoting this. The project team confirmed that plans are in place for pilot testing in West Africa in the near term.
  o The idea of choosing between strategies may need reconsideration as research finds that multifactorial interventions have more success improving uptake. For example, community based interventions when implemented in combination.14
• As for how the tool is used and promoted in countries, it should strengthen a country’s existing knowledge base and/or decision-making process or structure, rather than replacing it.
• Of course, there should be explicit documentation and guidance for countries to use the tool; however, the tool could also provide guidance and documentation on any elements which it promotes or suggests countries to do. It could perform a capacity building function and improve any existing knowledge-base on assessing epidemiological data, performing economic evaluations, bottleneck analysis, value elicitation, or community engagement, etc. CAPACITI should serve to strengthen any existing knowledge base and decision-support structure. Over the months and years to come, CAPACITI could develop documents and provide trainings/ workshops on use of the tool itself as well as on economic evaluation, bottleneck analysis, value elicitation, community engagement, etc.

14 https://www.thecommunityguide.org/content/task-force-findings-increasing-vaccination
• As the tool rolls out, it will be critical to develop a clear plan for monitoring and evaluating the tool for impact and to utilize feedback from its use in a naturalistic environment.
  o The tool is of high-quality and extremely comprehensive. In practice, the tool’s efficacy will also be determined by the feasibility to execute and complete the tool. If the length of the tool compromises its effectiveness, a lite version could be developed following early evaluation.

Country context framework

IVIR-AC praised the team for incorporating feedback from program implementation and encouraged the team to continue refining, as the framework could provide a very useful way for countries to systematically approach immunization prioritization. Because it is costly and time intensive to execute, it will be important to do a formal quantitative and qualitative evaluation of its use, including both process and outcome indicators. This could include a before and after study or one between countries. This would provide an assessment of measurable changes from using the tool.

IVIR-AC stressed the constant challenge of striking a balance to develop something feasible and still efficient. Although primary data collection is not required, which is some ways makes it easier to use and therefore more effective, that could mean that decisions rest on assumptions that are impressionistic, subjective, and not based on evidence. IVIR-AC cautioned against becoming too unwieldy in the effort to be all things to all people.

Innovation framework

For IVIR-AC, the Innovation framework was noted as the most challenging. Although they agree that it is important to have a country’s needs addressed with R&D, countries have a difficult time imagining a product way in the future. Also, what is the incentive to engage in the process when there is no commitment by developers. There is no guarantee on either side. So, maybe it would be best to focus on a short timescale (COVID-19 could be used to define what countries want, to see if their preferences can give rise to modifications in vaccines coming to market).

IVIR-AC noted that:

• People struggle to think about products that are not in existence yet.
• The process may select for doers not risk takers nor entrepreneurs.
• People have difficulty thinking innovatively, and it will be difficult to get them interested in the process of contributing to R&D in the long-term.
  o You could use methods that encourage innovation – where creativity is required, and diversity at the decision table, and thinking out of the box.
• If valuable data is being collected from countries, it could be used to generate revenue as a sort of market intelligence.
• In order to engage people, there may need to be formal communications and agreements drafted to assure countries and developers of vaccine development and vaccine utilization, respectively.

It would be interesting to know what industry thinks about this process. Currently, the discourse speaks less about industry engagement. How does industry currently decide on their R&D agenda?

It could be a good idea to improve the systematic process whereby CAPACITI is engaged with R&D. The team highlighted their hope to drive things forward by having R&D-centered CAPACITI focal points sitting at the country level.

Recommendations
IVIR-AC acknowledges the helpful modifications made to the Decision Support Tool (e.g. increased flexibility, inclusion of constraints) in response to IVIR-AC’s latest comments and recommendations.

**Decision Support Framework**

- With the following caveats, the decision support tool is ready to be made publicly available:
  - It would be useful to have additional capacity-building training modules/material in the medium term.
  - There should be an ongoing evaluation of the implementation of the decision support tool following its release.
  - Need to ensure that CAPACITI facilitates countries to strengthen capacity in use of existing processes and skills e.g. interpretation of epidemiological data and licensure dossiers, economic evaluation, bottleneck analysis, value elicitation, community engagement etc., rather than replacing it.
  - The wording in the Participation Section could be modified to ensure that programme recipients (e.g. caregivers) are given more prominence.
  - CAPACITI is comprehensive, but the trade-off is in its length. It is worth considering a light version in the future after early evaluation.
- For the comparison of vaccination strategies, there should be remaining caution in its use, as this has not yet been pilot tested. CAPACITI’s use as a strategy comparison tool needs to avoid the risk that two complementary strategies are compared (e.g., reminder vs. recall). Evidence shows that two or more interventions are likely to increase uptake than one alone. However, in some there could be legitimate choice between strategies: e.g., a choice between two methods of provider audit and feedback. This site may be a useful guide for classifications of strategies [https://www.thecommunityguide.org/content/task-force-findings-increasing-vaccination](https://www.thecommunityguide.org/content/task-force-findings-increasing-vaccination).
- These caveats apply to medium-term work and should not delay launching in December 2020.

**Country Context Framework**

- This framework is potentially very useful. It is good to incorporate a systematic approach to identify barriers to immunization.
- The focus should be on simplicity and feasibility, given early feedback from pilots.
- Since it is an expensive process in terms of human and financial resources, this framework needs formal evaluation – not just ad hoc feedback, but also before and after or between-country comparison study using qualitative and quantitative methods. Evaluation needs both process (e.g. have issues identified been accurate and have they led to change) and outcome indicators (e.g. has coverage and equity improved following use of the tool).

**Innovation Framework**

- It is recommended to apply the innovation framework to situations in which there is a short timeline for products coming to market (e.g. Developing Country Vaccine Manufacturers Network (DCVMN) production of a vaccine similar to one already on the market, or a COVID-19 vaccine), which can be leveraged.
- Two possible paradigms could be considered:
  - Market intelligence: Since the information is valuable to private manufacturers and expensive for countries to collect, this could be sold to manufacturers to generate revenue. Money earned can then be put into a fund to develop resources in vaccine data collection and decision making in countries who take part in the process. A suitable model could be the Pandemic Influenza
Preparedness framework funded by influenza vaccine manufacturers who benefit from influenza surveillance.

- Advanced market commitments: Information from the framework could be placed in the context of more formal communications, and eventually lead to binding commitments between suppliers and buyers of vaccines.

- To facilitate country stakeholders’ openness to innovation, CAPACITI should consider using specialized facilitation techniques which enhance their ability to think creatively and look at future needs. This article may also be useful, under “The Innovation” https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2690184/.

- The scope of the innovation framework should incorporate interventions to increase coverage and equity that are not product-based. These could improve uptake of vaccine products selected through use of the Decision Support Tool.

- In communicating CAPACITI, it would help to have a worked example to illustrate meaning throughout.
Background

Understanding pathogen-specific disease burden is critical to assessing the potential benefit of a targeted vaccine. Vaccine benefit or the impact of the vaccine to reduce pathogen-specific disease burden, is a fundamental part of priority setting for vaccine development, introduction and use, and essential when communicating the ‘full value’ of a vaccine.

Mortality estimates for enteric diseases are generated by two main modelling groups, the Institute for Health Metrics and Evaluation (IHME) and the Maternal Child Epidemiology Estimation (MCEE) group. A divergence of the groups’ 2013 and 2016 <5 year mortality estimates for Shigellosis infection-related diarrhea (MCEE reported 28,000 deaths, IHME reported 63,713 deaths) and ETEC, or Enterotoxigenic Escherichia coli (MCEE reported 42,000 deaths, IHME reported 18,669 deaths), has had implications on investment in the development of vaccines against these pathogens.

In 2018, IVB’s Product Development for Vaccines Advisory Committee (PDVAC) recommended to evaluate diarrheal disease burden models, which led to the development of an independent working group comprised of PDVAC and IVIR-AC members, as well as enteric vaccines experts- the Burden of Enteric Disease Working Group (BoED-WG). Since 2018, the BoED-WG has developed and is completing multiple work-streams to assess the source data, methodology, assumptions, and outputs of IHME and MCEE estimates. The BoED-WG also commissioned two systematic reviews to identify critical data to improve methodologies of both modelling groups. The group partnered and consulted with IHME and MCEE throughout the process. As a result of the completed workstreams and proposed iterations to methodologies, both modelling groups expressed intent to calculate a revised set of <5 mortality estimates for ETEC and Shigella.

WHO Secretariat of the Burden of Disease project presented the overarching approach, the planned and completed workstreams, an overview of the results, and recommendations for future <5 mortality estimates to IVIR-AC.

The project engaged in four workstreams:

- Data Gaps –to identify and address areas of commonality between the IHME and MCEE where additional evidence may improve future estimates.
- Study Quality Exercise: to improve the understanding and quality of the studies included in the modelling processes by assessing the quality of all ETEC and Shigella studies and measuring the impact of low quality studies on mortality estimates.
- Data processing exercise: a high-level assessment of how study data is processed in both models, and the impact of applying IHME model adjustments on mortality estimates.

The main results of the mortality work workstreams included:

- A comprehensive summary of odds ratios (ORs) of developing diarrhea when a pathogen is detected in stool for 15 pathogens, all age groups, and all WHO regions. ORs can be used as inputs to mortality burden models to improve future estimates. There is substantial heterogeneity of ORs by pathogen, age, child mortality strata and pathogen detection method which reflects the frequency of exposure, asymptomatic infection, or development of immunity.
- An analysis of case fatality rates for 15 pathogens, all age groups and WHO regions. Pathogen specific CFRs can be incorporated into modelling estimates to account for differences in mortality between pathogens. There is substantial heterogeneity in the estimated case fatality rates (CFRs) both within and between pathogens. For some pathogens, the CFR was higher in children under one year old, living in the WHO African region (AFRO), 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.

- For 2016 estimates, out of 36 studies for ETEC, none were used by both IHME and MCEE; and out of 72 studies for Shigella, none were used by IHME and MCEE. The lack of overlap reflects different inclusion criteria that are adopted by the groups. 40% and 58% of studies obtained the maximum quality score for Shigella and ETEC. Similar quality scores were observed for studies used by both groups, both for ETEC and Shigella.
- The IHME diagnostic test adjustments increase the Shigella mortality estimate by approximately twofold, and slightly decrease the ETEC mortality estimate. The other IHME adjustments have a negligible impact on the estimates. Alternative approaches to the diagnostic test adjustment are being considered, but if adopted, could likely decrease the gap between mortality estimates of both modelling groups for Shigella, ETEC, and other pathogens.

IVIR-AC was asked to comment on whether the workstreams could impact the assessment of pathogen mortality, on the relative value of vaccines, and on whether the approach should be incorporated in future enteric mortality modelling estimates.

**Morbidity Workstream**

To fully understand the full value of vaccines, components such as mortality, morbidity and socio-economic impact should be considered. The BoED WG conducted the assessment of mortality estimates and is now proposing to expand the scope of work to measure the impact of enteric infections on long-term morbidity. The pathogen-specific long-term morbidity burden is not captured in GBD estimates, which under-estimates the potential value and benefit of enteric vaccines. A comprehensive understanding of long-term morbidity is required to make informed decisions about vaccine development, introduction and use.

Repeated enteric infection causes intestinal damage resulting in malnutrition, wasting and longer term sequelae including growth faltering, cognitive and mental impairment. The group presented their proposed workstreams to systematically capture evidence illustrating the long-term morbidity impact of enteric pathogens including indicators and methodologies to measure such morbidity. The group will also assess whether the evidence collected on disease impact, and the existing studies/methods to measure morbidity could inform the development of a standardized framework to quantify the burden.

IVIR-AC was asked to comment on the proposed scope of work to measure the impact of enteric pathogens on morbidity, and if it is considered an appropriate next step for further evaluating the full burden, and ultimately the value, of enteric vaccines.

**Questions to IVIR-AC**

**Related to the differences in mortality estimates for enteric pathogens**

- 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 the impact of enteric pathogens on morbidity - proposed scope of work**

- 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 an appropriate next step for further evaluating the full burden, and ultimately the value, of enteric vaccines?

**Discussions/Considerations leading to IVIR-AC Recommendations**
Mortality Scope

IVIR-AC congratulated the group on their very important work highlighting the comprehensive scope of the BoED projects and the exemplary collaborative partnership. They applauded the group for contributing to the evidence base on global enteric disease mortality burden and highlighted the multiple publications generated by the group, which attested to their commitment and productivity. IVIR-AC felt that the groups’ collaborative and deeply investigative approach would be useful to other groups and encouraged the BoED team to publish not only the model comparison approach, but also the experience of working together with the two different groups to analyze their different approaches. Documenting the experience would be useful to encourage other groups to follow in the same footsteps.

IVIR-AC stressed that each workstream contributed to a better understanding of how mortality estimates are determined, and results of this work will impact the assessment of pathogen mortality going forward. One important next step could be to further strengthen the partnership with IHME and MCEE and possibly expand to include other groups. A working group could look into developing consensus definitions, or some standardization on approaches and/or inclusion criteria for modelling mortality estimates. In addition, the approach to ETEC and Shigella could be applied utilized for other pathogens, in partnership with IHME and MCEE, to gain a broader understanding of the implications of diverging approaches and/or inclusion criteria on mortality estimates for multiple pathogens.

IVIR-AC touched on:

1. It is always important to critically evaluate the inputs of the models. For example, each model may incorporate different elements in their mortality envelopes, which will of course lead to a divergence.
   a. The contextual aspects of the studies contained in the models should be examined with respect to socio-economic development and quality of the health system. Is the health system well resourced? Are the patients in the studies hospitalized or in a community setting? All these considerations need to be looked into, to better understand how to interpret the individual studies within a model, and how that might be influencing the case-fatality rate.
   b. You can include socio-economic aspects, including the health system infrastructure, as part of the meta-analysis’s adjusted factors for the case-fatality rate.
2. It is always important to assess the quality of the data in the different studies, so it is great that the project team graded the studies using the Newcastle system.

Morbidity Scope

IVIR-AC fully endorsed the inclusion of mortality plus long-term burden as part of an assessment of the full value of vaccines and stressed the importance of looking at the wider population and economic impact. IVIR-AC concurred that the focus on growth faltering was a good idea, especially building on the available GEMS study data. For the full value of vaccine assessment, they drew attention to the importance of mortality, and the economic impact, as an aspect of long-term burden. They suggested that the approach could potentially include a thorough analysis of economic impact, for example number of severe cases being hospitalized. The long-term morbidity burden could be linked to the human capital cost and the full value of vaccine could illustrate how reduction in long-term burden could increase different economic and human capital outcome measures, such as school attendance, school performance, and even wages.

IVIR-AC stressed again the importance of collaboration and left it could be extremely important and useful to the group to collaborate with existing studies, such as GEMS and the MAL-ED studies, which are beginning to publish some of their work. There are new findings which point to the long-term consequences of enteric pathogen infection on cognitive development and other aspects of development. IVIR-AC found the long-term burden workstreams presented to be appropriate and felt that a critical assessment of all outcomes which may be linked to enteric diseases would be important. It would be important to include growth faltering, as
well as long-term conditions and school attendance and beyond. It would be good to learn and borrow from other studies, such as ABCD, CHAINS, the GBD. It would be good to develop a working group with multiple partners, possibly from these existing studies. IVIR-AC also suggested using causal inference pathways statistics to investigate the causal links between enteric pathogen infection and the various outcome measures.

IVIR-AC also warned the group of potential confounders when looking at the long-term. For example, malnutrition, although it may be considered an outcome of enteric infections, it may also be causative when looking in the long-term. It will be important to examine potential confounders critically and it would be also be very useful to identify markers for long-term enteric infection, possible in the gut microbiome.

**Recommendations**

**Mortality Workstream**

- IVIR-AC commends both the high-quality scientific work and the high degree of exchanges and collaborations produced by all researchers and institutions involved in the process.
- The workstreams presented can affect the assessment of pathogen mortality and therefore relative value of vaccines against these pathogens. The results of the mortality workstreams should be included in future enteric mortality modeling estimates.
- The process, including the specific steps in the comparison of model estimates, should be documented: this is good practice and could serve as a model for future exercises. Such exercises could benefit other disease areas where multiple groups are conducting burden of disease estimates.
- Incorporating results can improve the robustness and credibility of mortality estimates. There might be a need for convergence of independent estimates and perhaps this could be achieved through this collaborative work with the proposal of consensus definitions, harmonized protocols for data selection and use, focusing only on the best available evidence as shown in the analyses (e.g. focusing only on studies with the most appropriate diagnostics methods or those conducted more recently as pathogen diversity might have changed over time), and accounting for local context considerations (e.g. adjustments for socioeconomic levels and health system development).
- The proposed publications that describe the comparison exercise, workstreams, and perspective of modelers could also discuss how the exercise and exchange have strengthened the collaboration among partners, and how it has (or has not) led to rethinking of the selection criteria for data inputs and/or methods by the modeling teams involved.
- If feasible, an assessment of the quality of the studies should be included in the systematic reviews of Odd Ratios and Case Fatality Rates. This inclusion could also allow assessment of how low-quality studies might be influencing the high heterogeneity observed in the results.
- IVIR-AC notes the great relevance of two significant findings: 1) that indeed no study was both used by IHME and MCEE to inform their estimates, and 2) that the diagnostic adjustments incorporated by IHME were responsible for increasing mortality estimates produced by IHME for Shigella, and decreasing mortality estimates for ETEC. These results seem to significantly contribute to the discrepancies in the mortality estimates for ETEC and Shigella. Moreover, it is important to highlight that the possible impact on mortality estimates of other enteric pathogens is unknown.

IVIR-AC agrees with the morbidity workstream moving forward, but stresses that progress is contingent on the reliable, high-quality evidence of causality.

**Morbidity workstream**

- IVIR-AC fully endorses the importance of long-term morbidity outcomes, while also highlighting the importance of mortality and acute morbidity outcomes. The assessment of the full value of vaccines must
include the impact on mortality and morbidity and possibly even broader population implications, once good quality evidence is available on causalities.

- IVIR-AC agrees with prioritizing a systematic review of evidence on the impact of enteric pathogens and diarrhea on long-term morbidity together with an assessment of the quality and external validity of that evidence; particularly, the strength of evidence about causality. This could be followed by meta-analyses, if the evidence is strong enough.

- IVIR-AC encourages the group to evaluate broader human capital considerations as consequences of long-term morbidity impact (e.g. growth faltering): for example, on the impact on school attendance and educational performance (e.g. school tests). Indeed, within the vicious cycle of poverty, other consequences that stem from impaired cognitive development may include loss of human capital and productivity. IVIR-AC suggests these be evaluated for inclusion in both their reviews as well as in the development of metrics for what might be the full value of vaccines.

- IVIR-AC highlights the importance of two longitudinal studies, Global Enteric Multicenter Study (GEMS) and Malnutrition and Enteric Disease Study (MAL-ED), for which results have started to come out\(^\text{15}\). The collaboration with the research team of these studies should be maintained and strengthened for addressing the long-term morbidity of enteric pathogens.

- The assessment of long-term morbidity is challenging given the difficulties of establishing causality. High-quality evidence (e.g. from randomized studies of interventions) seeking to support a causal association between diarrhea/enteric pathogens and malnutrition (“the double burden”) and perhaps with chronic non-communicable diseases (obesity, type 2 diabetes, metabolic syndrome, CVD, “the triple burden”) is encouraged. Accordingly, for the work moving forward, it is relevant to discuss, evaluate, and, if appropriate, borrow from existing studies (Antibiotics for children with severe diarrhea (ABCD), Childhood Acute Illness and Nutrition (CHAINS), risk factors for Global Burden of Disease (GBD)), to shed light and inform on which long-term conditions to include and how.

- Additionally, perhaps in collaboration with the two longitudinal studies (GEMS and MAL-ED), there may be space and need for the use of causal inference models. These can help assess the causal pathways between multiple variables (i.e. exposures of interest and confounders). Proper analyses of the data using directed acyclic graphs may allow for adequate covariate adjustment and inference of causal pathways, through the estimation of direct and indirect paths. This methodology allows the assessment of associations as causal paths, their significance and magnitude.

## ANNEX

### ANNEX 1 - IVIR-AC Meeting Agenda

#### DAY 1

<table>
<thead>
<tr>
<th>Duration</th>
<th>Title</th>
<th>Content and key questions to IVIR-AC</th>
<th>Purpose</th>
<th>Proposed speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>1200-1205 5’</td>
<td>Opening of Meeting</td>
<td>• Update on global strategies and issues of relevance to WHO</td>
<td>For information</td>
<td>K O Brien, Director, Department of Immunization, Vaccines and Biologicals</td>
</tr>
</tbody>
</table>
| 1205-1215 10’ | Introduction/Objectives of the meeting | • Administrative issues  
• Objectives of IVIR-AC meeting and outline of the 1st day | | P Lambach  
W Orenstein |
| 1215-1225 10’ | Background | • 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 | Problem statement | • Understanding risk-benefit of proceeding with immunization services during COVID outbreaks evoke the need for a better understanding of transmission dynamics  
• Questions to IVIR-AC  
  o Does the model address the key analytic question, i.e., | For recommendation | Susan Wang |
What is the risk of SARS-CoV-2 transmission to communities and to health workers:
- 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?
  - What is the risk of SARS-CoV-2 transmission to health workers?
  - How robust are the conclusions of the modelling work?
    - 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 characteristics translate into different transmission risks for communities and health workers and if so, how?

**Background reading materials:** Full report on risk of SARS-CoV-2 transmission

<p>| 1240 - 1300 | The risk of SARS-CoV-2 transmission to | Presentation of modelling approach to understand risk of SARS-Cov-2 transmission by varying (I) | K Frey / B Hagedorn |</p>
<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>15’</td>
<td>communities and to health workers in LMICs under different health service delivery conditions</td>
<td>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)</td>
</tr>
<tr>
<td>1300-1330 30’</td>
<td>Q&amp;A and Discussion of recommendations to SAGE</td>
<td>Discussion on conclusions for SAGE (to be continued in closed session)</td>
</tr>
<tr>
<td>V Pitzer and Joseph Wu</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**COVID-19 Session 2: Frameworks and methods to guide COVID 19 vaccine development**

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Notes</th>
</tr>
</thead>
</table>
| 1400 – 1410 10’ | Impact modelling of potential COVID vaccines | • Update on SAGE WG deliberations on policy-relevant use case scenarios and modelling needs.  
• Question to IVIR-AC:  
  • 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?  
  
  **Background reading materials:** Modelling questions: [https://www.who.int/immunization/policy/sage/SAGE_WG_COVID19_Vaccines_Modelling_Questions_31July2020.pdf?ua=1](https://www.who.int/immunization/policy/sage/SAGE_WG_COVID19_Vaccines_Modelling_Questions_31July2020.pdf?ua=1); Overview table of potential modelling groups, Value framework, CMCC Model Fitness-for-Purpose Assessment Report |
<p>| A Wilder-Smith |
| 1410 - 1430 20’ | What is the best use of a COVID-19 vaccine during time of limited supply? | 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&amp;A and Discussion of recommendations to SAGE | Discussion on conclusions for SAGE (to be continued in closed session) |
| W Ndifon and J Leask |
| 1500-1510 10’ | Wrap up | Summary of day’s findings and request any follow up from WHO Secretariat/IVIR-AC FPs for closed session |
| For information | W. Orenstein, Chair |</p>
<table>
<thead>
<tr>
<th>Duration</th>
<th>Title</th>
<th>Content and key questions to IVIR-AC</th>
<th>Purpose</th>
<th>Proposed speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>1200 - 1205</td>
<td>Introduction</td>
<td>• Recap of previous day and objectives for the day</td>
<td>For information</td>
<td>W. Orenstein, Chair</td>
</tr>
<tr>
<td>5’</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1205 – 1225</td>
<td>Problem statement</td>
<td>• Since 2019 WHO and UNICEF are reviewing modelling approaches to estimate national immunization coverage&lt;br&gt;• A decision is needed to select a model to replace or complement the currently used rule-based approach to these estimates&lt;br&gt;• Questions to IVIR-AC : &lt;br&gt;   o In light of use cases for WUENIC and observations from doing simulations, what does IVIR-AC see as the main pros and cons of an approach vis-à-vis the current rule-base method?&lt;br&gt;   o What model to estimate national immunization coverage for Member States would IVIR-AC recommend to WHO and UNICEF replace and or/complement WUENIC?</td>
<td>For recommendation</td>
<td>M Gacic-Dobo</td>
</tr>
<tr>
<td>10’</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1225 - 1245</td>
<td>Comparison of models available</td>
<td>• The models currently available and reviewed by WHO/UNICEF with previous support of IVIR-</td>
<td></td>
<td>M Diallo</td>
</tr>
<tr>
<td>Time</td>
<td>Session</td>
<td>Content</td>
<td>Background material</td>
<td>Speaker(s)</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>20’</td>
<td>AC will be presented to discuss pros and cons of each method</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1245 - 1255</td>
<td>Optimising WUENIC: improvements to the deterministic methodology and</td>
<td>Considerations to inform IVIR-AC on the options for managing WUENIC 2.0 and optimizing its</td>
<td>C Danovaro</td>
<td></td>
</tr>
<tr>
<td>10’</td>
<td>WUENIC 2.0</td>
<td>processes and outputs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1255-1335</td>
<td>Q&amp;A and Discussion</td>
<td>IVIR-AC discusses presentation, clarifies on content and acknowledges main issues</td>
<td>V Pitzer V Nankabirva W Orenstein</td>
<td></td>
</tr>
<tr>
<td>40’</td>
<td></td>
<td>Decision on discussion items for closed session: advice to WHO and UNICEF on model selection or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>WUENIC or a combination of approaches</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR-MAPs (Measles-Rubella Microarray Patches)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1430-1440</td>
<td>Accelerating the clinical development of MR-MAPs (Measles-Rubella</td>
<td>Content:</td>
<td>For information</td>
<td>B Giersing / M Hasso-Agopsowicz</td>
</tr>
<tr>
<td>10’</td>
<td>Microarray Patches): an introduction to workstreams.</td>
<td>- High-level summary of activities related to MR-MAP product development</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Rationale for MR-MAP use case sizing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Background material:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- MR-MAP target product profile (MR-MAP TPP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Executive summary and methodology of the Vaccine Innovation Prioritisation Strategy (VIPS) on</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1440-1510</td>
<td>Understanding where and how will MR-MAPs be used: Identification of</td>
<td>Content:</td>
<td>For information</td>
<td>C Mantel (MMGH Consulting) M Ko (MMGH Consulting)</td>
</tr>
<tr>
<td>30’</td>
<td>MR-MAP use cases and approach to size the MR-MAP use cases</td>
<td>- Identification and validation of use case scenarios to deliver MR-MAPs: overview of</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>methodology and results</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Methodology to estimate the size of the MR-MAP use cases: anticipated variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Key questions regarding the methodological approach and limitations of sizing of use cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Background material:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- A report to develop and validate the MR-MAP use cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Session</td>
<td>Notes</td>
<td>Recommendation</td>
<td>Facilitator</td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------</td>
<td>------------------------------</td>
</tr>
</tbody>
</table>
| 1510-1540  | Q&A and Discussion | • 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  | Wrap up       | • Summarize day’s findings and request any follow up from WHO Secretariat/IVIR-AC FPs for closed session                                                                                                     | For information          | W. Orenstein, Chair          |
### DAY 3

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Description</th>
<th>For recommendation</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1200–1205 5’</td>
<td>Introduction</td>
<td>• Recap of previous day and objectives for the day                                                                                                                                                          For recommendation</td>
<td>W. Orenstein, Chair</td>
<td></td>
</tr>
</tbody>
</table>
| 1205–1215 10’ | Background            | • 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.  
• IVIR-AC agreed in 2019 that this is not a real-world scenario and would not adequately inform policy.  
**Background documents:** will be made available on 18 Sep (see SharePoint)                                                                                           | For information    | M Hamel                          |
| 1215–1245 30’ | CHOICE framework      | • 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   | • 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                                                                 |                    | D C Lyimo, V Pitzer, H H Farooqui |
### Vaccine delivery costing consensus statement

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Description</th>
<th>Recommendations</th>
<th>For recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1345-1355 10’</td>
<td>Background</td>
<td>Recap of recommendations and updates by IVIR-AC in 2018 and 2019</td>
<td>KHT Yeung/R Hutubessy</td>
<td></td>
</tr>
<tr>
<td>1355-1415 20’</td>
<td>Consensus statement of vaccine delivery costs</td>
<td>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</td>
<td>A Levin</td>
<td></td>
</tr>
<tr>
<td>1415-1445 20’</td>
<td>Q&amp;A and Discussion</td>
<td>IVIR-AC discusses presentation, clarifies on content, finds consensus, and acknowledges main issues</td>
<td>M Jit and S Verguet</td>
<td></td>
</tr>
</tbody>
</table>

**Background reading materials:**

1. Draft of consensus statement with annex
2. Recommendations by IVIR-AC in Mar 2018
3. Recommendations by IVIR-AC in Mar 2019
4. Summary of updates to IVIR-AC in Sep 2019

### IA 2030 Modelling

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Description</th>
<th>Recommendations</th>
<th>For recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1500-1510 10’</td>
<td>Background</td>
<td>Background information for the estimation of global deaths averted/lives saved due to vaccination. Data will inform IA2030 M&amp;E Framework development and in particular one of the impact goals. Given the strategic priority of the IA2030 there is an increased need to estimate the number of deaths averted due to vaccination</td>
<td>A Lindstrand</td>
<td></td>
</tr>
<tr>
<td>1510-1530 20’</td>
<td>Analytical framework and methodologies for estimating the number of deaths averted due to</td>
<td>Presentation of the analytical framework and methodologies for data collection, extrapolation and projection of global, regional and country-specific estimates</td>
<td>W Msemburi</td>
<td></td>
</tr>
</tbody>
</table>
vaccination for 194 Member States from 2021-2030

- Questions to 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?

**Background information:** Analytical framework

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Activities</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1530-1550 20’</td>
<td>Q&amp;A and Discussion</td>
<td>IVIR-AC discusses presentation, clarifies on content and acknowledges main issues</td>
<td>S Verguet and J Wu</td>
</tr>
<tr>
<td>1550-1600 10’</td>
<td>Wrap up</td>
<td>Summarize day’s findings and request any follow up from WHO Secretariat/IVIR-AC FPs for closed session</td>
<td>For information</td>
</tr>
</tbody>
</table>

**DAY 4**

<table>
<thead>
<tr>
<th>Time</th>
<th>Section</th>
<th>Activities</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1230 - 1235 5’</td>
<td>Introduction</td>
<td>Recap of previous day and objectives for the day</td>
<td>For information</td>
</tr>
<tr>
<td>1235 – 1245 10’</td>
<td>Background</td>
<td>Overview of CAPACITI goals, 3 frameworks, and project status</td>
<td>B Giersing</td>
</tr>
</tbody>
</table>
| 1245 - 1255 10’ | Decision-support framework and Excel tool | Updates since IVIR-AC 2019 meeting (types of MCDA, balance between best practice and practicality)  

**Background reading materials:**

1. Decision-support tool (Excel)
2. Draft decision-support framework manuscript

For recommendation

P Thokala
<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Details</th>
<th>Presenter</th>
</tr>
</thead>
</table>
| 1255-1310 15’ | Country context and innovation frameworks | • Country context framework: rationale and link to decision-support framework  
• Innovation framework: previous iterations and current conceptualisation  
**Background reading materials:**  
1. Draft CAPACITI manuscript | S Botwright |
| 1310 - 1345 35’ | Questions to the committee: | • 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 |
| 1430-1440 10’ | Burden of Enteric Diseases: Background and problem statement | **Content:**  
• Understanding pathogen disease burden is critical to understanding the potential impact a vaccine may have, and informs priority setting for vaccine development, introduction and use;  
• 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.  
**Background material:**  
• Report from the first meeting of the BoED WG (https://pubmed.ncbi.nlm.nih.gov/32253097/)  
• Report from the PDVAC 2020 session on BoED | For information | G Giersing/M Hasso-Agopsowicz |
<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Content</th>
<th>Background material</th>
<th>For Information</th>
</tr>
</thead>
</table>
| 1440-1505 25’ | Efforts to assess the differences in mortality estimates for enteric pathogens. | • 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 | Draft article summarising the results of the CFR analysis  
Draft article summarising the results of the ORs analysis | J Baker  
V Pitzer  
M Hasso  
J Platts-Mills |
| 1505-1525 20’ | Q&A and Discussion | • 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                        |
| 1525-1535 10’ | The impact of enteric pathogens on morbidity: proposed scope of work. | • 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. |                                                                                           | I Khalil                                |
### Q&A and Discussion

- **Rationale for morbidity focus of BoED: MWG**

- **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?**

  **For recommendation**
  - S Verguet, P Luz, X Wang

### Wrap up and closure

- **Summarize day’s findings and request any follow up from WHO Secretariat/IVIR-AC FP’s for closed session**

  **For information**
  - W. Orenstein, Chair

---

**DAY 5**

**Closed session: IVIR-AC members only**

**1230 – 1600**

**IVIR-AC reporting/recommendations**
ANNEX 2 - List of Participants

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

List of participants

Advisory Committee Members

Habib Hasan Farooqui, Additional Professor, Public Health Foundation of India, India

Mark Jit, Professor Vaccine Epidemiology, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London, United Kingdom of Great Britain & Northern Ireland

Julie Leask, Professors, Susan Wakil School of Nursing and Midwifery, Sydney Nursing School, Faculty of Medicine and Health, Camperdown NSW 2050, Sydney, Australia

Jean-Daniel Lelièvre, Department of Clinical Immunology INSERM, CHU Henri Mondor 51 avenue Maréchal de Lattre de Tassigny, 94010 Créteil Cedex, France

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

Dafrossa C. Lyimo, Programme Manager, Immunization and Vaccines Development, Ministry of Health, Community Development, Gender, Elderly & Children, Dar es salaam, United Republic of Tanzania

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

Wilfred Ndifon, Director of Research, AIMS Global Network, AIMS Global Secretariat, No 1, KG 590 ST, Kigali, Rwanda

Walter Orenstein (Chair), Professor, Emory Global Health Institute, Emory University, 1599 Clifton Road, Suite 6.101, Atlanta, GA 30322, USA

Virginia Pitzer, Associate Professor, Yale School of Public Health, P.O. Box 208034, 60 College St, New Haven, CT 06511, USA

Stéphane Verguet, Assistant Professor, Department of Global Health and Population, Harvard T.H. Chan School of Public Health, 665 Huntington Avenue, Boston, MA 02115, USA

Xuan-yi Wang, Research Scientist, Shanghai Medical College, Fudan University, People's Republic of China
**Participants**

Robert F Breiman, Emory Global Health Institute, Emory University, 1599 Clifton Road, Atlanta, USA

Neil Ferguson, Imperial College, Faculty of Medicine, School of Public Health, London, South Kensington Campus, London, United Kingdom

Kurt Frey, Institute for Disease Modeling, Bellevue, USA

Brittany Hagedorn, Institute for Disease Modeling, Bellevue, USA

Nicholas Grassly, Imperial College London, United Kingdom

Ibrahim Khalil, University of Washington, USA

Jeremy Lauer, Strathclyde Business School, Glasgow, United Kingdom

Ann Levin, Health Economist, 6414 Hollins Drive, Bethesda MD 20817, USA

Carsten Mantel, MM Global Health Consulting, Berlin, Germany

Kelly Moore, Vanderbilt School of Medicine, Nashville, USA

Chris Morgan, Jhpiego, Melbourne, Australia

Praveen Thokala, University of Sheffield, United Kingdom

**Observers**

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

Fabián Alvarez, IFPMA, Geneva, Switzerland

Julia Baker, Emory Vaccinology Training Program, Atlanta, GA 30322, USA

Logan Brenzel, Bill and Melinda Gates Foundation, 440 5th Ave N., Seattle, WA 98109, USA

Austin Carter, University of Washington, USA

Alejandro Cravioto, Affiliated with the Faculty of Medicine of the Universidad Nacional Autónoma de México (UNAM), Mexico

Ijeoma Edoka, PRICELESS, Johannesburg, South Africa
Katy Gaythorpe, Imperial College London, London, United Kingdom

Dan Hogan, Gavi, the Vaccine Alliance, Chemin des Mines 2, Geneva, 1202, Switzerland

Ilesh V. Jani, Instituto Nacional de Saúde, Mozambique’s National Public Health Institute, Mozambique

Jaleela S. Jawad, Ministry of Health, Bahrain, Manama, Bahrain

Kari Johansen, European Centre for Disease Prevention and Control located (ECDC), Stockholm, Sweden

Melissa Ko, MM Global Health Consulting, Germany

Ben Lopman, Emory University, USA

Shabir Madhi, University of the Witwatersrand, Johannesburg, South Africa

Michael Lynch, Global Immunization Division, Centers for Disease Control & Prevention, Atlanta, GA 30329, USA

Noni E. MacDonald, Dalhousie University, IWK Health Centre, Canada

Calman MacLennan, Bill and Melinda Gates Foundation, 440 5th Ave N., Seattle, WA 98109, USA

Shabir A. Madhi, University of the Witwatersrand, Johannesburg, South Africa

Peter B McIntyre, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand

Todi Mengistu, Gavi, the Vaccine Alliance, Chemin des Mines 2, Geneva, 1202, Switzerland

Ezzeddine Mohsni, GHD/EMPHNET (Global Health Development / Eastern Mediterranean Public Health Network)

Kim Mulholland, Murdoch Childrens Research Institute, Parkville, Australia

Susan Nazarro, Bill and Melinda Gates Foundation, 440 5th Ave N., Seattle, WA 98109, USA

Kathleen Neuzil, Center for Vaccine Development and Global Health (CVD), University of Maryland School of Medicine, Maryland, USA

Hanna Nohynek, Finnish Institute for Health and Welfare (THL), Finland

Folake Olayinka, John Snow Inc (JSI), Virginia, USA

Sonia Pagliusi, DCVMN, Geneva, Switzerland

James A Platts-Mills, University of Virginia, Infectious Diseases Clinic, Fifth Floor, Outpatient Clinic, 1300 Jefferson Park Ave, Charlottesville, VA 22903, USA
Andrew J. Pollard, University of Oxford, United Kingdom

Firdausi Qadri, International Centre for Diarrheal Disease and Research, Dhaka, Bangladesh

Duncan Steele, Bill and Melinda Gates Foundation, 440 5th Ave N., Seattle, WA 98109, USA

Kirsten Vannice, Bill and Melinda Gates Foundation, 440 5th Ave N., Seattle, WA 98109, USA

Regional Offices

World Health Organization Regional Office for Africa, Brazzaville, Congo

Cuauhtémoc Ruiz Matus, Unit Chief of the Comprehensive Family Immunization Unit (IM), World Health Organization Regional Office for the Americas, Washington DC, USA

World Health Organization Regional Office for Europe, Copenhagen, Denmark

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

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

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

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

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

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

Ananda Amarasinghe, Regional Focal Point for Immunization System and Safety, World Health Organization Regional Office for the Western Pacific, Manila, Philippines

Syeda Aslam, Consultant, World Health Organization Regional Office for the Western Pacific, Manila, Philippines

Nyambat Batmunkh, Regional Focal Point for Immunization Programme Along the Life-Course, World Health Organization Regional Office for the Western Pacific, Manila, Philippines

WHO Secretariat

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

Melanie Bertram, Economic Evaluation and Analysis, World Health Organization, Switzerland
Adwoa Bentsi-Enchill, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Siobhan Botwright, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Maricel Castro, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Carolina Danovaro, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Laure Dumolard, Immunization Vaccines and Biologicals, World Health Organization, Switzerland
Eliane Furrer, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Marta Gacic-Dobo, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Birgitte Giersing, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Randie Gibson, Immunization Vaccines and Biologicals, World Health Organization, Switzerland
Tracey Goodman, Immunization Vaccines and Biologicals, World Health Organization, Switzerland
Mateusz Hasso-Agopsowicz, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Mary Hamel, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Louise Henaff, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Joachim Hombach, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Raymond Hutubessy, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Anna-lea Kahn, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Heather Kester, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Katrina Kretsinger, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Philipp Lambach, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Ann Lindstrand, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Melanie Marti, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Lisa Menning, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
W Msemburi, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Olivia Bullock, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Katherine O’Brien, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

Edith Patouillard, Programme Support & Management, World Health Organization, Switzerland

Marie-pierre Preziosi, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

Alexander Rosewell, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

David Schellenberg, Global Malaria Programme, World Health Organization, Switzerland

Stephanie Shendale, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

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

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

Susan Wang, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

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

Karene Yeung, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
ANNEX 3 - COVID-19 Special Session 2, Request for Information (RFI)

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

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

*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.

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

*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.

Version 31 July 2020
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%).

<table>
<thead>
<tr>
<th>Supply scenario</th>
<th>Total by end-2021</th>
<th>Incremental availability by end of quarter* (millions of doses)</th>
<th>Distribution across countries (LIC: low-income, LMIC: lower-middle-income, UMIC: upper-middle-income, HIC: high-income)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. COVAX Facility</td>
<td>2 B doses</td>
<td>100 100 400 600</td>
<td>800</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q4 Q1 Q2 Q3 Q4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. COVAX + direct country procurement</td>
<td>4.25 B doses</td>
<td>400 400 800 1200</td>
<td>1450</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. COVAX + direct country procurement (shared)</td>
<td>4.25 B doses</td>
<td>400 400 800 1200</td>
<td>1450</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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

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.
  - o Workers in health care
  - o Workers in care homes and other social care
  - o Teachers, childcare providers
  - o Emergency response and public safety personnel
  - o Sanitation, including sewage and garbage removal
  - o Utility workers (e.g., water, electricity, gas, communications)
  - o Public works and infrastructure maintenance/repair workers
  - o Transportation workers
  - o Food and agriculture workers
  - o Retail workers for provision of food and essential goods (e.g., pharmacies, medical supplies, fuel)
  - o Critical banking/financial services workers for processing and maintaining access to currency and payments
  - o Mortuary services
  - o 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:**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Questions for which most relevant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differences in COVID-19 severity by age</td>
<td>Q1-2</td>
</tr>
<tr>
<td>Different vaccine profiles</td>
<td>All</td>
</tr>
<tr>
<td>Separate analyses for high-, middle- and low-income countries or country groups</td>
<td>All</td>
</tr>
<tr>
<td>Uncertainty and sensitivity analysis to model parameters</td>
<td>All</td>
</tr>
<tr>
<td>Counterfactual analysis</td>
<td>All</td>
</tr>
</tbody>
</table>

**Desirable:**

(in no particular order)

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect (herd) effects of vaccination (including consideration of acquired immunity and its variation across countries) and age-dependent transmission risk</td>
</tr>
<tr>
<td>Differences in COVID-19 severity by comorbidities, ideally stratified by age</td>
</tr>
<tr>
<td>Additional health, social, and economic outcome measures, e.g.,</td>
</tr>
<tr>
<td>- COVID-19 cases, hospitalisations, cases with long-term sequelae, years lived with disability, DALYs, SEYLL;</td>
</tr>
<tr>
<td>- SARS-CoV-2 infection averted per dose; COVID-19 death averted per dose;</td>
</tr>
<tr>
<td>- COVID-19 YLL averted per dose;</td>
</tr>
<tr>
<td>- Excess deaths and years of life lost due to the COVID-19 pandemic generally;</td>
</tr>
<tr>
<td>- In GNI, poverty gap, GNI per capita, income inequality, employment</td>
</tr>
<tr>
<td>Potential reduction in infectiousness of breakthrough infections among vaccinated individuals</td>
</tr>
<tr>
<td>Potential differences in vaccine efficacy against mild or severe/fatal COVID-19 disease</td>
</tr>
</tbody>
</table>
- Risk/benefit analysis for vaccines with hypothetical risks of adverse outcomes (e.g., vaccine-associated enhanced disease) at different frequencies
- 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)
- Distribution of impacts across social groups (e.g., gender, rural/urban, race/ethnicity)
- Impact of vaccinating seropositives, and potential impact of pre-vaccination serological testing and exclusion of seropositives from vaccination
- Impact of inclusion/exclusion of pregnant women from groups eligible for vaccination
- 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
- Effect on coverage of different vaccine acceptance and demand assumptions and how this may vary among countries
- Scenarios exploring impacts of combinations of different COVID-19 vaccines with different characteristics
- Effects of different combinations of NPIs for different vaccination scenarios and epidemiological and country settings
- Cost-effectiveness analyses conducted from other perspectives (e.g., health system, government)
- Sensitivity analysis of results to potential viral mutation and antigenic change
- Detailed analysis of exemplar country(ies) that have good epidemiologic data
- Implementation of models or model results in interactive software that can be used in countries by decision makers to explore scenarios
ANNEX 4 - WUENIC 2.0 use cases

Regional / Global Monitoring framework. WUENIC is used in several regional and global monitoring frameworks as listed below. Sustainable Development Goals (SDG)

- Note on SDG Monitoring guiding principles: Country-owned, strengthening ability of countries to produce health statistics.
- Call for subnational disaggregation.
- Framework for global initiatives.
  - Beginning of IA2030 and Gavi 5.0.

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.
- 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 financing.16
  - For example, the Millennium Challenge Corporation (MCC) uses DTP3 and MCV1 to access countries’ eligibility.

---

16 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
ANNEX 5 - RTS.S Vaccine Technical Questions addressed by presenters

What is the difference between WHO-CHOICE and Generalized Cost-Effectiveness analysis?

WHO’s Choosing Interventions that are Cost-Effective (CHOICE) programme has been prominent in the field of economic evaluation for almost 20 years. During this time, they have promoted the Generalized Cost-Effectiveness Analysis (GCEA) methodology and developed tools for implementation of this method.

GCEA is a specific tool that supports priority setting and efficiency analysis by calculating the most economically efficient health benefit package. This enables the assessment of the allocative efficiency of the current package of health care interventions supported in a given setting, and to establish the most efficient potential use of resources into the future. This method can show the efficiency with which current and possible new resources are used.

GCEA is a departure from incremental CEA, which can be used as part of a decision-making process when adding to the margins of a package of services already in place in a country. Incremental cost-effectiveness analysis usually compares the costs and impacts of a new intervention to a comparator that is “current practice”. Incremental CEA makes an implicit assumption when the comparator used is current practice that this represents an efficient use of resources. GCEA, by using the null, allows for many alternatives to be considered simultaneously, and allows for new entrants to the market to not be disadvantaged by the existence of competing interventions.

How does GCEA apply to infectious diseases?

GCEA has been used in a number of studies to evaluate cost-effectiveness of single interventions and optimal packages for communicable diseases. These include earlier analyses for HIV, TB and Malaria, and a forthcoming update across these three areas.

- Malaria: Morel et al. Cost effectiveness analysis of strategies to combat malaria in developing countries. BMJ 200519

How is the “null” calculated as the counterfactual?

The null scenario represents a state whereby no interventions are being delivered for the disease of interest. To calculate the null requires three pieces of data: the epidemiological rate being impacted by the intervention (incidence, remission, case-fatality or disability weight); the effect size of the intervention; the current coverage of the intervention. A simplified example of the calculation used to remove these impacts is shown below (equation 1).

\[ \lambda_N = \frac{\lambda_C}{(1 - c \cdot e)} \]

Where
- \( \lambda_N \) = null hazard rate
- \( \lambda_C \) = current hazard rate
- \( c \) = current coverage of intervention
- \( e \) = effectiveness of intervention

17 https://www.bmj.com/content/331/7530/1431
18 https://www.bmj.com/content/331/7529/1364
19 https://www.bmj.com/content/331/7528/1299
Where interventions address the same outcome, the multiplicative form of the equation is used (equation 2).

$$\lambda_N = \frac{\lambda_C}{(1 - c_1 \cdot e_1) \times (1 - c_2 \cdot e_2) \times \ldots \times (1 - c_n \cdot e_n)}$$

For malaria, the OpenMalaria software was used, and to calculate the null scenario all interventions were “stopped” in 2013, and this scenario projected for 100 years to establish the null transmission rates.

**How to implement/look for evidence of synergistic effects of interventions?**

In general, interventions can impact health through an effect on any disease rate – incidence, remission or fatality – or by impacting disease severity. Interventions are evaluated first individually compared to the null, and then in combinations to identify the “expansion path”, or the optimal mix of interventions, for each disease area. By initially evaluating all interventions individually, we are able to more clearly see for a range of preventive services, such as Insecticide-treated nets (ITN)s, Indoor-residual spraying and RTS,S, how great the health benefit would be for each independently, before evaluating every possible combination of these services to identify the optimal mix. The expansion path is then calculated by first starting with the most cost-effective intervention, then sequentially adding interventions to determine the most cost-effective package at every step. The joint effect of interventions, when interventions affect the same rate, is estimated using a multiplicative function or data from randomized controlled trials of combinations of services.

**How to change existing for optimal package of interventions – transaction costs, political opposition etc.?**

It should be reinforced at this point that GCEA results are only one potential input into priority setting and decision-making processes. Cost-effectiveness analysis should always be considered as one of multiple criteria which correspond to local values and priorities. In addition, no “global package” of services will be fit for purpose for all countries. The Global Malaria Programme, and the UHC cluster, work with countries to establish locally contextual service packages and to support their implementation.

To use GCEA results optimally, once the position of allocative efficiency has been estimated, it is possible to engage in strategic planning i.e. bringing priority setting concerns explicitly into decision-making processes. It should be considered that the optimal service package cannot be immediately attained and may require multiple subsequent planning cycles to achieve. It is critical to identify be changes in the current set of activities that are politically feasible, affordable, technically possible, and which also improve health system efficiency, or interventions that would benefit from targeted price negotiation to reduce costs and improve the value-for-money. Opportunities for disinvestment or for increased investment can be identified. Without an explicit priority setting focus, however, such opportunities will be systematically missed.

**How does GCEA deal with uncertainty?**

Within these estimations of GCEA, we undertake one-way sensitivity analysis on a number of input values to assess the magnitude of change that is required to lead to a different policy recommendation. This is used to assess the impact of changing prices, coverage levels, impact sizes and discount rates on the cost-effectiveness ratios. Due to the enormous amount of inputs and outputs, we do not assess probabilistic uncertainty analysis as it is not feasible within the computing system.