Report on Immunization and Vaccines related Implementation Research Advisory committee meeting

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Contents

Abbreviations

BOD	Burden of Disease
BMGF	Bill and Melinda Gates Foundation
EPI	Expanded Programme on Immunization
CDC	Centers for Disease Control and Prevention (United States of America)
CFR	Case Fatality Rate
DRC	Democratic Republic of the Congo
EVD	Ebola virus disease
FPHVV	Full public health value of vaccines
GAVI	The Vaccine Alliance (Global Alliance on Vaccines and Immunizations)
GoC	Grade of confidence
HIC	High-Income Countries
HPV	Human Papillomavirus
HTA	Health Technology Assessment
IA2030	Immunization Agenda 2030
ICAN	Immunization Costing Action Network
ICVA	International Collaboration for Vaccine Acceptance Initiative
IHME	Institute for Health Metrics and Evaluation
IP	Intellectual Property
IRS	Indoor Residual Spraying
IVB	Department of Immunization, Vaccines and Biologicals
IVIR-AC	Immunization and Vaccines-related Implementation Research Advisory Committee
JHU	Johns Hopkins University
JRF	Joint Reporting Form
LLINs	Long-lasting insecticide-treated nets
LMIC	Low- and Middle-Income Countries
MCDA	Multi Criteria Decision Analysis
MCEE	Maternal and Child Epidemiology Estimate
MCV1	Measles containing vaccine first dose
MCV2	Measles containing vaccine second dose
MI4A	Market Information for Access to Vaccines
MoH	Ministries of Health
NITAG	National Immunization Technical Advisory Group
PAHO	Pan American Health Organization
PDVAC	Product Development for Vaccines Advisory Committee
QUIVER	Quantitative Immunization and Vaccines-related Research Advisory Committee

R&D	Research and Development
SAGE	Strategic Advisory Group of Experts
SDGs	Sustainable Development Goals
SES	Socio-Economic Status
TSE	Total System Effectiveness
UCSF	University of California, San Francisco
UHC	Universal Health Coverage
UNICEF	United Nations Children's Fund
WG	Working Group
WHA	World Health Assembly
WHO	World Health Organization
WUENIC	WHO/UNICEF Estimates of National Immunization Coverage

Introduction

Professor Walter Orenstein, chair of the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) welcomed members and participants, who then introduced themselves.

Dr Raymond Hutubessy gave an introduction of IVIR-AC. IVIR-AC has no executive, regulatory or decision-making function. Its role is to provide advice and recommendations on methods related to implementation research regarding immunization policies and practices to the Strategic Advisory Group of Experts (SAGE) and IVB Director of WHO related to immunization policies.

The IVIR-AC members were also briefed on the development of the Immunization Agenda 2030 (IA2030) which is the new global strategy for immunization, following up on the Global Vaccine Action Plan (GVAP 2011-2020). The vision of the IA2030 is a world where everyone, everywhere, at every age, fully benefits from vaccines for good health and wellbeing.

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 behavioural research to facilitate optimal and timely acceptance of vaccines.
- To define how disease and post-marketing surveillance should be conducted.

Topics fit within any of the following three themes:

- Research to minimize barriers and improve coverage of vaccines currently in use
- Research to conduct impact evaluation of vaccines in use
- Research to improve methods for monitoring of immunization programmes

Session 1: Total System Effectiveness

Introduction

Total System Effectiveness (TSE) is developed to assist country selection of products appropriate for their context, to promote equitable vaccine coverage and reduce the burden of vaccine preventable disease. It is intended as a platform for Low-and Middle-Income Countries (LMICs) to systematically evaluate products for selection, within their own contexts, and communicate preferences. TSE is conceptualized as three interlinked but independent frameworks: a barriers framework, a decision-support framework, and a research and development (R&D) / innovation framework.

The purpose of the TSE decision-support framework is to support a focal point within the ministry of health to coordinate a structured, evidence-based process to come to a context-specific recommendation with regards to a choice between different vaccine interventions. The TSE decision-support tool encourages country ownership through making the evaluation and output easily understandable to decision-makers. The unique value of this framework is that it allows a broad consideration of relevant issues, promotes a more structured and explicit process, and ensures the correct expertise is included for making recommendations.

The decision support tool was developed iteratively in consultation with ten countries across Africa and Asia from January 2018-July 2019. It is based on multi-criteria decision analysis (MCDA) and takes a one-off approach. There are five phases in the TSE decision-support tool: preparation, criteria workshop, evidence assembly, recommendation workshop, and conclusion. A total length of 3-5 months is recommended for the whole TSE process.

The first pilot of the TSE decision support tool for a policy recommendation was completed in Mali in April 2019, to support the National Immunization Technical Advisory Group (NITAG) in evaluating available Human Papillomavirus (HPV) vaccine products and reaching a recommendation for selection. The purpose of this session was to review the TSE decision-support tool and the experience from the pilot in Mali.

Review

One of the first step in the TSE decision-support tool for immunization is the selection of a committee with the right expertise and authority to make a recommendation that is accepted by major stakeholder groups (including the final decision-maker and key advocates). This prioritization committee should ideally comprise of a diverse group of people including citizen representatives, people involved in immunization delivery and management, epidemiologists,

health economists, etc. IVIR-AC encourages a review of methods for identifying relevant stakeholders and incorporate this into the stakeholder identification step of the tool.

After defining the objective of the recommendation and determining the composition of the committee, criteria on which to base the recommendation are selected in a criteria workshop. These criteria for TSE need to be carefully selected, especially if they are given quantitative weights. A number of points were made to this regard. First, if countries select criteria that are inter-related, counting them as separate criteria could lead to overweighing. Second, cost criteria are separated from other criteria in the decision support tool despite being vital criteria for many decision makers such as those in the Ministry of Finance. This split between cost- and non-cost criteria is subjective – as for example number of hospital beds is an economic cost but not counted as such in TSE. It would therefore be better not to separate cost and non-cost criteria.

With regard to the Mali exercise it was noted that some criteria that may be relevant despite not being considered include burden of disease, disease outcome prevented equity and vaccine impact. It was suggested that one way to help prioritization committees select criteria would be to develop a resource with sample criteria from which a country can select those that are relevant to the country.

IVIR-AC had some concerns about the resources and time required for the exercise, and whether it is sustainable using local resources only in all settings. It is important to evaluate the use of TSE in resource-poor countries. Many of the criteria involved require local data, or data from comparable countries. Prioritization committee secretariats will need resources to collect such data.

It is important to determine for which countries TSE is most useful, and how it relates to existing structures or processes for priority setting (such as Health Technology Assessment (HTA) agencies and NITAGs). As a validation exercise, it would be useful to compare the use of TSE with the decision-making processes in middle- and high-income countries with robust processes for vaccine-decision making (e.g. Thailand, Argentina).

IVIR-AC recommends that the TSE pilot phase is continued until the factors noted above are accounted for in testing. Furthermore, it will be appropriate to go beyond the pilot phase when there is saturation of issues that come up.

Discussion

The decision-support tool facilitates group discussions and supports consideration and impact of data uncertainty. The iterative development and selection of the criteria is considered a real strength of the tool and makes evaluation and output easily understandable to decision-makers, and it facilitates adoption of the recommendations by all involved stakeholders.

The choice of criteria will depend on who the experts in the committee are. It is important to consider how the committee reflects on which criteria are most important to vaccine recipients and providers.

Collecting relevant evidence is one of the steps in the decision-support tool. In some countries local data may not be available. In that case, IVIR-AC proposes it might be worthwhile to look at evidence from comparable countries. It was proposed that there might be a role for the WHO secretariat in providing guidance on how to use data from similar countries and /or developing a resource catalogue outlining evidence sources and make it available to countries.

The TSE decision-support framework is an independent framework but is interlinked with a barriers framework and an R&D/innovation framework. The barriers framework aims to contextualize recommendations made with the TSE decision-support tool according to country-specific program constraints and barriers to achieving equitable, high coverage. As such the barriers framework can inform the selection of criteria in the decision-support framework.

The decision-support tool could be expanded to include auto-reporting which makes the reporting of the process automatic.

<u>Questions to be answered</u>

- Feedback on methodology for TSE decision-support tool
- How do we validate the tool?
    - When will it be appropriate to move beyond the pilot phase?
    - Do we have go/no-go measures?
- Feedback on the proposed name: Country Platform for Vaccination Preferences

<u>Summary and recommendations</u>

The aim of TSE is to assist country selection of products appropriate for their context, in order to promote equitable vaccine coverage and reduce the burden of vaccine preventable disease. A TSE decision-support tool has been developed to support policy bodies in LMICs to evaluate the trade-offs between different vaccine interventions in order to come to a country-specific recommendation. The first pilot of the tool for a policy recommendation was in Mali (2019). The purpose of this session was to review the TSE decision-support tool and the experience from the pilot in Mali.

Recommendations

- IVIR-AC has followed the development of the TSE work since 2018 and appreciates the way the team has taken on feedback from IVIR-AC, other experts and country stakeholders to refine the tool. A strength of the tool is its iterative development, with continued modification based on country feedback.
- A key determinant of the value of TSE is its ability to align with other initiatives to support vaccine decision-making, including health technology assessment and NITAG strengthening. While there have been useful moves on a country level, there needs to be more conceptual thinking to allow national Health Technology Assessment (HTA) frameworks to fit within the TSE framework. These range from deliberative processes to use of a cost-effectiveness threshold.
- Currently the tool has been piloted for choices of vaccines although it has been developed for broader vaccination choices (e.g. a new vaccine introduction or delivery strategies). It has been noted that TSE may be a potential tool for choices of strategies to improve immunization coverage (e.g., checking vaccination records at school entry versus reminder systems in early childhood). However, it was recommended that the tool be first piloted for use in improving immunization coverage before it is promoted as such. This will ensure the process is suitable, such as whether scoring the associated criteria is feasible.
- The TSE framework should be flexible enough to adapt to the different ways that vaccine decision making is done. In particular, quantitative MCDA requires technical expertise to choose and weigh criteria to avoid overlap or double counting, so should only be recommended where such expertise is available.
- The decision to separate cost and non-cost criteria in TSE should be considered carefully and left to country stakeholders, because many quantities without explicit prices (such as cold chain and human resources capacity) can be considered costs from an economic perspective, and because financial criteria are often crucial to decisions.
- TSE should allow ways to incorporate views of vaccination providers, communities and individuals (e.g. parents/vaccinees) into the decision tools. Options include having these stakeholders on the prioritization committee, undertaking research, and/or using deliberative methods to elicit criteria that are important to communities in program considerations.
- IVIR-AC endorses the following name to replace TSE: country platform for vaccination preferences.

Session 2: Global vaccine acceptance and demand

Introduction

The WHO expert working group on measuring the Behavioural and Social Drivers of Vaccination aims to advance the development of tools and guidance to enable immunization programmes and partners to measure and address reasons for under-vaccination, and to track consistent and comparable data over time at a national and global level.

The tools under development include a quantitative survey questions for caregivers, including parents of children aged 0-5. Findings of this survey would enable insights into behavioural and social drivers of vaccine uptake. The survey incorporates four domains in the quantitative tool: 1) thinking and feeling, 2) social processes, 3) readiness to vaccinate, and 4) practical factors. In addition, there will be a qualitative tool for use in caregivers, healthcare workers, community health workers, immunization programme managers, and other key stakeholders. These tools will support high-quality data collection, analysis and application of findings to immunization programmes.

The plan for the development of the tools includes stages of cognitive and psychometric validation testing, as well as stakeholder consultations. A user guide aims to support local adaptation and implementation. Details of the plans for the tool testing, including a of list potential countries for field testing, were presented to IVIR-AC. IVIR-AC was requested to comment on the testing proposal within the timeframe and the criteria for selecting countries for testing the tools.

Review

A strength of the tools that are being developed is that they target different stakeholders. While the quantitative tool focuses on caregivers, the qualitative tool targets other groups in the wider community such as district authorities, religious leaders, etc. Both tools should capture external factors that lead to under vaccination, such as for example misinformation in social media, rumours, religious beliefs, etc. IVIR-AC emphasizes the importance of the tools being able to discriminate between vaccine non-acceptance and other factors for non- or under-vaccination, such as lack of access. Finally, the tools might help to find out who parents trust for vaccine information.

The tool aims to measure and address reasons for non-vaccination as well as under-vaccination. Even in countries with high-vaccination, there may be pockets of people who are unvaccinated or under-vaccinated. Determining the population, or denominator, you are looking at is

important in this context. From this perspective, it is also important to look at smaller countries, and not just large countries.

This is a global tool and therefore has be appropriate for use in high-, middle- and low-income countries as well as in different health systems. to cut across the system. While the focus of the pilot seems to be on low- and middle-income countries, it will be important to also include high-income countries in the pilot. These countries also deal with groups of people who show vaccine resistance and have children who are missing immunizations. The tool could allow for learning between countries and settings, for example on how to deal with vaccine objectors. Finally, it would be interesting to explore what the influence is of country immunization policy, i.e. whether vaccination is mandatory, whether it is free, etc.

The committee highlighted the growing use of social media and its influence on demand, vaccine hesitance and the spread of rumours in both rural and urban community. While it was thought to be important that the tool evaluate the impact of social media, it was agreed that it is hard to disentangle where it sits in the decision-making process.

Discussion

The committee discussed possible high-income countries for selection in the pilot. The Wellcome Global Monitor 2018 studied how people around the world think and feel about science and major health challenges and included an evaluation of vaccine confidence. This report could provide information on the basis of which to select countries (e.g. in Japan only 35% of people believe that vaccines are save). Other potentially interesting countries could be France, where there is large hesitancy, but vaccination is compulsory, or Belgium, where there are differences in the French and Dutch-speaking populations. However, the committee agreed that it might be most convenient to focus the pilot on English speaking countries and to adapt the tools to other languages in a later stage. Other selection criteria for inclusion of countries in the pilot could be vaccine coverage (absolute number, as well as inequality in coverage e.g. by socio-economic status (SES), education), and by health spending per capita.

The committee offered for consideration the impact of selecting a specific vaccine for the pilot since vaccine acceptance and demand may vary by vaccine.

Questions to be answered

- What comments do members have on the testing proposal within the timeframe?
- Are members satisfied with the criteria for selecting countries for testing the tools?

Summary and recommendations

- IVIR-AC considers the tool to be very valuable in providing information to the stakeholders on what is happening in communities about the social and behavioural drivers of immunization.
- The tool needs to provide room for both routine and periodic data collection. If used for routine data collection, care should be taken to minimize burden on health care staff.
- Since the tool will be accompanied by end-user guidance to support local adaptation and use, the researchers should ensure representation of low-, middle-, and high-income countries in the testing process. IVIR-AC therefore proposes to include at least one high income country for the testing of the tools.
- IVIR-AC recommends testing the tool in English-speaking countries first, before adapting the tool to other languages. Checking the process of interpretation to other languages is important but not the initial priority as it will be time-consuming to do properly. However, ensure that different global regions are represented.
- IVIR-AC recommends testing the tools both in countries with large numbers or large proportions of unvaccinated or under-vaccinated children, but also in countries with high coverage where vaccine hesitancy exists in sub-groups.
- Ideally, the cognitive testing should be done in more than 5 countries. This would require an increase in budget, which should be made available to assure the tool is useful in a variety of settings.
- Within countries, IVIR-AC recommends selecting a representative sample with regards to differences in attitudes, access (hard to reach, marginalized communities) and different geographical areas (urban, rural). Finding parents of zero dose children for testing the surveys is important. One option to consider is sampling through networks to look at connectedness.

Session 3: Ebola model comparison

Introduction

On 17 July 2019, the WHO declared the Ebola virus disease outbreak in the Democratic Republic of the Congo (DRC) a Public Health Emergency of International Concern. Real- time modeling, in which actual reported case data is used to adapt estimated projections and impact on a weekly basis, are used to help guide the public health response, including planning the strength, timing and location of interventions. A diverse range of model structures, assumptions, and fitting procedures may result in different projections and conflicting results about the impact of interventions, causing uncertainty for decision makers. Thus, a comparison of models is carried out to answer the following policy question: What is the accuracy of Ebola case predications for the current outbreak in DRC by the different models used to inform policy-decisions and outbreak response, and what model characteristics, data, or assumptions drives differences in predictions?

The model comparison includes four public sector models that inform WHO and/or the Ministry of Health (MoH) from the DRC and/or CDC on predicted number of cases of EVD and modeled impact of outbreak response activities and interventions using real-life data for the current outbreak in DRC. One of the models,[1,2,3] a stochastic microsimulation model of Ebola transmission that simulates each individual in the population and explicitly considers transmission in households, extended families, community and health care facilities, and accounts for individual variability in infectiousness and age-specific risk of infection, was reviewed in detail by IVIR-AC in March 2019.

[1] Ajelli M, Merler S, Fumanelli L, *et al*. Spatiotemporal dynamics of the Ebola epidemic in Guinea and implications for vaccination and disease elimination: a computational modelling analysis. BMC Medicine 2016;14:130

[2] Merler S, Ajelli M, Fumanelli L, Parlamento S, Pastore y Piontti A, Dean NE, et al. Containing Ebola at the source with ring vaccination. PLoS Negl Trop Dis 2016; 10(11): e0005093

[3] Merler S, Ajelli M, Fumanelli L, Gome MFC, Pastore y Piontti A, Rossi L, et al. Spatiotemporal spread of the 2014 outbreak of Ebola virus disease in Liberia and the effectiveness of non-pharmaceutical interventions: a computational modelling analysis. Lancet Infect Dis 2015; 15: 204-211.

The second model[4,5] is a branching process model that uses parametric estimation to estimate key delay distributions and basic reproduction number. The third model[6,7] is a deterministic, compartmental model in which individuals are tracked through 4 disease states: susceptible, incubation, infectious, recovered/ dead. The model is executed in a spreadsheet format and placed on public domain website, allowing easy independent replication and maximum transparency. Progression through the disease states is tiered using two levels of transmission risk: 1) Patients effectively isolated (defined as placement in an Ebola Treatment Unit and/or through effective vaccination of their contacts and contacts-of-contacts (with safe burial when needed), so as to prevent onward transmission); 2) Patients not effectively isolated. The final model[8,9] is an ensemble of models including simple parametric and non-parametric statistic models (e.g., negative binomial auto-regression and recursive Hawkes point process) as well as more complex, simulation models that have been collectively used to generate varying forecast ranges (short-, medium-, and long-term of expected cumulative case counts) and consider varying intervention scenarios related to vaccine coverage.

The objectives of the model comparison exercise are twofold. In Phase I the objective is to compare the accuracy of estimates that have been produced to-date by each modeling team using their existing methods and data, and to produce a short memo for the Ebola Response leadership in a variety of organizations and institutes. For Phase II the objective is to conduct a further in-depth comparison of models, using standardized scenarios to better understand how the models behave in terms of outcomes and to improve understanding of what drives differences in projections.

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[4] WHO Ebola Response Team. Ebola Virus Disease in West Africa – The first 9 months of the epidemic and forward projections. N Engl J Med 2014;371(16):1481-1495

[5] WHO Ebola Response Team. West African Ebola Epidemic after one year – slowing but not yet under control. N Engl J Med 2015; 372(6):584-587

[6] Meltzer MI, Atkins CY, Santibanez S, et al. Estimating the future number of cases in the Ebola epidemic–Liberia and Sierra Leone, 2014–2015. MMWR Suppl. 2014; 63 (3): 1–14.

[7] Meltzer MI, Santibanez S, Fischer LS, Merlin TL, Adhikari BB, Atkins CY, et al. Modeling in real time during the Ebola response. MMWR Suppl 2016 ; 65(3) ; 85-89.

[8] Kelly JD, Park J, Harrigan RJ, Hoff NA, Lee SD, Wannier R, Selo B, Mossoko M, Njoloko B, Okitolonda-Wemakoy E, Mbala-Kingebeni P, Rutherford GW, Smith TB, Ahuka-Mundeke S, Muyembe-Tamfum JJ, Rimoin AW, Schoenberg FP. Real-time predictions of the 2018-2019 Ebola virus disease outbreak in the Democratic Republic of the Congo using Hawkes point process models. Epidemics (2019), https://doi.org/10.1016/j.epidem.2019.100354

[9] Kelly JD, Worden L, Wannier SR, Hoff NA, Mukadi P, Sinai C, Ackley S, Chen X, Gao D, Selo B, Mossoko M, Okitolonda-Wemakoy E, Richardson ET, Rutherford GW, Lietman TM, Muyembe-Tamfum JJ, Rimoin AW, Porco TC. Projections of Ebola outbreak size and duration with and without vaccine use in Équateur, Democratic Republic of Congo, as of May 27, 2018. PLoS One. 2019 Mar 7;14(3):e0213190. Doi: 10.1371/journal.pone.0213190. PMID: 30845236.

The proposed methodologies include a descriptive comparison in which aspects of each model in terms of model characteristics, model inputs, assumptions, features, and attributes as well as variables and assumptions used, will be compared in a table. This is followed by a retrospective comparison of predictions with actual case numbers which will be depicted in plot(s) / graphical representation(s). In the second phase, speculative scenarios reflecting potential changes in response and transmissibility on the current outbreak in DRC will be modeled. These scenarios will reflect good, moderate, and weak outbreak control. Modeling groups will all be using the same most recent epidemiological data provided.

Review

There is currently not a clear distinction between the policy questions and the phases of the research. It was proposed to turn the policy question into the objective and to state the goals of the modeling comparison as follows: 1) To illustrate the variability between the models in terms of the predictions of Ebola cases for the current outbreak in DRC (using the current versions and assumptions of the models); 2) To identify model assumptions and structure, and data that drive any differences in predictions (using standardized scenarios)

The proposed plan to determine the accuracy of predictions that were previously made by the modelers has obvious merits. However, comparable predictions might not be available for all the models (i.e. predictions covering the same time windows).

When building a table with the assumptions that each model makes regarding the major epidemiological attributes of the Ebola outbreak, it is suggested that each team independently provides a list of what they think are the key drivers of their results. This can then be used to build a common table.

The methods for Phase II are less clearly developed. It is not clear how the models will be compared (e.g. visually, qualitatively, and/or quantitively. Criteria that will be used to say a model has accurate projections still need to be developed. Furthermore, more details need to be provided on what measure will be used to compare the model results. A description of the outcomes that will be compared should be given.

There is a difference between accuracy of model forecasts with available data (retrospective assessment) and predictions of future outbreaks and impact of interventions. It is not clear if the latter is included in Phase II, and to what extent the group will compare model predictions of different interventions?

There is value in comparing the models at the small geographical level, as well as at larger (health zone, country) level. This can provide insight in the fit of the model at the general situation and the small scale.

Discussion

The committee discussed the challenges of making predictions for this outbreak in the DRC because of complications such as violence. If there are unexpected “game-changes” during the epidemic, then any wrong predictions cannot be the fault of the model. On the other hand, it is possible to model negative impact events (e.g. model that for a week that you cannot get to access to people) and review the impact of these.

Another challenge is the fact that there may be different outbreaks going on simultaneously in DRC. From this latter perspective it is perhaps not useful to look at the total number of cases, but it might be better to look at separate geographic areas to allows for better predications and impact of interventions.

It will be important to explain why modelers choose a certain structure because different models were designed to answer different policy questions.

In the protocol the key pieces of information needed to run the models should be highlighted. While some models use very detailed input data, not all these data may matter, so it is important to indicate what the expected value of information is. For the model comparison a standard set of inputs should be provided to the modeling groups.

There does not currently seem to be a way to model the impact of asymptomatic infection and post-symptomatic people / survivors who may be able to transmit infection.

A previous model comparison exercise on artificially generated data has previously been carried out, but the purpose of this current model comparison is to use compare the models using data from the current outbreak in DRC.

Vaccination strategy is important in this exercise. In the ring vaccination strategy which is currently used, the number of people vaccinated is driven by the number of cases (and the sizes of the rings). This provides challenges to modeling vaccination, particularly with regard to determining the eligible population (denominator) for the calculation of coverage.

Further thought is needed about how to measure / reflect uncertainty in the model predictions.

An IVIR-AC member will join the Ebola model comparison consortium to provide continued input on the process.

Questions to be answered

- Does IVIR-AC have any suggestions for the proposed model comparison?

Summary and recommendations

On 17 July 2019, the WHO declared the Ebola virus disease outbreak in the Democratic Republic of the Congo (DRC) a Public Health Emergency of International Concern. Real- time modeling, in which actual reported case data is used to adapt estimated projections and impact on a weekly basis, are used to help guide the public health response, including planning the strength, timing and location of interventions. A diverse range of model structures, assumptions, and fitting procedures may result in different projections and conflicting results about the impact of interventions, causing uncertainty for decision makers. To gain insight in what causes these differences in projections, a comparison of models will be done. The proposal for the model comparison was presented to IVIR-AC with the request for comments and suggestions.

- This is an excellent initiative, which will be very useful to better understand the Ebola models which are used to inform the leadership of WHO and partners on strategic decisions with regards to Ebola response activities, including estimates of vaccine doses needed.
- We recommend explicitly indicating how the findings from this comparative exercise could inform and improve the control and mitigation of Ebola outbreaks (e.g. by documenting how inaccurate or conflicting forecasts in the past have hindered outbreak responses).
- The analysis plan corresponds well to the guidelines for multi-model comparisons of the impact of infectious disease interventions. However, for model identification, additional steps are required to minimize selection bias, including a review of the literature, an open call and the use of pre-defined criteria for model inclusion.

Phase I – Model description

- IVIR-AC recommends that the predictive power of the models should be preferentially evaluated using fine geographical scales (e.g. health zones). Models that make accurate predictions at such fine scales have the potential to give insight about the most likely geographical locations of future transmission events, where preventive and reactive interventions should be targeted. Even more, currently unaffected geographical areas should be used as negative controls during the training and testing processes to improve model predictive power.
- The evaluation team should consider making new predictions using the same training and test datasets collected during the time period of interest (between 1 August 2018 and the present). By using temporally adjacent sliding windows to select training and test datasets, it will be possible to take into account changes in the strength of the Ebola response that have occurred over time (e.g. due to changes in resource availability or security situation).

- It would be useful to compile a table that explicitly summarizes the assumptions that each model makes regarding the major epidemiologic attributes of the Ebola outbreak. In this table, each row would correspond to an epidemiologic attribute (e.g. proportion of asymptomatic infections), whereas each column would correspond to the assumptions a given model makes regarding that attribute.
- During phase 1 of this comparison exercise, for models that consistently (in retrospect) provide substantially inaccurate predictions, it would be important to investigate and articulate which aspects of the models were responsible for suboptimal performance (e.g. erroneous parameterization, invalid model structure, etc.).
- IVIR-AC recommends explicitly evaluating the uncertainty of model predictions by performing sensitivity analysis with respect to parametric values and model structure.
- IVIR-AC recommends explicitly defining measures for the predictive power of the model forecasts that is relevant to the planning and field operations of Ebola outbreak control.

Phase II – new iterations with standardized data/parameter set

- It's not clear how drivers of differences between model predictions will be determined. Identifying drivers of such differences is only useful in so far as it informs the development of a better model. The goal should be to identify the key model components that are most useful for producing reliable results, so that these can be used to build better models. The modelers should be encouraged to use the lessons learned to immediately improve their models to provide more accurate guidance to Ebola response teams.
- At the very least comparable parameter values should be assigned to equivalent parameters found in the different models to ensure that parameter values aren't the main drivers of differences between model predictions, but the need to assess structural drivers remains. It is also necessary to use comparable standardized datasets.
- The response scenarios for the simulations should be defined relative to current practice -- i.e. business as usual versus improved response versus weaker response (e.g. caused by disruption of the response due to violent protests).

Session 4: Measles-Rubella Eradication investment case

Introduction

All six WHO regions have committed to measles elimination by or before 2020, however, there is not currently a global eradication goal for measles and rubella. The Director General is requested to report, through the EB, to the 2020 WHA *"on the epidemiological aspect and feasibility of, and potential resource requirements for, measles and rubella eradication, taking into account the assessment of SAGE".*

In preparation for the SAGE meeting in October 2019, a report on the epidemiological aspects and feasibility of measles and rubella eradication was prepared. To inform this report, WHO convened a consortium of modeling and economic groups to estimate the likelihood, feasibility, assumptions as well as the cost and cost-effectiveness of measles and rubella elimination.

The modeling consortium consists of two multi-country measles models (the DynaMICE and PSU models) and two multi-country rubella models (the PHE and JHU models). In addition, sub-national modeling was done using a single-country measles model in Nigeria (the IDM model).

The modeling groups model the likelihood and time to elimination in 98 countries (were the majority of measles burden lies) using an "elimination" definition of an incidence low enough to allow transmission interruption. This is operationalized as a threshold of 5/1,000,000 true cases. Models evaluate the relative performance of vaccination strategies with regards to 1) expected future disease burden (measles and CRS cases, deaths and DALYs) by scenario, 2) proportion of simulations that reach "elimination" by scenario, and 3) first year in which burden falls below this elimination threshold, under each scenario. In addition, the cost and cost-effectiveness of the four scenarios were assessed.

Four vaccination scenarios were modeled: base case (status quo), continuing trends (limited set of improvements, introductions based on current commitments), intensified investments (rapid progress toward eradication), and constant investments (to reflect a level of consistent increase in coverage of 1% / year).

Review

General comments

SAGE has evaluated measles and rubella eradication twice before (in November 2010 and October 2016). The world is currently seeing alarming rates of measles (e.g. in Europe there are three times the number of cases compared to last year at this time) due to gaps in coverage and population immunity. In this context, thought should be given to the timeliness and adequacy of a new evaluation of measles and rubella eradication. It may for example be

worthwhile to add a worst-case scenario where MCV1 and/or MCV2 coverage rates are decreasing. This could potentially also provide a powerful advocacy tool for eradication.

What does IVIR-AC think are the strengths and weaknesses of the presented models?

A. Strengths

IVIR-AC is impressed by the amount of work and effort that has been put into this in a relatively short time frame. The approach of using four different models (two models for measles and two for rubella) in 93 countries is overall a good strategy. The models used for the analyses are robust, well described and characterized in multiple peer review publications (and on a website, https://www.vaccineimpact.org/). The employment of a finer scale model to assess the implications of spatial heterogeneity in vaccine coverage is a strength of the current approach, as is the assessment of multiple strategies / scenarios.

Another strength is the focus on the relative impact of different strategies for measles and rubella elimination, given that absolute estimates of the number of cases of disease are subject to multiple uncertainties and thus not easily captured by mathematical models.

The results show not only the variation in time to reach the elimination threshold, but also the need for vigilance for a prolonged period to prevent outbreaks from imported cases, highlighting need for investment in surveillance as well as (possible) SIAs.

B. Weaknesses

The descriptions of the four vaccination scenarios were difficult to understand and were not consistent between the different documents which were available to IVIR-AC for review. The titles of the scenarios were also not self-explicative. This lack of consistency and clarity is concerning. Furthermore, for the Nigeria country specific analysis there were three new scenarios (equitable, proportionate and inequitable) that were not explained. There is a clear need to standardize or more clearly present this confusing set of scenarios.

While a strength of the current approach is that scenarios include status quo and improved vaccination coverage, including continued SIAs, IVIR-AC proposes to further standardize the scenarios and possibly reduce the number of scenarios. With the current reality of measles outbreaks in many regions of the world, the rationale for three different best-case scenarios with similar clinical impact and cost-effectiveness results, is not clear. For example, scenario 2 (continued trends) and scenario 3 (constant (or continuous?) improvement) seem to be quite similar. They could potentially be merged into one single scenario or even condensed with scenario 4 (intensified investment). Moreover, coverage variation up to 2018 seems to vary quite a lot (more so than the projected variation in the different scenarios) suggesting these

nuances might not be relevant or realistic. In addition, it might be worth evaluating if a worst-case scenario is valid (worse than current base-case).

Outbreak response immunization is not included in any of the scenarios. Given the trends we are currently witnessing and the likelihood that these may continue occurring, it would make sense to include them at least in the worst-case scenario. If this is not feasible, this needs a clear acknowledgement as a limitation.

Important features of the models such as how the models incorporated case importation were not described anywhere.

Nigeria is currently the only country for which in-depth sub-national analysis are done, and this is only modeled by one group (as opposed to two). It would be good to do the sub-national analysis for at least one other country, possibly outside sub-Saharan Africa.

What are IVIR-AC's comments on the costing and cost-effectiveness methodology?
It is not clear why only costs for congenital rubella syndrome (CRS) have been considered as treatment costs for rubella. Rubella as a disease, even if mild, has associated costs. Furthermore, the researchers should revise how costs for CRS are calculated since the values obtained from two studies seem rather low for a disease that causes often permanent disability to the new-born. Further information on costing of CRS cases in Brazil may be obtained from: Lanzieri TM, Parise MS, Siqueira MM, Fortaleza BM, Segatto TC, Prevots DR. Incidence, clinical features and estimated costs of congenital rubella syndrome after a large rubella outbreak in Recife, Brazil, 1999-2000. Ped Inf Dis J 2004; 23(12):1116-22. Finally, it was questioned whether the costs of foetal losses (a known outcome of rubella during pregnancy) were considered.

The Routine Immunization Costs used in the analysis all go back to the BMG funded EPIC (Expanded Program on Immunization Costing and Financing of Routine Immunization) studies, which are now a bit old (most from 2010-11, except China 2015). IVIR-AC suggests finding a way to assess more recent costs. Alternatively, the routine immunization costs used can be adjusted to 2019 or projected beyond.

Surveillance costs are, if correctly understood, based on meningitis and malaria surveillance, which require the need to conduct proactively lab tests (malaria blood slides/RDTs, or lumbar puncture and lab work for meningitis). IVIR-AC questions whether these are the most adequate disease surveillance proxies for measles and rubella.

It is not clear how variation in input parameters, in particular for coverage, were taken into account. Moreover, the results for the 93 countries were condensed into "overall" or mean CER per model. This is an unfortunate simplification particularly because the authors went through the trouble of modeling 93 individual countries.

Discussion

While the costs of increasing coverage for LMICs does not show a linear function, and the costs of increasing coverage for the USA & Canada shows an increased exponential function for the costs of increasing coverage, the research team assumed the cost of increasing coverage as a linear relationship with the % of vaccine coverage and should thus be changed.

The equation presented on calculation of cost effectiveness = Net Cost (Additional Cost – Treatment Savings / DALYs averted) (slide 16) should be checked because it was not in line with what the research team explained in the meeting room. The cost-effectiveness calculations should also be checked (slide 23 - Cost and Effects of Measles Vaccination and slide 31 - Cost and Effects of Rubella Vaccination, last two rows) because not all the numbers seemed correct.

It was suggested to present cost-effectiveness results either in probabilistic term or as a range of possible ICERs, given the very big variation/uncertainty in modeling results.

Questions to be answered

- What does IVIR-AC think are the strengths and weaknesses of the presented models?
- What are IVIR-AC's comments on the costing and cost-effectiveness methodology?

Summary and recommendations

In order to better understand the investment, consequences and value-for-money of efforts to eliminate measles and rubella transmission globally, the relative impact, cost and cost-effectiveness of different strategies for measles-rubella elimination (and potential eradication) have been modeled by a consortium of mathematical modelers. The consortium consists of two multi-country measles models (the DynaMICE and PSU models) and two multi-country rubella models (the PHE and JHU models). In addition, sub-national modeling was done using a single-country measles model in Nigeria (the IDM model). These transmission models projected long-term cases, deaths and DALYs, along with the number and type of vaccinations given, under four vaccination coverage scenarios. To evaluate the cost-effectiveness of different scenarios, these outputs were used in an economic model which estimated the direct costs of vaccination and treatment associated with each scenario.

Recommendations on the impact modeling

- When presenting the summary of the impact modeling, it should be made clear that elimination of rubella is possible but not measles under the current scenarios analysed. However, it is worthwhile noting that a substantial reduction in measles disease burden and death is a laudable goal, even if it falls short of eradication.
- Presenting modeling, budget impact, and cost-effectiveness results by region and /or by income-group might allow region-specific recommendations to be made.
- For the 93 country-specific results, IVIR-AC recommends analysing results by country to determine if factors such as income level, country size, demography, population density, or coverage (and of which dose) is the greatest determinant to time to reach elimination threshold.
- IVIR-AC recommends comparing results from the subnational Nigeria model to each of the national models to infer the impact of incorporating spatial heterogeneity, i.e. compare national model 1 to national model 2 and then how each of these two model results compares to the result of the subnational Nigeria model extrapolated to the national level.
- In the subnational model, for the 3 different ways of distributing/increasing vaccine coverage and the 3 scenarios that were evaluated, evaluate in a 3X3 format whether it is more important to optimize vaccine distribution or to increase vaccine coverage. Variation in y-axis of the plots seemed greater than the variation between the three box-plots within each plot and this should be explored.
- The intermediate coverage scenarios should be dropped and only the base-case and most aggressive coverage scenarios should be presented to the October SAGE meeting.

Recommendations on the costing and cost-effectiveness methodology

- Presenting the costing and cost-effectiveness averaged over 93 LMICs was not very informative as heterogeneity across countries was not reflected and almost all scenarios were cost-effective or cost-saving. A graphical or tabular solution to presenting the 93 country level costing and impact estimates separately would facilitate the understanding of the results relevant to decision making.
- When presenting to decision-makers it is important to talk about the budget implications and affordability of measles and rubella eradication. Overall costs and benefits attributed to each scenario (but not necessarily the ratio) need to be presented to provide insight in how much eradication is going to cost and how much will be saved. Resource requirements of eradication might be underestimating the last mile (e.g. increasing marginal costs toward high coverage; the estimate is lower for measles than for polio and this may not be realistic given the R0 of measles).

- Presenting results in a dashboard might be informative. The elements to be included could be: time towards eradication including which countries will reach elimination by when, investments needed, cost savings, benefits in terms of cases/death avoided, CE ratio.
- The uncertainty in both the epidemiological parameters (represented by the 200 stochastic runs) and the economic parameters (represented by sampling from the distributions of the cost parameters) should be taken into account.

Recommendations for a future research program / continued program of work

- Some of the above recommendations can be completed in time for the presentation of the work to the October 2019 SAGE meeting; however, most of them need to be implemented as part of a longer-term programme of work.
- For this future program of work, IVIR-AC recommends investigating what global vaccination strategy would achieve worldwide elimination of measles, in addition to further subnational and disaggregated analysis per socioeconomic status and geographical settings. As part of this future program of work, the definition of elimination of measles should be revised to reflect the disruption of sustained transmission, as opposed to reaching a predetermined elimination threshold. Once it is clear which global strategy would achieve elimination according to the new definition of elimination, costs should be added, and cost-effectiveness and budget impact analysis carried out. In addition, uncertainty/sensitivity analyses should be performed. Further, the models should be validated, based on data from the Americas to determine if they would have predicted the successful elimination of measles in those two continents.

Session 5: Economics of RTS'S vaccine for policy and decision making

Introduction

Despite continuous efforts with existing proven interventions that work, progress on reducing the number of malaria cases worldwide has stalled, and in some places declining trends are reversing. This is particularly true in high burden areas of sub-Saharan Africa. New preventive tools are urgently needed to complement the handful of existing preventive interventions which include long-lasting insecticide-treated nets (LLINs), intermittent preventive treatment of malaria and, in limited settings, indoor residual spraying (IRS) or seasonal malaria chemoprophylaxis.

RTS,S/AS01 is the first approved malaria vaccine which is partially effective in preventing malaria and with potential for high impact. When given in 4 doses to children 5-17 months of age, over 4 years of follow up there was a 39% reduction in clinical malaria and a 29% reduction in severe malaria, a 62% reduction in severe malaria anaemia and a 29% reduction in blood transfusions, as well as a 37% reduction in malaria hospitalization and an 18% reduction in all cause hospitalizations[10].

Even with moderate vaccine efficacy, the impact of the RTS,S vaccine is expected to be high because children in moderate to high transmission areas suffer multiple episodes of malaria in a year. If, like for other childhood vaccines, high coverage can be achieved, particularly in the poorest populations at highest risk of disease and death, the vaccine can address some of the disproportionate burden of severe malaria and death in infants and young children under two years of age, and in the poorest children. As such, the RTS,S vaccine can provide added benefit to that provided by ITNs, but also reach children who do not have access to ITNs or other preventive tools.

Different economic evaluations have been done to inform the optimization of scale-up of malaria interventions. These modeling studies have aimed to answer questions of when to increase coverage of existing interventions and when to introduce new interventions. Ideally, such analyses are done across a wide range of transmission settings and capture non-linear costs (where coverage of an intervention to very high levels may become increasingly expensive). Four economic evaluations of RTS,S/AS01 vaccine in the context of other preventive interventions, in different high burden malaria settings, were presented and differences

[10] RTSS Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomized, controlled trial. Lancet 2015; 386: 31-45.

between study results were discussed[11,12,13,14]. Some of the differences in results between the economic analysis may have been due to different baseline coverage of interventions (of LLINs), differences in assumed unit costs of interventions (particularly SMC and RTS,S), and assumptions on population level coverage of LLINs.

IVIR-AC was asked to advise on how to perform economic analyses of RTS,S vaccines in the context of existing preventive malaria interventions and to deliberate the policy considerations.

Review

Economic evaluation must be considered in a global approach using MCDAs to address the prioritization of the different prevention methods, as differences in acceptability and practical implementation of these methods can be very variable.

IVIR-AC furthermore considered that economic evaluation must take into account the uncertainties about the future effectiveness and therefore cost and tolerance of different prevention methods (e.g. antimalarial resistance, insecticide resistance, loss of bed nets effectiveness, possible selection of vaccine variants through vaccination, shifting the age of infection with the vaccine (see Burkina Faso), etc.).

To conduct economic evaluation on UHC, it is important to define the outcomes of interest (e.g. level and distribution of health, financial risk protection) through stakeholder engagement. Then these outcomes should be explicitly included into economic evaluations.

Another important consideration is the incorporation of equity, including for financial risk protection. Also, heterogeneity across SES should be considered, in malaria burden, in vaccine/intervention coverage, delivery costs, and in malaria transmission.

Economic evaluation of vaccines should be conducted in the context of malaria intervention packages (e.g. bundle of multiple interventions), consideration of local health system features (e.g. types of delivery platforms) and be interpreted in the context of local control and elimination policies.

[11] Sauboin C, Van Vlaenderen I, Van Bellinghen L-A, Standaert B. Reducing malaria mortality at the lowest budget: an optimization tool for selecting malaria preventive interventions applied to Ghana. MDM Policy Pract 2019;4(2): 2381468319861346.
[12] Liu L, Portnoy A, True Z, Fink G, Verguet S. The health and financial benefits for households from averting malaria wit RTS,S/AS01 vaccine in Zambia: an extended cost-effectiveness analysis. Disease Control Priorities in Developing Countries, 3rd Edition Working Paper #26. January 24, 2019.
[13] Winskill P, Walker PGT, Griffin JT, *et al*. Modelling the cost-effectiveness of introducing the RTS,S malaria vaccine relative to scaling up other malaria interventions in sub-Saharan Africa. BMJ Global Health 2017; 2:e000090
[14] Winskill P, Walker PG, Cibulskis RE, Ghani AZ. Prioritizing the scale-up of interventions for malaria control and elimination. Malar J 2019; 18:122

In the context of prioritizing different health interventions in a context of constrained budget, economic evaluation on malaria prevention must take into account indirect beneficial effects such as the impact of malaria prevention on the occurrence of secondary (bacterial) infections.

Discussion

Acceptability and feasibility of the implementation of interventions is important. Bednets need to be used correctly and consistently every night to be fully effective. It has been shown in many settings, that it is difficult to get coverage of bednets above 60% and that it is challenging to maintain this over time. Furthermore, there are increased marginal cost with increased coverage.

In addition, the committee discussed the importance of equity considerations, particularly because malaria disproportionally affects the poorest children. Vaccination might be able to address some of these equity concerns.

In addition, it is important to think about health system performance. Treatment for example, only works where there is a functional health system and the health system may not functional where the rural poor live, who are at highest risk of malaria mortality.

An important consideration is that the benefit package selected is the most appropriate for a specific setting and/or situation and this depends on the starting point (what is the current coverage of interventions) as well as the level of control achieved with current coverage of interventions.

Considerations of end users and citizens are important; people might prefer a combination of interventions (i.e. both bednets and the vaccine) in order to maximize protection. The involvement of end users and citizens in selecting criteria for evaluation (in MCDA) is important.

Questions to be answered

- How economic/financial vs other considerations (e.g. equity) should used to support policy making for UHC?
- How to perform economic analyses of RTS,S vaccines in the context of existing preventive malaria interventions and what are the policy considerations?

Summary and recommendations

Different economic evaluations have been done to inform the optimization of scale-up of malaria interventions. These modeling studies have aimed to answer questions of when to increase coverage of new interventions and when to introduce new interventions. Some of the differences in results between the economic analysis may have been due to different baseline coverage of interventions (of long-lasting insecticide-treated nets (LLINs)), differences in

assumed unit costs of interventions (particularly SMC and RTS,S), and assumptions on population level coverage of LLINs. IVIR-AC was asked to advise on how to perform economic analyses of RTS,S vaccines in the context of existing preventive malaria interventions and to deliberate the policy considerations.

- The committee would like to highlight the following points: (i) the burden of malaria including morbidity and mortality in malaria-endemic countries is high; (ii) that, currently, preventive interventions against malaria (e.g. long-lasting insecticide-treated bednets, indoor residual spraying, intermittent preventive treatment, seasonal malaria chemoprevention) are all partially effective and challenging to implement in the most disadvantaged communities and poorest households; (iii) Assessing individual preventive interventions against malaria as competing interventions and introducing them sequentially should be avoided; and (iv) that malaria prevention may significantly impact on the incidence of secondary malaria cases.
- Therefore, rather than assessing malaria preventive interventions in sequence and as competing interventions it should be assessed as packages of multiple and combined interventions. This involves greater consideration of local health system features, within the context of UHC and national benefit package design; and interpretation in the context of local control and elimination policies. Furthermore, the synergistic effects and uncertainty in both impact and costs of the different preventive interventions (e.g. resistance, bednet effectiveness, waning vaccine efficacy over time) must be fully examined. Rollout of a malaria vaccination programme interacts with the existing package of preventive malaria interventions and should be evaluated as complementing this existing package.
- In the modeling, it is critical to consider compliance with each intervention. For example, the effectiveness of bednets is dependent on nightly compliance with sleeping under the net. In contrast, vaccination only requires compliance to make a few visits to a vaccine provider to complete the recommended course of vaccinations.
- To support policymaking for UHC including malaria control and elimination, evidence from economic analyses should be considered in an open and transparent deliberative decision making process, and should include considerations of both efficiency and equity including reduction in health disparities and financial risk protection. Hence, malaria-specific economics evaluations should incorporate heterogeneity across socioeconomic status of malaria burden and transmission, intervention coverage, and delivery costs.

Session 6: WHO guide on standardization of economic evaluations of immunization programmes

Session for information

Summary

The 2008 WHO guide for standardization of economic evaluations of immunization programmes was developed to provide guidance to those who conduct or critically appraise economic evaluations of immunization programmes at the local, national, and global levels. The guide was also used to help programme staff assess transparency, completeness, and comparability of economic evaluations that have been conducted for their own country, or for other countries in the region. Since the publication of the 2008 WHO guide, there have been a growing number of vaccine options, with increasingly high costs of newer vaccines. There have also been methodological developments in the vaccine and economics world, for example on differential discounting, the broader economic impact of vaccines, cost-effectiveness thresholds, and the handling of uncertainty. In light of these developments, an update of the guideline was carried out. Some of the changes in the second version of the guide include: The addition of a flowchart for choosing the type of analysis; More detail provided on the perspective and scope of the analysis; Change in discount rates and addition of differential discounting as one of the discounting approaches to use; Changes in estimating costs and effects; Provision of a more detailed flowchart on choosing between static and dynamic models; Changed method of accounting uncertainty and revised recommendations on cost-effectiveness thresholds; Increased emphasis on the decision-making process and the importance of including factors such as equity-related aspects, broader economic benefits and budget impact when communicating results to policy makers.

Session 7: Standardization of vaccine delivery costs

Session for information

Summary

Different methodologies and terminologies have been employed by micro-costing and planning tools for immunization programs. Standardization of vaccine delivery costing was first raised in the March 2018 IVIR-AC meeting. In that meeting, IVIR-AC concluded that standardization of costing tools is vital for comparing delivery costs across countries, across products and across delivery strategies. In the March 2019 IVIR-AC meeting, a literature review on three existing guidelines and three WHO costing tools was presented. The need for a standardization guideline was reinforced. However, given the availability of existing related guidelines from BMGF and other costing tools which were not included in the literature review, IVIR-AC recommended more detailed discussions and proposed to develop joint guidelines. In July 2019, eleven experts from different organizations and institutions in immunization economics gathered in Basel. They re-defined the scope of review, adding more guidelines and tools for consideration, so that a total of three guidelines and ten tools (some of which are vaccine specific, e.g. for HPV vaccination, oral cholera vaccines, typhoid vaccine, etc.) are included.

A matrix of selected guidelines and tools was drafted to facilitate a comparison. A preliminary analysis of these guidelines and tools on vaccine delivery costs was conducted based on this matrix and was presented in this IVIR-AC meeting. The three guidelines were compared on three aspects: target intervention, focus and purpose, while the ten tools were compared on eighteen perspectives, including purpose, intended use, perspective, etc. Commonalities and differences were identified, including the absence of uncertainty analysis as a built-in function in most costing tools, and differences in cost categories used in the tools.

The conclusion is that both commonalities and gaps exist among current guidelines and tools in various perspectives. Further efforts will be made in harmonizing the differences and fill-in the gaps in the standardization of vaccine delivery costs guideline. A future workshop on further steps might be planned.

Session 8: Burden of Disease Estimates for Enteric Pathogens

Session for information

Summary

Prioritization and investment in vaccine product development are guided by global burden of disease estimates. For enteric diseases burden the two main modeling groups providing estimates are the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, Seattle, and the Maternal Child Epidemiology Estimation (MCEE) group led by Johns Hopkins Bloomberg School of Public Health. Although earlier estimates of global diarrhoea mortality estimates for under five-year-olds were closely aligned, more recent estimates have diverged, particularly with regard to number of deaths attributable to different enteric pathogen.

The Product Development for Vaccines Advisory Committee (PDVAC) of WHO recommended in 2018 to explore the reasons for the differences between the IHME and MCEE estimates, and to assess the respective strengths and weaknesses of the estimation approaches adopted, including a review of the data on which the estimates are based.

In March 2019, IVIR-AC commented on the proposed approach to compare and characterize the IHME and MCEE input data to identify key variables in the models, on the review of the forensic data analysis, and the validity, scope, methodology and scientific approach for the proposed systematic reviews.

IVIR-AC now received an update on the ongoing work which is divided into four current workstreams. The data gaps work stream aims to generate additional data through two systematic reviews to provide the modeling groups with information to strengthen their approach. The first systematic review aims to Update Odds Ratios for the probability of detecting a pathogen, given diarrhoea. The second systematic review aims to assess the assumption that case fatality rate is the same for all pathogens. The second work stream on study quality aims to grade the quality of the studies utilised by both groups using the Newcastle-Ottawa Scale with the purpose of improving the understanding of how the burden estimates are impacted by the quality of included studies. The third workstream on data processing provides a high-level assessment of similarities and differences in study data and is addressed through a data comparison and meta-analysis. Finally, in work stream four, a model comparison exercise is carried out to assess the relative differences in model outputs generated by both groups, when a common dataset is applied to both models.

Session 9: WHO/UNICEF Estimates of National Immunization Coverage (WUENIC)

Introduction

The current WUENIC methodology uses a rule-based approach informed by data officially reported to WHO and UNICEF by Member States, surveys as well as data reported in the published and grey literature[15,16]. When checked against the 18 items to be reported under the "Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement" (GATHER), WUENIC meets all GATHER criteria except item 11, as no formal comparison with other "models" has been undertaken. Item 16, "Report a quantitative measure of the uncertainty" is not fully applicable, as WUENIC is not a mathematical model.[17] Instead, WUENIC uses a "Grade of Confidence" (GoC) approach, that leverages the accumulation of endorsements to the estimates.[18]

Seeking to further improve the transparency of data inputs as well as the estimation process, and explore alternative approaches, in early 2019, WHO and UNICEF opened an call for Expressions of Interest (EOI) for Modeling Approaches to Produce Estimates of National Immunization Coverage which address the specific objectives to develop a model, or another analytical approach, to produce annual estimates of vaccination coverage. EOI were received from three academic organizations, namely WorldPop (U. of Southampton), Imperial College of London, and the Swiss Tropical and Public Health Institute (Swiss TPH) and all three were engaged to further develop their modeling proposals. All three groups proposed Bayesian modeling approaches and will use publicly available data as inputs. WorldPop proposes to generate an ensemble of candidate models exploring temporal, antigen, and country correlation, with model estimation and fit implemented in an Bayesian framework using nested Laplace approximations (INLA). Imperial College London will use a two-step modeling procedure, first using a Bayesian hierarchical beta-binomial model to estimate national-level coverage for years with high-quality surveys and then a time-series regression (Gaussian process) to infer national estimates for intra-survey years. The Swiss TPH will explore a series of models including explorations of interpolate or extrapolation forward from survey data, using different denominators for administrative data, excluding input data deemed to be of "poor

[15] Burton A, Monash R, Lautenbach B, et al. WHO and UNICEF estimates of national infant immunization coverage: methods and processes. Bulletin of the World Health Organization 2009, 87:535-541. https://www.who.int/bulletin/volumes/87/7/08-053819/en/

[16] Burton A, Kowalski R, Gacic-Dobo M, Karimov R, Brown D. A formal representation of the WHO and UNCIEF Estimates of National Immunization Coverage: A computational logic approach. PLoS One 2012,7(19): e47806.

[17] GATHER Assessment of WUENIC Methodology, available at https://www.who.int/immunization/monitoring_surveillance/routine/coverage/en/index4.html

[18] Brown DW, Burton AH, Gacic-Dobo M, Karimov RI. An Introduction to the Grade of Confidence Used to Characterize Uncertainty Around the WHO and UNICEF Estimates of National Immunization Coverage. The Open Public Health Journal, 2013, 6, 73-76.

quality", predictions based on the relationship between survey and admin data, etc. This group may also explore using different approaches for different groups of countries. The Swiss TPH also proposed a stakeholder analysis to better understand the current uses of WUENIC and users' perceptions, including credibility, about the current approach and the estimates themselves. The EOI received, which include more details on the approaches proposed, are included in the background material shared with IVIR-AC members. Following delays in contractual procedures, all three groups only recently started working on their models. It is expected that all three groups will have their models developed by early 2020.

Review

The current WUENIC methodology uses a rule-based approach informed by data officially reported to WHO and UNICEF by Member States, surveys as well as data reported in the published and grey literature[19,20]. Transparency on how current WUENIC estimates as well as estimates derived by alternative methods are developed is important. For the current WUENIC estimates, it might help to provide a flow diagram that shows data inputs and decisions regarding data use. For the alternative methods it will also be important to understand how the inputs relate to the outputs and the modeling groups should make an effort to describe their model in detail and to provide open source code. While all groups proposing alternative methods offer to provide some open source code, it is not clear how easy this will be to understand.

When checked against the 18 items to be reported under the "Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement" (GATHER), WUENIC meets all GATHER criteria except item 11, as no formal comparison with other "models" has been undertaken and item 16, "Report a quantitative measure of the uncertainty", which is not fully applicable, as WUENIC is not a mathematical model.[21] Instead, WUENIC uses a "Grade of Confidence" (GoC) approach, that leverages the accumulation of endorsements to the estimates.[22] The call for Expressions of Interest (EOI) for Modeling Approaches to Produce Estimates of National Immunization Coverage addresses item 11 by providing a formal comparison with other "models". In addition, the alternative modeling methods can address item 16 by providing estimates of uncertainty to address this WUENIC weakness. Providing estimates of uncertainty is important as it says something about reliability of the estimate of

[19] Burton A, Monash R, Lautenbach B, et al. WHO and UNICEF estimates of national infant immunization coverage: methods and processes. Bulletin of the World Health Organization 2009, 87:535-541. https://www.who.int/bulletin/volumes/87/7/08-053819/en/

[20] Burton A, Kowalski R, Gacic-Dobo M, Karimov R, Brown D. A formal representation of the WHO and UNCIEF Estimates of National Immunization Coverage: A computational logic approach. PLoS One 2012,7(19): e47806.

[21] GATHER Assessment of WUENIC Methodology, available at https://www.who.int/immunization/monitoring_surveillance/routine/coverage/en/index4.html

[22] Brown DW, Burton AH, Gacic-Dobo M, Karimov RI. An Introduction to the Grade of Confidence Used to Characterize Uncertainty Around the WHO and UNICEF Estimates of National Immunization Coverage. The Open Public Health Journal, 2013, 6, 73-76.

national immunization coverage. If there is high uncertainty, then this also shows the importance of getting better data.

There are limits on doing a good validation because there is no gold standard to compare the coverage estimates with. The cross-validation such as is proposed by some of the alternative methods, are useful but cannot be considered a true validation. Ideally the estimates would be compared with high quality survey data. However, in many cases there are only sub-national data which is problematic, because they do not necessarily reflect what is happening at national level. Furthermore, subnational data are often difficult to triangulate because of population movements etc. IVIR-AC wants to re-emphasize the importance of good quality input data and wants to reiterate that efforts to strengthen data quality are very important.

When evaluating the alternatives, it becomes clear that each methodology has its own strengths and weaknesses. It is important that these new models build on the strengths of the current WUENIC methodology, while addressing some of the WUENIC weaknesses. It is also important that the alternatives include multiple data sources and that they acknowledge any biases within these sources.

The IVIR-AC reviewers provided some comments on the pluses and minuses of the proposed alternative modeling methodologies. For WorldPop the pluses are: the track record of working with relevant stakeholders, the development and dissemination of R package, and the capacity building aspect, while the minuses were: that data processing steps may obscure how data inputs are used, that the advanced methodology may not be very transparent to the average user, and potentially the acceptance of spatial correlation among countries and correlation among antigens. For the Imperial College / LSHTM method the pluses were mentioned to be: experience developing vaccine coverage estimates for India and the UK, a fairly straightforward approach, and the ability to move towards subnational estimates, while the minuses are thought to be: that it seems to rely heavily on survey data and that it is unclear how/if other data inputs are really incorporated, and that the modeling methodology is not very transparent. For the Swiss TPH approach the following pluses were recognized: strong stakeholder engagement component, proposal to evaluate and possibly bring in other data sources (e.g. covariates), and it is the most similar to the existing approach, while minuses were listed as: potentially too responsive to current stakeholder feedback, and details on methodology are vague.

Discussion

The additional methods might allow for the use of additional quality input data which are available but not yet used in the current WUENIC methods, such as for example information on conflict, or stock-outs. As such they provide a real opportunity to improve the current WUENIC

methods, especially when such new data can be used quantitatively. A combination or hybrid of different methods might ultimately be feasible.

The alternative approaches will also require some level of country buy-in. It would therefore be important to involve country level stakeholders and show them how their data is used in the alternative methods.

In future there may be increasing need to report equitable access to vaccination which may require estimates at sub-national level.

At country level the WUENIC estimates are often used in addition to the data collected in the country. Some challenges, both for countries making immunisation coverage estimates themselves, as well as for the WUENIC estimates, is that countries sometimes have little knowledge about their populations (e.g. very remote villages, migratory populations). While the WUENIC mandate is to provide country-level estimates, parallel efforts are undertaken to strengthen sub-national and national data collection and to improve both estimates of nominators (e.g. through use of electronic data collection systems and/or health records) and denominators (e.g. by improving civil registrations).

Questions to be answered

- Does IVIR-AC have any concerns on the process proposed to review the estimation coverage approach or suggestions on how to make it more transparent?
- What high-level principles does IVIR-AC suggest for evaluating alternative methodologies?

<u>Summary and recommendations</u>

The current WUENIC methodology uses a rule-based approach informed by data officially reported to WHO and UNICEF by Member States, surveys as well as data reported in the published and grey literature. Seeking to further improve the transparency of data inputs as well as the estimation process, and explore alternative approaches, in early 2019, WHO and UNICEF opened a call for Expressions of Interest (EOI) for Modeling Approaches to Produce Estimates of National Immunization Coverage which address the specific objectives to develop a model, or another analytical approach, to produce annual estimates of vaccination coverage. EOI were received from three academic organizations, namely WorldPop (U. of Southampton), Imperial College of London, and the Swiss Tropical and Public Health Institute (Swiss TPH) and all three were engaged to further develop their modeling proposals. IVIR-AC was requested to comment on the proposed process to review the estimation coverage approach and to propose high-level principles for evaluating the alternative methodologies.

Proposed process to review estimation coverage approach

- IVIR-AC does not have any major concerns on the process proposed to review the estimation of coverage approach and agrees with the proposed plan to work with several technical teams to find and assess alternative approaches (not replacing WUENIC).
- To improve the transparency of the current WUENIC approach and to facilitate comparison with alternative approaches, it would be helpful to illustrate the current approach with a flow diagram of data inputs and decision rules.

High-level principles for evaluating alternative methodologies

- Alternative models are encouraged to incorporate multiple data sources, while recognizing the strengths and weaknesses of each.
- For reasons of transparency it should be possible to see what data inputs are used in the alternative approaches. In addition, we encourage all possible efforts be made to make the model code freely available and well annotated so that the approach is as widely accessible and applicable to as many users as possible. Training on proper implementation and interpretation of the models should be provided.
- Alternative approaches should include formal quantification of uncertainty. Modelers should not shy away from large uncertainty as quantifying uncertainty can help to identify when and what additional data is needed for the future in order to reduce uncertainty.
- Appropriate validation should be ensured. Alternative models should be validated against data. Furthermore, proposed methods for cross-validation and "leave-one-out" validation may not be sufficient. While these are useful as forms of internal validation and can identify particularly influential data points, they are not testing models against "gold standard" data. IVIR-AC recognizes that the absence of a "gold standard" is a limiting factor. Well conducted subnational surveys may be useful and serve that purpose.
- Models need to be communicated clearly to country level stakeholders and take feedback into account to ensure country buy-in and ownership. IVIR-AC suggests the establishment of feedback mechanism between WHO/UNICEF and country focal points according to theory of change. The work of Swiss TPH in understanding the local process and use of the data will help this.
- Models are only as good as the data they are based on. Parallel efforts are needed to improve country-level capacity for data collection and interpretation. When requesting country-produced data, it may be better to try to also request sub-national level data from countries, including sub-national surveys. Experience from other areas such as

burden of disease studies or health service utilization suggested that the lower the level of the data requested the better the quality of the data (REFERENCE).

- Principles of transparency and engagement with country stakeholders should ideally apply to all vaccine coverage estimates, whether or not they inform WEUNIC.

Annex 1: Agenda

Wednesday, 18 September 2019

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
13.00 – 13.30	Registration			
13.30 – 13.45	Welcome - introduction and Charge to the Committee			K. O'Brien R. Hutubessy W. Orenstein
13.45 -15.15	***Session 1:*** Total System Effectiveness	- Introduction and context by B. Giersing (10 min) - Presentation on the TSE decision-support tool by S. Botwright (20 min) - Experience from the TSE pilot in Mali by A. Sidibe and I. Diarra (15 min) - IVIR-AC reviewers' comments (each 5 min) Discussion (20 min)	Does the committee have any feedback on the methods used in the TSE decision-support tool? How can WHO validate the tool and at which stage will it be ready for wider roll-out?	IVIR-AC members: M. Jit J. Leask WHO focal point: B. Giersing

Wednesday, 18 September 2019 - continued

15.15-15.45	**Coffee/tea break**			
15.45 – 16.45	***Session 2:*** Global vaccine acceptance and demand	- Introduction and context by L. Menning (10 min) - Measuring Behavioural and Social Drivers of Vaccination – working group update by J. Leask (20 min) - IVIR-AC reviewers' comments (each 5 min) Discussion (20 min)	- What comments do members have on the testing proposal within the timeframe? - Are members satisfied with the criteria for selection of countries for testing the tools?	IVIR-AC members: DC. Lyimo V. Nankabirwa WHO focal point: L. Menning
16.45 -17.00	**Summary of Day 1**			
17.00	**Adjourn**			

18.00 **Cocktail**

Thursday, 19 September 2019

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
9.00-10.30	***Session 3:*** Ebola model comparison	- Introduction and context by AM. Henao-Restrepo (10 min) - Ebola model comparison by B. Cowling (20 min) - IVIR-AC reviewers' comments (each 5 min) Discussion (20 min)	Does IVIR-AC have any suggestions for the proposed model comparison?	IVIR-AC members: J.Wu M. Brisson W. Ndifon WHO focal point: AM. Henao-Restrepo
10.30-11.00	**Coffee/tea break**			
11.00-12.30	***Session 4:*** Measles investment case	- Introduction and context by K. Kretsinger (10 min) - Measles and Rubella model comparison by M. Jit (20 min) - Measles and Rubella Cost-Effectiveness by A. Levin (20 min) - IVIR-AC reviewers' comments (each 5 min) Discussion (20 min)	What does IVIR-AC think are the strengths and weaknesses of the presented models? What are IVIR-AC's comments on the costing and cost-effectiveness methodology?	IVIR-AC members: Q. Bassat P. Luz WHO focal point: K. Kretsinger

Thursday, 19 September 2019 – continued

12.30-13.30	**Lunch**			
13:30-15.00	***Session 5:*** Economics of RTS'S vaccine for policy and decision making	- Introduction and context by M. Hamel (5 min) - Recent RTS,S economics papers by P. Winskill, C. Sauboin, S. Verguet and E. Patouillard (20 min) - Data, Deliberations, Decisions (DDD) Framework by M. Bertram (5 min) - IVIR-AC reviewers' comments (each 5 min) Discussion (20 min)	Does IVIR-AC have any comments and/ or additions on the proposed considerations?	IVIR-AC members: S. Verguet J-D. Lelièvre WHO focal point: M. Hamel
15.00-15.30	**Coffee/tea break**			
16.00-16.30	***Session 6:*** WHO guide on standardization of economic evaluations of immunization programmes ***– for information***	- Introduction and context by R. Hutubessy (5 min) Update on the finalized WHO guide on standardization of economic evaluations of immunization programmes by P. Beutels (15 min) Discussion (5 min)	No questions – committee update	WHO focal point: R. Hutubessy

Thursday, 19 September 2019 – continued

15.30 – 16.00	***Session 7:*** Standardization of vaccine delivery costs ***– for information***	- Introduction and context by M Jit (10 min) Methods of standardization of vaccine delivery costs by S. Huang (15 min) Discussion (5 min)	No questions – committee update	WHO focal point: R. Hutubessy
16.30-17.00	***Session 8:*** Enteric disease burden ***– for information***	Introduction and context by B Giersing (10 min) Update on the ongoing modeling work by M. Hasso-Agopsowicz (15 min) Discussion (5 min)	No questions – committee update	WHO focal point: B. Giersing
16.50-17.30	**Summary of Day 2**			
17.30	**Adjourn**			

Friday, 20 September 2019

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
09.00-10.30	***Session 9:*** WUENIC	- Recap on current estimation approach and context by C Danovaro (10 min) - Updates on the process for alternative modeling methodologies and next steps by M Diallo and C Danovaro (30 min) - IVIR-AC reviewers' comments (each 5 min) Discussion (20 min)	Does IVIR-AC have any concerns on the process proposed to review the estimation coverage approach or suggestions on how to make it more transparent? What high-level principles does IVIR-AC suggest for evaluating alternative methodologies?	IVIR-AC members: Y. Teerawattananon V. Pitzer WHO focal point: M. Gacic-Dobo
	MEETING CLOSURE OPEN SESSIONS			
10.30-11.00	**Coffee/tea break**			
11:00-13.00	**CLOSED SESSION**			
13.00-14.00	**Lunch**			
14.00 -16.00	**CLOSED SESSION**			

16.00	**Adjourn**			

Annex 2: List of Participants

Advisory Committee Members

Quique Bassat, Paediatrician and ICREA Research Professor, ISGlobal Barcelona Institute for Global Health, Hospital Clínic - Universitat de Barcelona, Barcelona, **Spain**

Marc Brisson, *Professor, Mathematical Modeling and Health Economics of Infectious, Diseases Department of social and preventive medicine, Faculty of Medicine, Laval University****, Canada (unable to attend)***

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, Proferssor, Susan Wakil School of Nursing and Midwifery, Sydney Nursing School, Faculty of Medicine and Health, Camperdown NSW 2050, Sydney, **Australia**

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

Anna Lena Lopez, *Director, Institute of Child Health and Human Development, Research Associate Professor, University of the Philippines Manila-National Institutes of Health, Manila,* ***Philippines (unable to attend)***

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 (unable to attend)***

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

Mary Nyamongo, *Executive Director and co-founder, African Institute for Health and Development (AIHD), Nairobi,* ***Kenya (unable to attend)***

Walter Orenstein (Chair), Professor**,** Emory Global Health Institute, Emory University, 1599 Clifton Road, Suite 6.101, Atlanta, GA 30322, **United States of America**

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

Yot Teerawattananon, Founding Leader of Health Intervention and Technology Assessment Program & Senior Researcher Scholar of Thailand's Research Fund, Health Intervention and Technology Assessment Program, Department of Health, Ministry of Public Health, Nonthaburi, 11000 **Thailand (via webex)**

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

Joseph Wu, Professor, Division of Epidemiology and Biostatistics, School of Public Health, The University of Hong Kong, Pok Fu Lam, **Hong Kong SAR, China**

Participants

Ayodele Adeyemo, No 29 Agadez Crescent, Wuse II Abuja, Federal Capital Territory, **Nigeria (via webex)**

Philippe Beutels, Associate Professor, Health Economics and Modeling Infectious Diseases

Vaccine and Infectious Disease Institute, University of Antwerp, 2610 Antwerp, **Belgium (via webex)**

Ben J. Cowling, Professor and Division Head, Division of Epidemiology and Biostatistics, School of Public Health, The University of Hong Kong, Pok Fu Lam, **Hong Kong SAR, China (via webex)**

Mamadou S. Diallo, Senior Statistician, UNICEF, New York, **United States of America (via webex)**

Ibrahima Diarra, EPI Manager, Ministry of Health, Bamako, **Mali (via webex)**

Azra Ghani, Malaria Modeling Group Lead, Imperial College London, South Kensington Campus, London SW7 2AZ, **United Kingdom of Great Britain & Northern Ireland (via webex)**

Ann Levin, Health Economist, Bethesda MD 20817, **United States of America**

Ira Longini, Professor of Biostatistics, Department of Biostatistics, College of Public Health and College of Medicine, University of Florida, **United States of America**

Michael Lynch, Global Immunization Division, Centers for Disease Control & Prevention, Atlanta, GA 30329, **United States of America**

Peter Winskill, Imperial College Research Fellow (ICRF), MRC Centre for Global Infectious Disease Analysis, Imperial College London, South Kensington Campus, London SW7 2AZ, **United Kingdom of Great Britain & Northern Ireland (via webex)**

Observers

Scott Gordon, Director, Malaria Vaccine Implementation Program, PATH, Seattle, Washington, **United States of America**

Hope Johnson, Head, Programme Outcomes and Impact Monitoring & Evaluation, Policy & PerformanceGavi, the Vaccine Alliance, Chemin des Mines 2, Geneva, 1202, **Switzerland**

Dan Hogan, Head, Monitoring and Evaluation, Policy and Performance, Gavi, the Vaccine Alliance, Geneva, 1202, **Switzerland**

Tewodaj Mengistu, Senior Programme Officer, Monitoring and Evaluation, Policy and Performance, Gavi, the Vaccine Alliance, Geneva 1202, **Switzerland**

Christophe Sauboin, Director, Value Evidence, GSK Vaccines, GlaxoSmithKline, Wavre, **Belgium**

Regional Offices

Abdoul Karim Sidibe, NPO Routine Immunization, World Health Organization Country Office, Bamako, **Mali**

WHO Secretariat

Melanie Bertram, Technical Officer, Economic Analysis and Evaluation, Health Systems and Innovation, World Health Organization, Switzerland

Siobhan Botwright, Consultant, Initiative for Vaccine Research, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

Saskia den Boon, Consultant, Implementation Research and Economic Analysis, Initiative for Vaccine Research, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

Carolina Danovaro, Scientist, Immunization Strategic Information, Expanded Programme on Immunization, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

Eliane Furrer, Technical Officer, Initiative for Vaccine Research, World Health Organization, Switzerland

Marta Gacic-Dobo, Manager, Immunization Strategic Information, Expanded Programme on Immunization, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

Birgitte Giersing, Technical Officer, Initiative for Vaccine Research, World Health Organization, Switzerland

Mateusz Hasso-Agopsowicz, Consultant, Initiative for Vaccine Research, World Health Organization, Switzerland

Mary Hamel, Senior Technical Officer, Initiative for Vaccine Research, World Health Organization, Switzerland

Ana Maria Henao-Restrepo, Team Leader, Implementation Research and Economic Analysis, Initiative for Vaccine Research, World Health Organization, Switzerland

Shuoning Huang, Intern**,** Initiative for Vaccine Research, Implementation Research, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

Raymond Hutubessy, Economist, Initiative for Vaccine Research, Implementation Research, World Health Organization, Switzerland

Katrina Kretsinger, Medical Officer, Expanded Programme on Immunization Plus, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

Lisa Menning, Technical Officer, Expanded Programme on Immunization, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

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

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

Janna Shapiro, Intern, Initiative for Vaccine Research, Implementation Research, World Health Organization, Switzerland

Stephanie Shendale, Technical Officer, Expanded Programme on Immunization, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland