Report on the Immunization and Vaccines Related Implementation research (IVIR)

Advisory Committee Meeting
Geneva, 17-19 September 2014
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1. Executive Summary

THEME: Research to conduct impact evaluation of vaccines in use

Comprehensive WHO VPD burden and impact assessment framework

Is the proposed framework useful?

Were there any emerging gaps presented or any concerns?

- IVIR-AC welcomes the proposed framework and agrees with WHO’s role in facilitating a hub of burden of disease and impact assessment work including an associated network of experts.

- IVIR-AC’s role and scope within the proposed framework should entail: reviewing evidence, identifying gaps, biases and limitations, assessing research methodology, commenting on analytic approaches, correctly utilizing models, and maintaining participation of at least two IVIR-AC members in each sub-group to be established.

- Sub-groups should identify any clear gaps and both value-added and unnecessary duplication of effort to better direct future modeling and vaccination program work.

- In order to sustain the impact framework in line with relevant policy questions at global and local levels, institutional capacity is needed while funding from various partners is streamlined according to the proposed framework.

- IVIR-AC encourages partners in the immunization field and other interested parties to contribute to the framework and to utilize it.

Pertussis impact modeling review

What are the best modeling approaches to address policy questions defined by SAGE regarding pertussis vaccines?

- The models seem to be appropriate in terms of structure to better understand both schedule optimization in various countries and transmission settings, and how high-income country (HIC) experiences can inform potential resurgences in low-and-middle-income countries (LMICs).

- Availability and quality of data is the key problem, thus IVIR-AC calls for better surveillance systems in all countries, particularly in LMICs where virtually no data exist.
• An IVIR-AC sub-group under the WHO VPD burden and impact assessment framework will be formed to identify specific data needs as an input for various models by conjoining modeler needs with epidemiologic expertise.

• IVIR-AC members P. Beutels, P. McIntyre and B. Gessner volunteered to join the sub-group and report back to the IVIR-AC in 2015.

WHO pertussis burden modeling

Does the proposed model provide reliable burden of pertussis estimations?

• IVIR-AC recognized that the new global pertussis burden model had significant limitations in that results from the expert solicitation exercise were too broad, the age groups too wide (should be focused on children under age five years only if the primary objective is to estimate the burden of severe disease, including death) and the very wide range of potential estimates for model parameters that it utilized did not reduce uncertainty in pertussis burden estimates in a useful way.

• IVIR-AC suggests convening a sub-group to explore the potential way forward to revise the presented global pertussis model in combination with new pertussis data available since 2012 in the literature and from the WHO IER group. This sub-group should include the mathematical modeling groups presented in the previous pertussis impact modelling session.

Meningitis A impact assessment

Is the proposed approach adequate to assess meningitis A vaccination?

• IVIR-AC agreed the dynamic model presented is the appropriate approach to understanding the long-term impact of current campaigns and of future meningitis A vaccination strategies.

• Assumptions of the model need further sensitivity and uncertainty analysis, such as varying assumptions of duration of natural immunity following infection or carriage, age structure determinants of the model, and a term to force seasonality into the model, among others within the model. IVIR-AC recommends that an improved presentation of results is needed to capture the stochastic nature of the model i.e. reporting the uncertainty intervals around average model predictions.

• Finally, IVIR-AC emphasized the need to understand investments in prevention of serogroup meningococcal meningitis by estimating the economic impact and benefits of MenAfriVac, vaccination programme, as well as of various vaccination strategies for the future.
Impact evaluation of Hep B vaccines

*Is the proposed approach adequate to assess hepatitis B vaccination?*

- IVIR-AC found the work presented to be of high quality and exemplary of how sub-groups under the WHO VPD burden and impact assessment framework may function, both in terms of process (i.e., IVIR-AC’s involvement) and activities carried out (e.g., comprehensive and detailed systematic literature reviews).
- IVIR-AC highlighted the need for modeling of scenarios to also include comparisons of no birth dose versus birth dose; in particular, there would be value in defining the impact of a birth dose in terms of immunogenicity, and to better understand the issues related to its implementation, such as cost and cost-effectiveness across local, country and regional levels.
- To better inform decision makers in middle-income countries (MICs), IVIR-AC identified the need to incorporate liver cancer screening, treatment options, and outcomes into models.
- IVIR-AC suggested that there is value in comparing the current model with a previously developed model used by Gavi and WHO. These comparisons should include provisions to compare outcomes of both models with the same data inputs and model assumptions.
- IVIR-AC identified the need for addressing quality of life with chronic hepatitis infection in addition to mortality outcomes in impact evaluation studies.

Decade of Vaccine Economics (DOVE)

*Is the proposed approach adequate? Do the individual model components meet the state of the art modeling requirements?*

- IVIR-AC recognized that the ambitious nature of the DOVE study aims to provide global estimates of resources needed for accomplishing the objectives of the Global Vaccine Action Plan (GVAP) and providing return on investment information to donors. IVIR-AC made the following observations about limitations of methodology used and recommended these be acknowledged and addressed more thoroughly in order to enhance the utility of the document for donors and vaccine agencies.
- Many of the individual disease model components do not meet idealized state-of-the-art modeling requirements, but IVIR-AC acknowledges that this is a massive task because of the scale of the DOVE project. Where possible, disease model comparisons should be done to more adequately determine the face validity of the model predictions.
- Therefore IVIR-AC felt that the current DOVE model should not be used to compare impact between vaccines due to concerns related to oversimplified assumptions regarding linearity in benefits with coverage and substantial amount of data extrapolation. The relationship between coverage and impact will be very different between pathogens and vaccines.
• IVIR-AC felt users of both the model and the model results should be made explicitly aware that the marginal costs and benefits scale linearly with vaccination coverage in many of the disease models. This simplifying assumption has a differential impact for the assessment of various disease burdens, and users seeking to apply these data to inform vaccine program choices would need to fully understand its potential influence on priority ordering for different vaccine candidates.

• IVIR-AC felt that increased transparency and clarity regarding all methods used would provide a stronger basis for a broad range of stakeholders to understand what the DOVE project can and cannot provide. Rather than additional explanation, IVIR-AC asked for concise and precise documentation of assumptions and methods. For example, this would include justification of decisions made with regard to data quality grading and percentage of missing data prior to imputation for each input parameter.

• IVIR-AC highlighted that given the many assumptions and extrapolations of the different model components, more refined sensitivity and uncertainty analyses are needed.

• IVIR-AC suggested that should future efforts in the DOVE modeling work take place, inclusion of immunization program performance and process indicators, as the current model assesses the return on investment only in terms of outcome indicators.

**HPV Cost-effectiveness tool (PRIME)**

*Does IVIR-AC consider PRIME to be a suitable model to use as a demonstration tool and to provide a conservative estimate of the cost effectiveness of vaccinating girls prior to sexual debut in LMICs? If there is opportunity to develop PRIME further, what areas of extensions and/or development to PRIME would IVIR-AC consider most useful?*

• IVIR-AC agreed that PRIME is a suitable model to use as a demonstration and planning tool to answer the simple question of whether vaccinating pre-adolescent girls with HPV vaccines is cost-effective. Other dynamic issues around HPV implementation cannot and should not be addressed with PRIME (e.g. screening, different schedules etc.) and the model purpose and limitations should be communicated clearly to potential users.

• IVIR-AC questioned whether PRIME provides appropriately conservative estimates given: a) the 95% coverage assumption for the 3-dose schedule; b) the GLOBOCAN project incidence numbers used which in some settings are not necessarily conservative; c) and the relevance of cervical cancer screening program implementation in some countries. It was recommended that sources and ratings of data quality should be described when presenting the model. Furthermore, PRIME should conduct more detailed uncertainty and sensitivity analysis to better understand the influence of these assumptions on the model outcomes.

• Rather than expanding PRIME to include cervical cancer screening and herd effects, IVIR-AC recommends developing a separate dynamic model (that may be built on existing models used in HICs) for one or two countries with available data (e.g. Tanzania and Thailand), which may also be used to further validate PRIME.
• Given the questions on HPV implementation and implications for national immunization budgets in LMICs, it is important to consider inclusion of budget impact analysis in PRIME rather than cost-effectiveness alone.

• In line with past IVIR-AC recommendations on complex infectious disease models there is a need to develop an emulator-interface\(^1\) to be used as a complementary user-friendly tool for decision-making to better account for variable HPV transmission dynamics and settings.

**Typhoid disease burden, impact and economic assessment**

*Disease burden:* Is the proposed approach robust as a base case?

*Transmission models:* What are the specific scenarios or sensitivity analyses on impact estimates that are required? Are the current model structures appropriate for global impact modeling?

*COI/CEA:* The variation in the cost of illness by geographic regions is not captured. How best could this be addressed?

• IVIR-AC noted the absence of data on a number of key parameters and assumptions used for the analyses presented. IVIR-AC recommended that further analysis should be done where data are available, such as on urbanization, water quality, food safety and security. Further stratification on existing heterogeneity in the data and burden of typhoid within countries and local settings was suggested. The IVIR-AC also discussed the utility of performing an Expected Value of Information analysis to determine model drivers and key parameters to direct investments in future research and data collection.

• IVIR-AC observed that the CFR used for burden of disease calculations might be conservative. Also, some members felt there may be publication bias from the meta-analysis contributing to uncertainty in the estimate (studies showing high CFR may be more likely to get published than those that show low CFR).

• As a main driver of the BoD and Cost of Illness (COI) models the CFR should incorporate access to and utilization of care more comprehensively in both models. IVIR-AC noted that deaths were up to four-fold higher in the COI model where an incidence adjustment accounted for the lack of access to and utilization of care in both hospitalized and non-hospitalized cases. Therefore IVIR-AC recommends an erratum in the forthcoming publication in Lancet Global Health highlighting that the published BoD estimates may underestimate deaths in the current global context where access to and utilization of care may be limited.

• Most of the key parameters such as CFR, productivity, and hospitalizations for the BoD and COI model are based on data from literature reviews comprised primarily of vaccine trials of varying sizes, which may introduce publication bias due to small numbers and/or a focus on populations that are eligible for these types of trials.

\(^1\) An emulator mimics the behavior of the complex model from which it was derived based on the input-output relationship of many runs of that complex model. The influence of changing influential parameters can then be instantaneously explored by a lay person through a user-friendly interface for the emulator, with the advantage that the underlying complexity is taken into account.
• IVIR-AC observed that heterogeneity in transmission should be considered since it may have implications for vaccine effectiveness within the impact modeling. More uncertainty analysis is required because vaccine effectiveness of various schedules remains largely unknown for the variety of conjugate vaccines and ecological factors in settings where they likely to be used.

• The productivity losses utilized as the main driver for the economic burden study are based on a single average from six countries, which may not be generalizable. IVIR-AC recommends stratifying by group of countries and settings important to typhoid transmission and burden.

• IVIR-AC recognizes that new data arising from proposed multi-centre studies in Africa and in south Asia (expected to begin in 2015 and extend for three years) will provide valuable inputs adding substantial precision to the burden of disease models.

• Given the timelines of the various analyses reviewed, IVIR-AC requests the study team to present updates to the Committee in 2015, at minimum, and by conference calls as needed.
THEME: Research to minimize barriers and improve coverage of vaccines currently in use

Reasons for non-vaccination

What kind of evaluation and methods are required to understand the root causes?

- To understand the root causes of non-vaccination, IVIR-AC suggests promoting and supporting community research studies linked to effective vaccine policy and media communications.
- To understand the root causes of non-vaccination, IVIR-AC suggests promoting and supporting community research studies linked to effective vaccine policy and media communications.
- IVIR-AC recognizes that there are a variety of disparate factors related to non-vaccination, relating to political, ethnic, tribal or religious-based active barriers for immunization for all children living in a certain area (like in the FATA region of North West Pakistan and Boko Haram-held territory in Nigeria), concerns about adverse events regarding specific vaccines, and individual non-acceptance of vaccines. These factors require different strategies to improve coverage.
- IVIR-AC observed that the WHO VPD burden and impact assessment framework should be populated by evidence from community studies on determinants, and acknowledged both the value and limitations of global answers to local problems with regard to non-vaccination.
- The outcomes of the deliberations of the SAGE meeting in October 2014 and that will focus on vaccine hesitancy should help guide the way forward on the broader set of non-vaccination implementation research issues for the IVIR-AC sub-group.
- An IVIR-AC sub-group should be established to work on research protocols (designs and instruments), considering when and how these may be used. IVIR-AC members M. Amuyunz-Nyamongo, S. Sow and M. Weiss volunteered to join the sub-group and report back to the IVIR-AC meeting in 2015.

Integration of care for pneumonia and diarrheal diseases

What are priority research questions to support the integration of delivery of vaccines with other health interventions?

- IVIR-AC observed that the question is no longer whether to integrate but how, when and where to integrate.
- To study the integration of immunization services with other health interventions, IVIR-AC identified the need for standardization of research tools and protocols to be applied locally, by antigen and schedule, and to determine how to communicate the evidence on integration to decision-makers, programme managers, health workers and the community. However, IVIR-AC cautioned that integration must not compromise the quality of successful immunization programs, and that documenting this should be an integral part of implementation research activities.
• In line with the recommendations from the IVIR-AC Ad Hoc meeting in June 2014, IVIR-AC recommended to use the presented proposal project on “Evaluation of GAPPD interventions: example for Mazabuka District in Zambia” as a case study. IVIR-AC members Rachel Feilden and Yot Teerawattananon agreed to assist with reviewing the assessment tool that is being developed for Zambia (and which is intended to be used in other countries) and report back to IVIR-AC at the 2015 meeting.

• IVIR-AC observed the need to document and learn from the experiences of other ongoing disease programs integrating immunization activities to inform research and implementation.

**Missed opportunities for vaccination**

*What are the key next steps in terms of research in this area?*

• IVIR-AC observed that the fundamental question for evaluating missed opportunities is the impact on overall immunization coverage, and thus impact assessments must be carried out to measure this outcome.

• Studies of missed opportunities should include documentation of reasons for the missed opportunity, strategies to address these reasons, and measurement of impact (including on overall immunization coverage) with robust methodology.

• IVIR-AC suggested that these types of studies should be implemented rapidly in the African region using an adapted version of the protocols and tools from the experiences in Latin America. Rather than establishing a sub-group, IVIR-AC suggested that a consultant be identified to implement this work in collaboration with PAHO colleagues and the AFRO office to ensure the context that would inform adaptation, and report back to the IVIR-AC meeting 2015.

**Non-specific effects (NSE) of vaccines research agenda**

*What are priority research questions inform policy?*

• IVIR-AC reviewed the epidemiologic and immunologic data presented to SAGE and concurs with the SAGE view that these data do not provide a basis to adjust policy. IVIR-AC cautioned that the epidemiological data reviewed consists mainly of observational studies and a few RCTs with high risk of bias; immunological data were derived from studies not specifically designed to assess the issue of non-specific effects of vaccines.

• IVIR-AC will work to guide the development of standard protocols and implementation of high quality prospective studies (including RCTs where feasible), as observational studies are unlikely to provide conclusive evidence. At a minimum, studies should mimic RCT circumstances and should be sufficiently powered to assess whether there are gender differences related in regards to non-specific effects of vaccines.

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2 To establish a sub-group to propose elements of the menu of solutions on the integration of care with immunization programs; adherence to a two year time line with a selective approach to proposed integration at service delivery and management levels; and identification of a network of social scientists in different disease areas including country managers.
• Immunological analysis should become an essential part of future RCTs with clear methodology describing the outcomes being measured, their temporal relation to immunization and how results can be interpreted.

• Future NSE studies should consider inclusion of not only mortality but also morbidity outcomes.

• IVIR-AC supports the proposal to establish a multi-disciplinary team with IVIR-AC participation to review the evidence and identify research questions. The priority research questions will continue to be refined by IVIR-AC informed by the deliberations from the proposed ad-hoc expert groups.

• IVIR-AC members M. Brisson and B. Gessner volunteered to lead a sub-group to implement the work described above and to report back to the IVIR-AC meeting 2015.
THEME: Research to improve methods for monitoring of immunization programs

Coverage surveys

Are the revised methods useful to address existing shortcomings?

- IVIR-AC agreed that the revised method for coverage surveys is the proper way forward, but that statistical expertise will be required to implement the survey in the field.
- IVIR-AC identified the need for incorporating GPS technology to keep up with real time information and to improve the quality of survey sampling.
- To identify the unreached, IVIR-AC recognized the need for qualitative studies and piloting of surveys in hard-to-reach settings such as in rural and urban areas of Bangladesh and Zimbabwe.
- IVIR-AC identified the concern of interpreting the new survey data in comparison with the data collected from previously used methods. Difficulties in monitoring progress and comparing cross-sectional data across methods and time must be addressed.

Gavi perspective on implementation research

What are the suggested research questions to improve process of the impact estimates/investment overall?

- IVIR-AC observed that the session was a product of many discussions related to WHO and GAVI Secretariat to create a consistent plan for communication in order to optimally utilize IVIR-ACs capacity.
- IVIR-AC agreed that the WHO VPD burden and impact assessment framework should be used to coordinate and leverage work from IVIR-AC and by using resources available in existing GAVI investments to fill the critical gaps in implementation research.
- IVIR-AC noted that Gavi’s impact evaluation is important and should be used globally if the quality is ensured through an independent review process.
- If GAVI seeks advice (like review of models of interest to [or sponsored by] Gavi) from IVIR-AC, Gavi staff are encouraged to engage IVIR-AC (via its Secretariat) from the start so that the Committee can provide early and pivotal commentary, rather than reviewing close to final stages of work, when it is not feasible to address critical concerns. IVIR-AC would provide to the WHO Secretariat its technical opinion on work presented and leave official endorsement to the WHO.
Dr. R. Breiman opened the third meeting of the WHO Immunization and Vaccines-related Implementation Research Advisory Committee (IVIR-AC). IVIR-AC has no executive, regulatory or decision-making function. Its role is to provide advice and recommendations to the Strategic Advisory Group of Experts (SAGE) and Director of the Immunizations, Vaccines and Biologicals (IVB) Department of the World Health Organization (WHO). The key objectives of IVIR-AC are:

- To appraise methods to estimate disease burden and resolve differences in disease burden estimates.
- To characterize critical factors around vaccine demand and hesitancy.
- 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.

IVIR-AC aims to make critical recommendations for the Decade of Vaccines (DoV) – Global Vaccine Action Plan (GVAP), and the advancement of priorities for vaccine preventable disease in the 21st century.

Four new members were inaugurated at this IVIR-AC meeting:

- Dr. Mary Amuyunzu-Nyamongo, Executive Director and co-founder at African Institute for Health & Development (AIHD).
- Dr. Marc Brisson, Associate Professor, Faculty of Medicine at Laval University.
- Dr. Brad Gessner, Scientific Director and Chief Epidemiologist at Agence de Médecine Préventive (AMP).
- Dr. Yot Teerawattananon, Founding Leader of Health Intervention and Technology Assessment Program and Senior Researcher Scholar of Thailand’s Research Fund at the Ministry of Public Health Thailand.

Given the relevance of immunizations and implementation research to the Ebola epidemic in West Africa, IVIR-AC discussed the current situation with focus on the potential role of vaccines and involvement in impact evaluations of the outbreak response. The committee was updated on the status of two candidate vaccines beginning phase I trials in the coming weeks. IVIR-AC discussed the need to review available evidence to speed up research and implementation processes in the epidemic areas in a productive, safe and ethical manner.
3. Comprehensive WHO VPD burden and impact assessment framework

Introduction

Research for Universal Health Coverage (UHC) was established as a top global priority in the 2013 World Health Report, and the WHO acknowledges that achieving UHC cannot be achieved without evidence from scientific research in public health. Such research also aligns with the GVAP strategic objective: to extend equitably the benefits of immunization to all people. WHO vaccine research can contribute to improved approaches to expanding coverage, supplying evidence for robust policy making, and improving immunization development and delivery systems. The IVIR-AC is responsible for implementation research involving immunizations within WHO.

Challenges to Research for UHC and immunization programs in low-and-middle-income countries (LMICs) arise mostly from limited human resource capacity, limited data availability and lack of established infrastructure. There is need in LMICs and other settings to better understand the barriers to and success of immunization programs. Failure to coordinate efforts within vaccine-related scientific research will likely lead to: a global lack of consensus on methods, unproductive duplication of work, and inefficient resource use.

Thus, IVIR-AC proposes a comprehensive collaborative framework to guide future research in VPD burden and impact evaluations. The framework provides an overview of available evidence on vaccine specific burden of disease, disease and economic impact assessments including decision-making tools. IVIR-AC will function as an information hub for facilitating the framework, consisting of a network of experts and platform for information and evidence sharing and gap analysis to identify research needs. Subgroups of experts will be formed and work according to the IVIR-AC ToR to coordinate research agendas, establish further networks of experts, and harmonize and standardize guidance documents and tools available for use within each topic. Moving forward with the proposed framework IVIR-AC seek inputs from members and other partners to take steps for prioritizing work in line with SAGE recommendations, establishing subgroups for research areas in need, and continually updating the IVIR-AC. Linking IVIR-AC subgroups with existing groups such as the Research and Innovations Subgroup of the Measles and Rubella Initiative (M&RI) would be encouraged.
Review

There is a clear need for the proposed framework, and it is important for WHO to play a role in this work to provide both credibility and a global network of country level partners. The creation of subgroups will better coordinate research priorities and reduce unproductive duplications of work, while identifying existing knowledge gaps to streamline funding and better understand existing uncertainties. Subgroups should be wary of a tendency to “model over the gaps” in evidence, and use their expertise to identify important parameters/estimates to target for accurate measurement in the future. The potential workload is large, and resource constraints and sustainability of this framework must be considered for the future.

Discussion

According to the committee members the framework is needed and useful. Creation of a hub for evidence and continuous review will enable directed and productive research efforts in the future. The role and scope of work for each subgroup should however be clearly defined and continual communication with IVIR-AC is essential.

This framework will generate a large amount of work requiring detailed analysis and review; there is potential for oversimplification and sustainability issues must be addressed. Thus, subgroups should be aware of the tendency to ignore heterogeneity and formulate assumptions for key missing data. Subgroups should work to identify important parameters that may vary between settings, and may strongly influence models, that should be collected with future efforts.

The framework may facilitate understanding the usefulness of duplicating work with heightened subgroup expertise, in comparison to individual donors. Coordination and collaboration resulting from the framework may enable central endorsement of research gaps, which may better streamline research funding and avoid unproductive projects or duplications.

For country level partners the framework itself may not empower local institutions to utilize and benefit from the coordination and collaboration of research; therefore incorporating an institutional capacity strengthening and empowerment component to the framework may have significant added value for users in reality.

This presentation and discussion should be considered as the first step in the framework development to facilitate a dialogue, and constructive commentary should be welcomed.

Questions to be addressed

• Is the proposed framework useful?
• Were there any emerging gaps presented or any concerns?
Summary and recommendations

IVIR-AC welcomes the proposed framework and agrees with WHO’s role in facilitating a hub of burden of disease and impact assessment work including an associated network of experts.

IVIR-AC’s role and scope within the proposed framework should entail: reviewing evidence, identifying gaps, biases and limitations, assessing research methodology, commenting on analytic approaches, correctly utilizing models, and maintaining participation of at least two IVIR-AC members in each sub-group to be established.

Sub-groups should identify any clear gaps and both value-added and unnecessary duplication of effort to better direct future modeling and vaccination program work.

In order to sustain the impact framework in line with relevant policy questions at global and local levels, institutional capacity is needed while funding from various partners is streamlined according to the proposed framework.

IVIR-AC encourages partners in the immunization field and other interested parties to contribute to the framework and to utilize it.
4. Pertussis impact modelling review

Introduction

In November 2012, SAGE expressed concern about the apparent resurgence of pertussis in some industrialized countries despite high vaccine coverage with acellular (aP) vaccines, which in some settings was associated with an increase in infant pertussis deaths. SAGE then established a pertussis working group which presented its report to SAGE in April 2014. This report included a review of epidemiological data on pertussis from 19 developing and industrialized countries in various world regions and with wP or aP-based programs achieving high vaccine coverage rates, effective disease control and the ability to provide high quality data. Given the natural periodicity of pertussis disease resurgence was defined as a larger burden of disease than expected when compared to previous cycles in the same setting. The main outcome of the report is that pertussis vaccination is highly effective in reducing disease from B. Pertussis, with a large decline in overall global incidence and mortality compared with the pre-vaccination era in both wP and aP-using countries.

To date, there is no evidence for a widespread global resurgence of pertussis. There is however evidence that resurgence has occurred in 5 of the 19 countries reviewed, 4 of which were exclusively using aP vaccines. The increased number of cases in the only wP-using country in which resurgence was observed was considered to largely reflect other factors than the wP vaccine used (surveillance, laboratory methods, and low vaccine coverage). Recent modelling studies from Australia, England and Wales, and the US as well as data from a baboon model supported the hypothesis that wP to aP transitions may be associated with disease resurgence. Although the reasons for the resurgence were found to be complex and varied by country, SAGE concluded that the shorter duration of protection and likely reduced impact on infection and transmission conferred by aP vaccines play critical roles.

No evidence suggests that a change in strain has reduced vaccine effectiveness or caused recent resurgences. In response, WHO published an update to clarify that the previous statement on the choice of vaccine contained in the 2010 vaccine position paper no longer holds true and that countries currently using wP should continue to use wP vaccines for primary pertussis infant vaccination and that the switch from wP to aP vaccines for primary infant immunization should only be considered if the inclusion in the national immunization schedules of large numbers of doses (including several boosters) can be assured; this has major financial implications due to the much higher cost of aP vaccines and much larger number of doses required.
SAGE identified the conditions necessary for pertussis resurgence and the effective strategies for resurgence prevention as important for modelling research.

Three disease transmission models were presented to determine the burden of disease and impact of various vaccination strategies on pertussis transmission.

Public Health England (PHE) developed an age-structured, deterministic, dynamic model to describe pertussis transmission dynamics, in which notifications represent a proportion of infections and secondary infections have a reduced probability of being reported. The model was parameterized using pertussis notification data and vaccine uptake projections from 1956-2013 with a POLYMOD\(^3\) social contacts and mixing matrix. Results revealed, incorporating a shorter duration of protection from aP vaccine compared with wP vaccine yielded results consistent with the epidemiologic data on pertussis resurgence from the UK, and predicted that incorporation of an adolescent booster containing aP may reduce overall burden marginally but was unlikely to result in herd protection of unimmunized infants.

The Centres for Disease Control and Prevention (CDC) developed a deterministic model of the US population in which secondary infections are unreported but transmissible. United States National Notifiable Disease Surveillance System (NNDSS) data from 1950 onwards was used to fit the model with other US coverage and population data; a POLYMOD contact matrix was used and vaccine effectiveness assumptions were formulated from a recent case-control study. The best fitting model indicated that decreases in both per-dose efficacy and duration of protection between aP and wP vaccines produced results in keeping with recent upsurges in pertussis observed from the US. These differences in protection also modelled well an observed shift in age of pertussis distribution from adolescents to young children after 2006.

The University of Melbourne (UM) and University of New South Wales in Australia developed a deterministic, age-structured, dynamic model using data from the State of New South Wales, in which pertussis immunity is derived from most recent experience: infection, vaccination or none. The model was fitted using historical disease notification, death, coverage, and serosurvey data with a POLYMOD mixing matrix. Model results found that natural exposure is a key driver of lasting population immunity, producing long-lasting immunity in contrast to that derived from pertussis vaccines with, small changes in vaccine coverage impacting on transmission decades later. Additional doses resulted in additive herd protection. Within the limits of the number of observation years available, the model found only a slightly shorter duration of protection for aP compared with wP vaccine.

All the models presented were fitted using country-specific data, so use outside of the contexts in which they were developed is potentially limited by data availability and model extension. Nevertheless, models using similar structures with appropriate data inputs may be relevant for predicting potential resurgences of pertussis in LMICs.

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Review

The models presented are well developed by strong academic groups. These models all examine the circumstances under which resurgence can be expected in country specific contexts. The impact of different boosting strategies on disease incidence and resurgence are particularly significant components of the UM and CDC developed models. Consistent findings indicate that duration of immunity is a significant contributor to the likelihood of transmission, that there is a difference between natural infection, wP, and aP vaccines, and suggest that more booster doses are better for controlling transmission and maintaining immunity. The generalizability of these models is limited due to their country specific data and being in early stages of development. At this point, none of the models have been applied to data generated from LMICs and there is a lack of data from high mortality settings.

The models presented suggest that aP vaccine has lower efficacy than wP vaccine, and may be the cause of resurgences seen in the USA and UK. The Australian model demonstrated that falls in in vaccine coverage may result in outbreaks decades later; and that various schedules of boosting may differentially impact the potential for resurgence. Adolescent booster doses may reduce incidence, although not among infants who suffer severe disease and increased mortality; while a pre-school/18-month booster dose may reduce incidence in the infant population. Contacts patterns and herd immunity may be crucial to explaining the impact of boosting and vaccination, but suitable data are not available from LMICs.

Discussion

The differences in impact between aP and wP vaccines on infection and transmission is important to keep in mind, and vaccine choice and potential to result in resurgence should be further explored in models and review of epidemiologic data. Pertussis epidemiology among aP-using and wP-using countries should be examined.

The current models vary booster schedules and impact of additional aP doses, but many unknowns in schedule and impact remain. The priority aims of any boosting schedule should align with the WHO and SAGE goal of protecting children-under-five, and further modelling for schedule optimization should strive towards this. Heterogeneity (i.e. in burden, transmission, resources, and immunization capacity) between countries is important to consider for decisions of booster scheduling to maximize vaccine benefits.

These models were fitted using data from few high income countries (HICs), and the need for high quality data from other countries, especially LMICs, was identified. This was echoed by the SAGE call for prospective country level data on pertussis epidemiology, especially in LMICs and age groups affected by severe disease and mortality (i.e. under-fives).

Serological data at the population level may be useful as a parameter to fit to models, but more work is needed to clarify the use and interpretation of such data in the context of estimating disease burden and vaccine impact. Data on levels of maternal antibody at birth are scant outside of HICs and could be informative with respect to guiding thinking about background risk of severe early infant pertussis, and contribute to model input parameters.
Again, lack of quality data is the key limitation for further modelling and for generalizability of models to other countries and settings. This emphasizes the importance of targeted surveillance to generate more, high quality data on the current status of severe early infant pertussis, especially in LICs with high pertussis burden prior to implementation of EPI programs.

IVIR-AC should convene a subgroup focused on identifying knowledge gaps and characterizing data needs with an understanding of variable feasibility within countries. The subgroup should leverage modeller and epidemiologic expertise to better understand causes of resurgences and protection of children under-five.

Modellers should meet and can test the models with the age specific data derived by Colin Sanderson and the data sets from the countries reviewed by the SAGE pertussis Working Group.

**Question to be addressed**

- What are the best modeling approaches to address policy questions defined by SAGE regarding pertussis vaccines?

**Summary and recommendations**

The models seem to be appropriate in terms of structure to better understand both schedule optimization in various countries and transmission settings, and how high-income country (HIC) experiences can inform potential resurgences in low-and-middle-income countries (LMICs).

Availability and quality of data is the key problem, thus IVIR-AC calls for better surveillance systems in all countries, particularly in LMICs where virtually no data exist.

An IVIR-AC sub-group under the WHO VPD burden and impact assessment framework will be formed to identify specific data needs as an input for various models by conjoining modeller needs with epidemiologic expertise.

IVIR-AC members P. Beutels, P. McIntyre and B. Gessner volunteered to join the sub-group and report back to the IVIR-AC in 2015.
5. WHO pertussis burden modelling

Introduction

There have been many attempts at developing a pertussis model to better estimate the burden of pertussis. Difficulties in developing an adequate model arise from the complexity of pertussis and extreme surveillance data limitations outside of a limited number of HICs. In 2011 a method for informing parameter values utilizing available data from HIC and expert opinion was developed and reviewed by QUIVER, which aims to estimate country level pertussis burden by age groups in various settings (i.e. LMICs).

Model inputs include country-specific population by age from UNPD and WHO and UNICEF estimates of first and third dose of pertussis containing vaccine coverage (DTP1, DTP3). The model outputs annual estimates of infections, cases and deaths by country, age, and vaccination status for 2000 through 2012. Child deaths and mortality rates estimate the burden of severe pertussis in the under-five population, assuming no deaths due to pertussis occur after age five. The model estimated that between 54,000 and 57,000 deaths due to pertussis occur annually, with an increasing number of deaths over time. The model predicts a reduction in mortality rate over time, indicating a declining burden.

The model is completely uninformed by data and assumptions made for the many parameters rely on expert opinion alone (i.e. probability of infection, case and death conditioned on child mortality and vaccination status). Further limitations are due to lack of adjustment for waning immunity and no distinction between wP and aP use. The probability assumptions do not change over time, which likely will not reflect reality. High uncertainty and variability in expert judgements and these limitations result in a high degree of uncertainty and variability in model estimates.

The availability of data on pertussis infections, cases, and deaths, particularly from LMICs and high burden settings is extremely important to direct future data collection efforts, underscored by the many assumptions necessary for modeling efforts.
Review

The model presented was previously reviewed by IVIR-AC, and the same commentary as previously made still apply. A large amount of effort and investment has gone into the modeling work for pertussis with little illumination of the most uncertain variables. There are opportunities for better collaboration between modelers, epidemiologists and other partners to pinpoint necessary data for collection to inform future modeling. The division of countries into three broad categories based on mortality is a positive aspect of the work that should be continued. Because severe morbidity and mortality is concentrated in the first year of life, future efforts should focus more on this time period and on understanding burden and impact for this age group. The uncertainty in model estimates is enormous and obvious, and not much progress has been made. Some revised estimates of effectiveness of 1 or 2 pertussis doses against mortality have not yet been taken into consideration. The consensus as discussed at the April 2014 SAGE meeting is that 1 dose confers a >50% protection from the risk of death and 2 dose in excess of 80%.

The substantial lack of data to inform this model is very worrisome, and the reliance on a limited number of expert opinions to parameterize the model makes the estimates as subjective as the experts themselves. The next minimum step would be to validate the model with quality data, however moving forward with this model is not recommended as the best option for assessing and estimating pertussis burden.

Discussion

The approach used for this model is simple, despite complexities that exist within pertussis transmission and immunity from various vaccine strategies. The simplicity of the model may be necessary due to data limitations; however there seems to be more available data than was used to fit this model. Actual hospitalization and death data exist from HIC settings and can be better leveraged for modeling; additionally surveillance programs in some LMICs may be used to obtain more data on pertussis.

There is opportunity now, with better communication and collaboration in the modeling work between various groups of investigators, to better understand what information is presently available and how their work can be used to validate models and better identify essential data to be collected in the future.

Understanding key elements for modeling is important. Discussion identified CFR, waning vaccine protection, and differences with aP and wP induced immunity as the key parameters to measure and incorporate into models.

SAGE has requested improved estimates of pertussis burden emphasizing the importance of this work. The focus should be to use data that are available in a basic exercise to understand the nature of pertussis in the population most affected by severe disease and death (i.e. children under-five). Validation will be the next step to understanding global pertussis trends. However modeling attempts should rely more on available data and less on expert opinion to be useful. Determining an interim strategy for improved estimates is essential due to resurgences occurring in various countries around the world. It was agreed that the best way forward was to give up on the current modelling effort and to capitalize on the more elaborate ongoing modelling work. As this will take time to have some more definitive output it was suggested that for the time being to derive
pertussis burden estimates it would be better to update the results of the vary basic model published by Crowcroft et al. with using current coverage numbers and assuming that 1 dose of pertussis vaccines has 50% efficacy against death and 2 doses 80%.

Questions to be addressed

- Does the proposed model provide reliable burden of pertussis estimations?

Summary and recommendations

IVIR-AC recognized that the new global pertussis burden model had significant limitations in that results from the expert solicitation exercise were too broad, the age groups too wide (should be focused on children under age five years only if the primary objective is to estimate the burden of severe disease, including death) and the very wide range of potential estimates for model parameters that it utilized did not reduce uncertainty in pertussis burden estimates in a useful way.

IVIR-AC suggests convening a sub-group to explore the potential way forward to revise the presented global pertussis model in combination with new pertussis data available since 2012 in the literature and from the WHO IER group. This sub-group should include the mathematical modeling groups presented in the previous pertussis impact modelling session.
Introduction

The Meningitis Vaccine Project (MVP) and partners developed an affordable meningococcal A (MenA) conjugate vaccine, MenAfriVac® (Serum Institute of India Ltd.). The vaccine was licensed and WHO prequalified, prior to large scale roll out in countries of the African meningitis belt starting December 2010. The MVP has approached the evaluation of the MenAfriVac vaccination programme with four objectives: estimating the impact of mass vaccinations among the 1 to 29 year-old population on disease burden and carriage; assessing vaccine immunogenicity and safety in infants and young children; learning from the experience of meningitis C vaccination programmes in the UK; and finding optimal vaccine schedules for long-term disease control in the African meningitis belt region following the initial mass vaccination campaigns. Accordingly, review of available evidence and modeling efforts are being pursued to better understand MenAfriVac impact and to determine optimal vaccination schedules for future use in the region.

The MenA Modeling Project, in partnership with the MVP/WHO, aims to develop and apply mathematical models of MenA transmission and disease to investigate the optimal use of MenAfriVac in the long term. The model presented is a parsimonious, Susceptible-Infective-Removed with Immunity-Susceptible (SIRS) type, age-structured model with stochastic periodic forcing. It was fit using demographic, carriage, disease, coverage, and vaccine effectiveness data. Because contact pattern specifics and immunity following carriage data are unknown, a range of scenarios were fit to best predict observed transmission.

The model predicts that current mass vaccination campaigns (with 95% coverage) may control MenA for up to 15 years (assuming 10 years of vaccine-induced protection), but will be followed by a large resurgence exceeding pre-campaign levels. Model results indicate that future EPI delivery of MenAfriVac will mitigate this post-campaign resurgence, and higher levels of EPI coverage lead to lower MenA incidence. Periodic mass campaigns among 1 to 4 year-olds was a superior strategy for reducing MenA incidence only if future EPI coverage was lower than 60%. The best strategy identified by the model is a combination of routine EPI delivery with catch up campaigns.

The model is still in early stages of development and limited sensitivity analyses have been run at this point. Improvements to published work have been made with age structuring and stochastic model components, flexibility in examining vaccination strategies, and utilization of African and MenA specific data. Uncertainties remain requiring assumptions to be made for certain model parameters.

6. Meningitis A impact assessment
Review

The method presented is the correct approach for understanding the long term impact of MenAfriVac mass campaigns on disease burden and transmission and optimizing future vaccination strategies in Africa; however, there are issues to be addressed. A fundamental limitation is the lack of contact patterns and social mixing data from the region, making this parameter entirely based on assumptions. More sensitivity and uncertainty analyses should be performed to further study duration of immunity resulting from various vaccination strategies (i.e. campaigns vs. EPI). In future stages of work sensitivity analyses should explore the interaction of MenAfriVac vaccination programs with other (non-A) meningococcal serogroups. It is essential to improve the presentation of the overall results, to highlight the variability in results due to the stochastic nature of the model; rather than simply showing an average of model simulations, a range should be displayed to reflect valid uncertainty in predictions of impact from various vaccination strategies.

Discussion

Incorporating economic and cost effectiveness analysis with model comparisons of various vaccine strategies is important to understanding the best manner to move forward with MenAfriVac. Short-term and long-term cost implications and budget impact analysis must be included when utilizing models in countries to determine vaccination strategies and to better inform decision making.

Herd protection is not well understood at this point, and would be a good area to explore with future work. Research and measurement of vaccine coverage and level of population immunity should be conducted to observe differences between routine EPI use and campaigns. More uncertainty analyses of the assumptions of herd protection and duration of immunity would be beneficial.

Sensitivity analysis on the model structure should be done, while acknowledging that this model is in early stages of work. Critical elements for further sensitivity analyses are: duration of immunity, immunity following carriage, and local contact/transmission patterns.

Furthermore, the stochasticity of the model should be better communicated and presented via reporting of variability or uncertainty intervals of parameters and results. Reporting stochastic ranges may alter the interpretation of differences in impact between various vaccine strategies.

Question to be addressed

- Is the proposed approach adequate to assess meningitis A vaccination?
Summary and recommendations

IVIR-AC agreed the dynamic model presented is the appropriate approach to understanding the long-term impact of current campaigns and of future meningitis A vaccination strategies.

Assumptions of the model need further sensitivity and uncertainty analysis, such as varying assumptions of duration of natural immunity following infection or carriage, age structure determinants of the model, and a term to force seasonality into the model, among others within the model. IVIR-AC recommends that an improved presentation of results is needed to capture the stochastic nature of the model i.e. reporting the uncertainty intervals around average model predictions.

Finally, IVIR-AC emphasized the need to understand investments in prevention of serogroup meningococcal meningitis by estimating the economic impact and benefits of MenAfriVac, vaccination programme, as well as of various vaccination strategies for the future.
7. Impact evaluation of Hepatitis B vaccines

Introduction

Global coverage of three doses of hepatitis B virus (HBV) vaccine has increased dramatically from 1% in 1990 to 81% today. However a lot of variation in coverage exists between countries. Furthermore, the impact of HBV vaccine and in particular the utility of a birth dose is not well understood due to the long time horizon from infection to sequelae and death. WHO has initiated an HBV project to synthesize and critically appraise immunological and disease data, vaccination and infection measures, and implementation level data of vaccine programs to provide a comprehensive evidence base for HBV burden and control. The project goals are to assess global and country level impact of HBV vaccine and develop a communication and data sharing platform for HBV immunization.

A static model was developed to assess global impact of HBV vaccine. The model was fitted using data from systematic literature reviews on vaccine effectiveness as well as primary global data on demography, carriage prevalence and coverage. This is a multiple cohort structured model defined by age and gender; it assumes endemicity of HBV and its transmission and does not include herd immunity effects. The model outputs (by age and gender) are: number of carriers, hepatocellular carcinoma (HCC) cases, and HBV related deaths.

A dynamic model is currently under development to assess country level impact of HBV vaccinations and understand the utility of a birth dose. The model cohorts are defined by age group (i.e. under 15-years and over 15-years of age), and includes both perinatal and effective transmission within the population. This model was fitted using demographic, carriage and vaccine coverage data from selected countries including Gambia, South Korea, and China. Stochastic transition rates will be an essential element of the model structure to better reflect transmission patterns; vaccination strategies to be explored will include the time of birth dose and additional doses within EPI use.

Review

This work is an example of how a subgroup of the proposed WHO VPD Burden and Impact Assessment framework can be used in an encouraging and productive manner. The processes and model assumptions are well thought through and IVIR-AC member participation is strong. The systematic reviews conducted are rather impressive with broad scope and vast amounts of information synthesized for model parameterization; in many cases the data needed exists, but require a lot of effort is required to identify them. HBV presents a situation in which modelling is very beneficial due to the long time horizon of disease, even with all data available researchers would have to wait decades
to measure vaccine effectiveness and impact in terms of HCC and mortality outcomes. Models are necessary for understanding such long term benefits of vaccinations, although limitations of estimates should also be acknowledged.

The current model ignores migration, which seem to be an acceptable limitation due the difficulty in predicting future migration patterns and potential impact on HBV transmission and vaccination. This work is a progressive step in the modelling of HBV, but uncertainty should be accounted for and explicitly stated. In the future cost-effectiveness analysis should be performed and the sources of costing data should be carefully evaluated prior to use.

**Discussion**

There is a need for additional scenario analysis within this modelling work to compare various vaccination strategies. Current scenarios all contain a birth dose with varied number of EPI doses; however these do not further understanding of the utility of a birth dose essential to future policy making decisions and budget prioritizations for HBV vaccine. Therefore subsequent modelling should compare varied EPI doses (i.e. 2 and 3 doses) both with and without a birth dose. This will better answer questions of marginal costs and benefits of a birth dose in terms of epidemiology and economics. A systematic review is currently being conducted to collect data on this research question and it will be incorporated later on.

Policy makers are faced with questions of how to combat HBV disease and death today. The impact of vaccination is not evident for decades due to the lag between childhood infection and adult disease (i.e. HCC) and death. Thus incorporation of screening and treatment into modeling is important for decision-makers on the questions they are trying to answer today.

The model presented should be compared with the HBV model previously developed by Susan Goldstein. GAVI and other major players in vaccinations currently use the Goldstein model for investment decisions making this comparison useful.

Mortality and number of HCC cases are the current outcomes of interest within the model, however morbidity outcomes should more carefully be examined due to the lengthy nature of HBV related sequelae and disease and the potential impact on quality of life and productivity. Incorporating morbidity may strongly influence vaccine effectiveness and impact estimates over time.

There is a lack of adequate data to validate and further parameterize the model. This highlights the potential for resources to be directed at collecting high quality data on essential factors for HBV epidemiology and vaccination programs, keeping modelling and policy questions in mind.

**Question to be addressed**

- Is the proposed approach adequate to assess hepatitis B vaccination?
Summary and recommendations

IVIR-AC found the work presented to be of high quality and exemplary of how sub-groups under the WHO VPD burden and impact assessment framework may function, both in terms of process (i.e., IVIR-AC’s involvement) and activities carried out (e.g., comprehensive and detailed systematic literature reviews).

IVIR-AC highlighted the need for modeling of scenarios to also include comparisons of no birth dose versus birth dose; in particular, there would be value in defining the impact of a birth dose in terms of immunogenicity, and to better understand the issues related to its implementation, such as cost and cost-effectiveness across local, country and regional levels.

To better inform decision makers in middle-income countries (MICs), IVIR-AC identified the need to incorporate liver cancer screening, treatment options, and outcomes into models.

IVIR-AC suggested that there is value in comparing the current model with a previously developed model used by GAVI and WHO. These comparisons should include provisions to compare outcomes of both models with the same data inputs and model assumptions.

IVIR-AC identified the need for addressing quality of life with chronic hepatitis infection in addition to mortality outcomes in impact evaluation studies.
8. Decade of Vaccine Economics (DOVE)

Introduction

The Decade of Vaccines Economics (DOVE) modeling work was commissioned by the GVAP Costing and Financing Steering Committee with members from WHO, UNICEF, Gavi Secretariat, and BMGF, in response to a request by SAGE in 2012 to explore and develop methods for evaluating costs and funding gaps, and to better link costs of the Decade of Vaccines with the resulting benefits. Following the recent publication of the costs of the DoV, additional work on modelling aimed to accomplish three short-term objectives: 1) develop a user-friendly model that could be updated at regular intervals by the Steering Committee partners; 2) explore and enhance the methods developed previously within a longer time frame and take advantage of new information; and, 3) evaluate the ROI of the DoV thus far and provide additional results up to the year 2020. The main outcome of this work is the development of the model itself.

The DOVE Project provides broad global and regional estimates based on the scope of the GVAP in order for the global community to continue to support and allocate appropriate resources to the DOVE objectives. The DOVE models of cost of illness (COI), costing, financing, and funding gap (CFF), and return on investment (ROI) were presented. The ROI model is based on a combination of the COI averted and costing models, considering 10 different antigens. The CFF model includes the costs and financing of national immunization programs and the funding gap for 18 different antigens. The models’ scope is very large encompassing all 73 Gavi countries and 94 GVAP countries for the DoV from 2011-2020. The models were developed to be adaptable and updatable as research questions and new data become available.

Based on the recommendations from the ad-hoc IVIR-AC consultation in June, the data sources used for model development were graded based on a 1-5 scale of quality, and most data were given a moderate to high score. The Gavi strategic demand forecast data is the backbone source of information for the estimates of deaths and cases averted. Other data are sourced from disease antigen and health impact models utilized by Gavi and BMGF to estimate deaths and cases averted. Model assumptions were varied in scenario and sensitivity analyses.

These models were developed only for aggregate assessments, and not for country-level analysis; and, thus are not meant to be used directly for country and local level decision making. The developers acknowledged that many inputs were not available at the country level, and therefore extrapolations and multi-country averages were used to create assumptions which underpin the models.
Review

The scope of the DOVE models is vast and an extremely ambitious task for modellers to take on covering 18 disease antigen models and all of the GVAP and Gavi countries over a decade. Four issues with the DOVE models to be addressed regarding the assumptions and methods used are: transparency, validity, and sensitivity and uncertainty.

There is a lack of clarity and transparency for the lay reader, which in part may be due to the complexity of the work. Little documentation is provided on: the disease impact models chosen, the criterion for grading data sources, the generalizability of the data and assumptions used, and the amount of extrapolations performed. The validity of the model is difficult to assess without a considerable investment of time due to the large number of extrapolations made, many of which are linear in nature and unlikely to reflect reality. Finally, more refined sensitivity and uncertainty analyses of these models will be of considerable value to better examine different scenarios and permit more in-depth varying of the model's parameters and assumptions. It is essential to address these limitations and issues with the work in future efforts related to the DOVE modeling project.

Discussion

The DOVE models seem adequate for broad global “ball park” estimates useful to assess the costs, financing, funding gap, and return on investment of the GVAP. However, many of the disease model components are not robust enough to permit more precise modeling such as vaccine or country specific estimations. These are among the issues identified to be prioritized for further work.

Transparency is a key objective with the DOVE models presented. Although lengthy documentation was provided, the assumptions, data grading processes, decision justifications, equations, and proportion of missing data with resulting extrapolations and imputations were not clearly or explicitly stated. Documentation should be improved by becoming more concise and precise in explanations of the processes and methods used, having some overview materials written in lay person terminology, and by stating the uncertainties that remain in the DOVE models in technical briefing notes.

Increasing transparency, clarity and accessibility of the underlying assumptions and methods will allow for the model to be updatable as specified in the characteristics and goals of the DOVE models, and also will enable the exercise to be validated. Experienced modelers on the IVIR-AC had difficulties understanding in full many of the assumptions made, and therefore call attention to improving transparency and usability as a major issue at this time.

Further elucidation on the data grading processes should be provided. Documentation should include the results of grading and the justification of decisions with criterion used.

It is essential to reconsider the extrapolations of incremental costs and benefits that are primarily assumed to be linear in the base case of the ROI model. Uncertainty analyses and variations around these linear assumptions must be conducted.
Clarifying the purpose of the DOVE models and explaining appropriate use of results is crucial. The models were presented for obtaining global estimates useful for demonstrating the effects of GVAP investments, thus users of these models should be made explicitly aware of the intended purpose and limitations of these models in order to ensure that the results are appropriately summarized, communicated, used, and interpreted.

Questions to be addressed

• Is the proposed approach adequate?
• Do the individual model components meet the state of the art modeling requirements?

Summary and recommendations

IVIR-AC recognized that the ambitious nature of the DOVE study aims to provide global estimates of resources needed for accomplishing the objectives of the Global Vaccine Action Plan (GVAP) and providing return on investment information to donors. IVIR-AC made the following observations about limitations of methodology used and recommended these be acknowledged and addressed more thoroughly in order to enhance the utility of the document for donors and vaccine agencies.

Many of the individual disease model components do not meet idealized state-of-the-art modeling requirements, but IVIR-AC acknowledges that this is a massive task because of the scale of the DOVE project. Where possible, disease model comparisons should be done to more adequately determine the face validity of the model predictions.

Therefore IVIR-AC felt that the current DOVE model should not be used to compare impact between vaccines due to concerns related to oversimplified assumptions regarding linearity in benefits with coverage and substantial amount of data extrapolation. The relationship between coverage and impact will be very different between pathogens and vaccines.

IVIR-AC felt users of both the model and the model results should be made explicitly aware that the marginal costs and benefits scale linearly with vaccination coverage in many of the disease models. This simplifying assumption has a differential impact for the assessment of various disease burdens, and users seeking to apply these data to inform vaccine program choices would need to fully understand its potential influence on priority ordering for different vaccine candidates.

IVIR-AC felt that increased transparency and clarity regarding all methods used would provide a stronger basis for a broad range of stakeholders to understand what the DOVE project can and cannot provide. Rather than additional explanation, IVIR-AC asked for concise and precise documentation of assumptions and methods. For example, this would include justification of decisions made with regard to data quality grading and percentage of missing data prior to imputation for each input parameter.

IVIR-AC highlighted that given the many assumptions and extrapolations of the different model components, more refined sensitivity and uncertainty analyses are needed.
IVIR-AC suggested that should future efforts in the DOVE modeling work take place, inclusion of immunization program performance and process indicators, as the current model assesses the return on investment only in terms of outcome indicators.
9. HPV cost-effectiveness tool (PRIME)

Introduction

A gap in the modeling of disease burden and vaccine impact for human papilloma virus (HPV) was identified by literature reviews, in that most models for LMICs were developed in HICs using global datasets rather than country-specific data sources. A simple economic tool for LMIC stakeholders was needed for country level analyses and to inform decision-making in these settings. Thus, the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model was developed as a user-friendly demonstration and planning tool for LMIC stakeholders to estimate the cost-effectiveness of HPV vaccination introduction.

PRIME is a simple proportionate outcomes model for HPV currently available in both MS Excel and R versions. The model provides conservative estimates on impact and CE of vaccinating girls prior to sexual debut at country level. Extensive cross model comparisons were conducted between PRIME and other more complex models, and despite its simplicity PRIME replicated the qualitative results of such other models in almost all 26 comparison studies. Various global datasets were used to validate the model further, and this was published in Lancet Global Health to facilitate reproducibility and use of the model in intended settings.

The simple spreadsheet tool is directed toward country level decision-makers in LMICs for use with local data to determine whether introduction of HPV vaccination would be cost effective or not. The PRIME model only considers vaccination of 12 year old girls with three doses. The tool should not be used for assessing more complex scenarios such as male HPV vaccination, various vaccination strategies, or in combination with screening and treatment options. Funding for future work will likely be directed towards in-country pilots, integration with the C4P tool, inclusion of herd immunity and waning immunity effects into the model as well as further uncertainty analysis.

Review

The PRIME model is well developed and validated, however some limitations should be noted. The delivery strategy that the model relies on is unclear and different options (i.e. school versus facility based) may have different cost implications important to LMICs. However, there are plans to link PRIME with the C4P tool to better represent the cost of different delivery strategies. Additionally, the statement that PRIME delivers a conservative estimate may not be the case. The model assumes 100% coverage for 3 doses of HPV vaccine, which is highly unlikely in many LMICs. However, this will not affect cost-effectiveness in a static model. Also, the estimates for incidence of cervical cancer rely on the GLOBOCAN datasets, which tend to be overestimates (e.g., Thailand). Although PRIME is an important and well developed tool, relevant policy makers must consider options of screening and treatment in combination with or as alternatives to vaccination. Therefore, it is important to incorporate the cost effectiveness of options for controlling cervical cancer in future modelling work. Furthermore, it is essential to integrate budget considerations into impact analysis for HPV vaccine to assess realities of affordability and sustainability of immunization programs prior to introduction within local contexts.

Discussion

The inability to assess screening options is an acknowledged limitation of the PRIME model, which assumes that with introduction of vaccination no changes in screening will occur (although existing screening programmes are assumed to be maintained at their current levels). Therefore the most appropriate use of PRIME is within contexts that do not have screening options available for HPV and cervical cancer, or alternatively have existing screening programmes with stable coverage levels. With efforts to combat cervical cancer increasing in LMICs particularly in the AFRO region, this is an important component to incorporate with future modelling work either within PRIME or complementary tools.

Many of the model limitations are due to its simplicity. There are trade-offs between making tools easy-to-use and accurate. Work to include effects such as herd immunity, waning immunity and various delivery strategies will introduce additional complexities and perhaps make the model less “user-friendly”.

PRIME was designed to answer a specific set of simple questions, therefore many dynamic issues around HPV implementation cannot and should not be addressed with the current version of PRIME. The appropriate use of PRIME should be adequately communicated to users.

The ability to extend the scope of PRIME to include screening and herd effects may be limited, as it was not designed to answer these questions. Therefore it may be more beneficial to develop complementary dynamic models for one or two countries for which quality data exist on HPV (e.g., Tanzania) to answer more complex questions and also to validate the simple answers provided by PRIME. Key partners such as GAVI agreed that incorporation of more complex effects such as herd immunity into PRIME would over-extend the model and should instead be included in future models.

5 http://globocan.iarc.fr/Default.aspx
The information package that accompanies PRIME is extremely important for decision-makers. Users would benefit from the development of an emulator-interface to be used as a complementary user-friendly tool for decision-making which takes into account the HPV transmission dynamics in a number of specific countries. An emulator mimics the behaviour of the complex model from which it was derived based on the input-output relationship of many model runs. The effect of changing influential parameters can then be instantaneously explored by a lay person through a user-friendly interface for the emulator, with the advantage of taking into account the underlying complexity.

Questions to be addressed

- Does IVIR-AC consider PRIME to be a suitable model to use as a demonstration tool and to provide a conservative estimate of the cost effectiveness of vaccinating girls prior to sexual debut in LMICs?
- If there is opportunity to develop PRIME further, what areas of extensions/development to PRIME would IVIR-AC consider most useful?

Summary and recommendations

IVIR-AC agreed that PRIME is a suitable model to use as a demonstration and planning tool to answer the simple question of whether vaccinating pre-adolescent girls with HPV vaccines is cost-effective. Other dynamic issues around HPV implementation cannot and should not be addressed with PRIME (e.g. screening, different schedules etc.) and the model purpose and limitations should be communicated clearly to potential users.

IVIR-AC questioned whether PRIME provides appropriately conservative estimates given: a) the 95% coverage assumption for the 3-dose schedule; b) the GLOBOCAN project incidence numbers used which in some settings are not necessarily conservative; c) and the relevance of cervical cancer screening program implementation in some countries. It was recommended that sources and ratings of data quality should be described when presenting the model. Furthermore, PRIME should conduct more detailed uncertainty and sensitivity analysis to better understand the influence of these assumptions on the model outcomes.

Rather than expanding PRIME to include cervical cancer screening and herd effects, IVIR-AC recommends developing a separate dynamic model (that may be built on existing models used in HICs) for one or two countries with available data (e.g. Tanzania and Thailand), which may also be used to further validate PRIME.

Given the questions on HPV implementation and implications for national immunization budgets in LMICs, it is important to consider inclusion of budget impact analysis in PRIME rather than cost-effectiveness alone.

In line with past IVIR-AC recommendations on complex infectious disease models there is a need to develop an emulator-interface to be used as a complementary user-friendly tool for decision-making to better account for variable HPV transmission dynamics and settings.

6 An emulator mimics the behavior of the complex model from which it was derived based on the input-output relationship of many runs of that complex model. The influence of changing influential parameters can then be instantaneously explored by a lay person through a user-friendly interface for the emulator, with the advantage that the underlying complexity is taken into account.
Introduction

Overview of global typhoid vaccine policy and strategy for prevention and control

Two typhoid vaccines are currently licensed globally and are recommended by SAGE for use; a live attenuated oral vaccine (Ty21a) and an injectable polysaccharide vaccine (Vi). Although safe and moderately efficacious, the duration of protection and requiring a parallel platform for vaccination limit their use in the public sector, especially in endemic LMIC settings. Therefore the focus of vaccine development was shifted to typhoid conjugate vaccines. Currently there are approximately eleven manufacturers interested in development of typhoid conjugate vaccines and at least two vaccines licensed nationally in India.

The Coalition against Typhoid (CaT) is a group of organizations and experts, committed to control of typhoid fever through the use of typhoid conjugate vaccines in conjunction with other control measures such as water, sanitation, and hygiene (WASH), particularly in high burden LMICs. Based on 2008 vaccine investment strategy, Gavi has included typhoid conjugate vaccine in their portfolio. The current funding support window for Gavi eligible countries is open until 2017 and can be activated as soon as a WHO prequalified typhoid conjugate vaccine is available. The current recommendations for typhoid vaccine use are based on the Vi and Ty21a vaccines. Recommendations for use of typhoid conjugate vaccine by SAGE, and subsequent WHO global policy will be required to support their use in the public sector. The International Vaccine Institute (IVI) has with the support of CaT secretariat worked towards developing a package of information that will be useful for policy-making, this includes global typhoid disease burden estimates, cost of illness, and plans to conduct CEA to better demonstrate the potential impact of conjugate vaccines in endemic settings.

Current global burden estimates for typhoid range from 12 to 27 million cases and 130,000 to 580,000 deaths per year. The Institute for Health Metrics and Evaluation (IHME) publishes global typhoid burden estimates on an annual basis; however their methodology has been criticized for certain limitations (i.e. reliance on few data of questionable quality, disaggregation between modelling of typhoid and paratyphoid incidence, modelling of the cast fatality rate (CFR) parameter, and lack of consideration of population heterogeneities). IVI has revised methodologies in an attempt to refine the estimates of typhoid incidence and deaths.
Disease burden estimates

IVI investigators performed a series of comprehensive systematic reviews to inform influential parameters including: typhoid incidence (22 studies), blood culture sensitivity (10 studies), risk factors related to safe water (12 studies), and CFR. Their inclusion of age-distribution as well as risk factors related to safe water is novel in comparison with older methods. The IVI model focuses on LMICs, where the large majority of typhoid cases occur. IVI investigators acknowledged that the CFR was based on weak evidence due to the limited data available from only hospital settings. Consequently a review of hospitalization rates due to typhoid fever was conducted to assess the proportion of those infected that contributed to the available data, and a rate of 7.7% was determined. The estimated total CFR in Asia was 0.43, and sensitivity analysis was performed around a base case of 1% from 0.55 to 1.95% CFR for all regions. The estimates of burden are expected to be conservative because of the assumption that all deaths occur in hospitals, and little data available on CFR is an acknowledged model limitation.

The IVI disease model estimates that 10 to 15 million cases and 75,000 to 208,000 deaths due to typhoid fever occur annually. This estimate is lower than previous burden predictions in terms of incidence but maintains similar numbers of deaths. IVI model also presented risk-unadjusted burden estimates that ranged from 18 million to 24 million cases and 131,000 to 344,000 deaths per year.

IVI investigators acknowledged particular areas of uncertainty, which they varied in sensitivity analysis. Risk factor correction, BC sensitivity, and CFR were varied to obtain a range in estimate of the number of typhoid deaths from 77,000 to 274,000. The use of one risk factor correction for all regions, lack of current data from Latin America, reviews of only English language resources, and data availability (particularly to inform CFR) were all identified as model limitations.

Mathematical models and evaluation of vaccination strategies and impact

Mathematical modeling efforts by groups at IVI, Novartis, and Yale University were brought together by CaT and aimed to evaluate vaccination strategies against typhoid; the Novartis model does not yet include vaccination and was excluded from the presentation. Both the IVI and Yale models are SIRS, stochastic, and age structured considering 3 vaccine types: polysaccharide, conjugate, and live attenuated oral vaccine. Both vaccine models were fit to data from a cluster randomized effectiveness trial of Vi typhoid in India, which demonstrated that carriers play a limited role in transmission of the disease. The basic reproductive number (R0) of typhoid in the models varied between 2.3-2.8.

Models estimated similar vaccine effectiveness and agreed in high transmission settings. Evaluation of conjugate vaccines gave similar results, assuming 100% coverage at 9 months for single-dose, and a second strategy of an additional dose at 15-18 months with 75% coverage. Little difference was detected between 1 and 2 dose effectiveness estimates, both around 80% after 20 years of vaccination. However in high endemicity areas models predict much lower effectiveness of approximately 20%. Adult doses and commitment to vaccination overtime will likely be needed to reach desirable levels of vaccine effectiveness.
Cost Effectiveness Analysis and Cost of Illness study

IVI modelled COI and CEA for typhoid disease and various vaccine schedules. The COI model utilized the IVI disease burden estimates presented with costs in 2010 US dollars (USD) and a decision tree approach to estimate direct and indirect costs. Treatment seeking rates, hospitalization rate, and CFR were similar to those used in the disease burden models. However this model incorporated an adjustment for care-seeking behaviour to better estimate deaths outside of hospital settings.

According to the model there are 780,000 hospitalizations and 9.3 million outpatients due to typhoid per year, costing 1.1 billion USD in productivity losses and 130 million USD in direct medical costs globally. Although inpatients were found to have higher cost per episode, total treatment costs were driven by larger numbers of outpatients. The cost per patient for typhoid was found to be higher than for malaria; however EPI parameters are not available from Africa and indirect costs are based mostly on data from the Asian region.

Cost effectiveness analysis (CEA) was carried out to determine differences between one time vaccination and routine introduction of vaccine. A static model for impact was used, with aspirations for developing a more complex dynamic model in the future. Typhoid conjugate vaccine was included assuming 96% efficacy and 20 year protection. Because vaccine price is unknown a variety of potential pricing between 0.5 and 3.0 USD was modelled.

CEA utilized WHO-CHOICE thresholds of gross domestic product (GDP) cut-off points. It was found that if the vaccine price was lower than 1x GDP per capita, vaccination was highly cost effective, and when vaccine price exceeded 3 x GDP per capita it was not cost effective. Additionally, routine vaccination was found to be more cost effective than campaign delivery strategy.

Review

Disease burden estimates

The team at IVI did a tremendous job putting together the data, which is challenging due to typhoid occurring in parts of the world where gathering data is problematic. Recent data are not available from many settings, and inclusion of data from ongoing surveillance projects such as the Typhoid Surveillance in Africa Program (TSAP) could tremendously improve model estimates of burden. Additionally the IVI model does not take into account heterogeneities in urbanization and risk within urban slum areas, important to typhoid transmission.

Although the risk-factor-based adjustment does incorporate access to safe water, other risk factors (e.g. food safety and urbanization) play a strong role in typhoid disease are not accounted for in this analysis. Importantly, the CFR used in the model is very conservative due to reliance on hospitalization data. Incorporation of access to healthcare may drive the CFR up or down depending on the setting. Additionally, antibiotic resistance was not considered and may also contribute to increase in CFR where prevalent.
Mathematical modeling

The modeling approach used is acceptable and incorporates a lot of data that are available. Additionally the validation of estimates between the two models is encouraging. There is a need to tailor the modelled scenarios to match burden of severe disease and death following first year of life (i.e. doses after 9 months of age). The model should better explain the uncertainties that exist and assumptions made to understand how reliable the estimates of burden are. Information analysis should be conducted to understand what parts of the data are essential to the model to direct future data collection and make parameters more precise in the future.

CEA & COI study

Since the COI model is based on the burden of disease model, the above review also applies. For the COI model, there are some issues that result from the systematic literature reviews which utilize highly heterogeneous data for meta-analysis. There is a high risk for publication bias in key parameters such as hospitalization rates and CFR. Additionally the validity of generalizing few studies with local level data for global estimates is limited; even comparisons of costs between typhoid and malaria should be avoided due to differences in methodologies. There is need for better data from high endemicity settings, especially due to heterogeneity between locations. The utility of global estimates for heterogeneous burdens and costing analyses is questionable, and country and district level analysis would likely be more beneficial.

Discussion

Burden of disease

Diagnostics for typhoid complicate the epidemiologic data and model estimates. Currently there are no good tests for informing population level exposure and antibody tests are difficult to perform and have low sensitivity in low resource settings where typhoid is endemic. This highlights the need for better studies on exposure and diagnostics for disease. Furthermore, the difficulty in performing tests highlights an additional adjustment that may need to be incorporated because there is a tendency to pre-emptively treat patients rather than test in many settings. Those who receive blood culture tests are likely in a population that may not be representative. Sensitivity analyses around blood culture should therefore be varied in the future to incorporate these factors.

Model inputs based on data from within hospital settings are an important limitation. Particularly for the CFR estimate, only hospitalization data were used. This may significantly underestimate the number of cases of typhoid and deaths due to typhoid, and consideration of including access to and utilization of care among non-hospitalized cases within the model parameters is essential.

The model should be better leveraged for conducting information analysis to determine which parameter is key to improving the accuracy of estimates of typhoid incidence and disease “correct”. This can help drive future data collection and priority setting for surveillance efforts.
There is more heterogeneity in typhoid transmission and disease that must be considered in the model. The meta-analyses performed and follow up analysis do not address potentially large differences in settings and populations.

**Mathematical Modeling**

The two models presented were similar, however the intention is not to converge the two as they serve different purposes within typhoid research. Because data limitations exist, the two models can also be used to validate one another and better estimate typhoid burden and potential impact of various vaccination strategies.

Typhoid is known to be extremely heterogeneous and local data is better for informing effective control strategies. Thus the usefulness of global models for local problems is difficult to understand. Lack of adequate data to fit global models is also limiting. It may be more beneficial to develop local complex and accurate models to understand burden and impact.

Although heterogeneity is important to consider, global funders such as Gavi require global estimates of burden and impact to be able to allocate resources to typhoid control and prevention. Therefore developing complex local models that feed into more broad global estimates may be the way forward.

The need to collect detailed quality data on typhoid was continually emphasized. Information analysis to identify the important gaps and influential parameters will better direct resources to collect essential information.

Both models base their vaccine effectiveness estimates on only one study, and therefore more information and data on the effectiveness of conjugate vaccines from rigorous trials is essential for informed recommendations to be made.

**CEA and COI study**

The economic modeling incorporates access to care in estimating parameters such as CFR. This adjustment factor changed the mortality estimates (from the burden model) by four-fold. It seems that this is an essential factor to incorporate into the burden model to harmonize methods and more accurately assess deaths due to typhoid outside of hospital/facility settings.

The process utilized for modeling burden and COI was complimented, and the efforts by IVI and other modeling groups are recognized as well intended and executed.

This scope of work should be contextualized better in terms of time frames and scale up of typhoid conjugate vaccines. It is estimated that there is a minimum two-year window until SAGE will review all of the evidence to formulate recommendations on typhoid conjugate vaccine use. Therefore critiques and suggestions can be incorporated into the work to better inform decision-making.
Questions to be addressed

- **Disease burden**: Is the proposed approach robust as a base case?
- **Transmission models**: What are the specific scenarios or sensitivity analyses on impact estimates that are required? Are the current model structures appropriate for global impact modeling?
- **COI/CEA**: The variation in the cost of illness by geographic regions is not captured. How best could this be addressed?

Summary and recommendations

IVIR-AC noted the absence of data on a number of key parameters and assumptions used for the analyses presented. IVIR-AC recommended that further analysis should be done where data are available, such as on urbanization, water quality, food safety and security. Further stratification on existing heterogeneity in the data and burden of typhoid within countries and local settings was suggested. The IVIR-AC also discussed the utility of performing an Expected Value of Information analysis to determine model drivers and key parameters to direct investments in future research and data collection.

IVIR-AC observed that the CFR used for burden of disease calculations might be conservative. Also, some members felt there may be publication bias from the meta-analysis contributing to uncertainty in the estimate (studies showing high CFR may be more likely to get published than those that show low CFR).

As a main driver of the BoD and Cost of Illness (COI) models the CFR should incorporate access to and utilization of care more comprehensively in both models. IVIR-AC noted that deaths were up to four-fold higher in the COI model where an incidence adjustment accounted for the lack of access to and utilization of care in both hospitalized and non-hospitalized cases. Therefore IVIR-AC recommends an erratum in the forthcoming publication in Lancet Global Health highlighting that the published BoD estimates may underestimate deaths in the current global context where access to and utilization of care may be limited.

Most of the key parameters such as CFR, productivity, and hospitalizations for the BoD and COI model are based on data from literature reviews comprised primarily of vaccine trials of varying sizes, which may introduce publication bias due to small numbers and/or a focus on populations that are eligible for these types of trials.

IVIR-AC observed that heterogeneity in transmission should be considered since it may have implications for vaccine effectiveness within the impact modeling. More uncertainty analysis is required because vaccine effectiveness of various schedules remains largely unknown for the variety of conjugate vaccines and ecological factors in settings where they likely to be used.

The productivity losses utilized as the main driver for the economic burden study are based on a single average from six countries, which may not be generalizable. IVIR-AC recommends stratifying by group of countries and settings important to typhoid transmission and burden.
IVIR-AC recognizes that new data arising from proposed multi-centre studies in Africa and in south Asia (expected to begin in 2015 and extend for three years) will provide valuable inputs adding substantial precision to the burden of disease models.

Given the timelines of the various analyses reviewed, IVIR-AC requests the study team to present updates to the Committee in 2015, at minimum, and by conference calls as needed.
11. Reasons for non-vaccination

Introduction

At the June 2014 Ad-Hoc meeting of the IVIR-AC non-vaccination was discussed regarding experiences in Pakistan for oral polio vaccination. Understanding different root causes driving non-vaccination is important for effective design of interventions in particular settings. IVIR-AC discussed the lack of quality standardized guidelines for research methods for measuring the root causes of non-vaccination to improve research methods and implementation. SAGE echoed the need for guidelines and research in this area.

SAGE endorsed the definition of hesitancy: “Vaccine hesitancy refers to delay in acceptance or refusal of vaccines despite availability of vaccination services. Vaccine hesitancy is complex and context specific varying across time, place and vaccines. It includes factors such as complacency, convenience and confidence.”

SAGE acknowledged that vaccine hesitancy may be present in situations where low vaccine uptake is occurring due to poor availability, lack of offer or access to vaccines, unfeasible travel distances to clinic, and poor programme communication but was not the priority to address in these situations. Vaccine hesitancy can be described by a matrix of contextual influences, individual/social influences, and vaccine and vaccination-specific issues.

No single intervention strategy addresses all instances of vaccine hesitancy, though a systematic review found that dialogue-based, directly targeted approaches can improve vaccine uptake, including engaging leaders, social mobilization, mass media, improving convenience, reminders, training health-care workers, and increasing awareness.

A community focused research study was conducted in Pune, India by the Swiss Tropical and Public Health Institute (Swiss TPH), the Centre for Health Research and Development in the Maharashtra Association of Anthropological Sciences (MAAS) to understand community ideas about disease and vaccine and how they influence confidence and hesitancy. The study hypothesized that local cultural ideas about the nature, perceived risks and local priorities for help and treatment affect the acceptability and ultimate uptake of vaccines.
The research focused on pandemic influenza outbreaks in Pune, a focal centre for the disease since 2009 and an identified area of concern for non-vaccination in the future. Pune is also the site of production for the live attenuated influenza vaccine (LAIV) manufactured by the Serum Institute of India (SII). The study was designed within a framework of cultural epidemiology using multiple methods, adapted from an earlier community-focused research study in Zanzibar, Kenya and DR Congo of oral cholera vaccine acceptability. Research activities included a community-based survey using vignettes, clinician interviews, case studies, policy review and media analysis.

Preliminary qualitative results indicate that there was limited awareness of vaccine options within the community, inadequate promotion by the health system, and lack of experience with adult vaccinations in the past. Additionally doubts of the value of vaccine against influenza from individuals were voiced, and there were perceived limitations of access to the vaccine.

In highly preliminary analysis of survey data it was found that increasing age and lack of knowledge about perceived causes of influenza were associated with non-acceptance; while, increasing education, perceptions of contamination or dirty settings as cause for disease, and high health seeking behaviours were associated with vaccine acceptance. No negative perceptions or mistrust was found to be reason for non-vaccination in this community study.

The community-focused study in Pune can be capitalized upon to develop further guidelines and approaches to understanding root causes of vaccine non-acceptance, and highlights the importance of local community context to this issue. There is both value and limitations with finding global answers to local problems and a need to identify harmony and dissonance of global, national, and local priorities. An IVIR-AC developed framework should include community determinants and local contextualization to collect and convert effectively information on root causes of hesitancy and acceptance into vaccine policy.

**Review**

The study presented from Pune is a good example of community-focused research to better understand non-vaccination. However, these study methods are expensive and time consuming. This study is just the first step for determination of the root causes in a local context, which must be followed by design of interventions and implementation. Next steps should include post implementation evaluation of and impacts on coverage, as well as doing rigorous community based studies to determine whether and how identification of determinants of non-vaccination or limited uptake may contribute to improved coverage.

The complexity of determinants of vaccine acceptance should be acknowledged. In a previous study in Zanzibar, differences in acceptability of vaccines were associated with delivery strategies. We must also be careful in our interpretation of vaccine refusal and hesitancy information based on community level data not to generalize inappropriately. Uptake and community determinants of coverage require an ongoing monitoring component attentive to dynamic and behavioural issues. Evaluation of strategies that consider community perceptions requires ongoing monitoring implementation.
Discussion

This work is the first step in an unfinished agenda; after identifying determinants and individual factors associated with non-vaccination, we must find ways to improve uptake by targeting those determinants. There needs to be a framework for translating research findings for decision makers to implement targeted solutions to low-coverage communities or groups.

The need for standardized tools that measure social behaviour and perceptions driving vaccine non-acceptance has been identified. Tools in development by industry are largely based on HIC perspectives and issues, but can potentially be adapted to LMIC settings in the future. The aim for these tools is to allow community level analyses to link to global contexts for better understanding of persistent problems and effective solutions. Similar tools will enable rigorous research trials with monitoring and evaluation to be applied.

Avoiding “guess work” in non-vaccinations is important highlighting the need for research; the value of qualitative methods, however, should be acknowledged for understanding barriers to vaccination. Coverage survey methods should also include some qualitative open-ended questioning to understand non-vaccination. Surveyors visiting houses have enormous opportunities for assessing, understanding, and measuring root causes of non-vaccination at this point of contact.

Leveraging community health workers who play a critical role in perceptions of health systems and immunizations could be an effective tool for improving communication and enabling an interface between mothers, facilities and vaccines.

Studies such as the one in Pune rely heavily on small numbers and key informants, which may skew results. The value and usefulness of survey and questioning methods may also be limited.

The role and added-value of global analysis in situational research and issues such as non-vaccination is unclear. The trajectory of future work should instead be towards a research framework that encompasses good practices in investigation and tools for policy-makers to identify whether non-vaccination is a problem or not in their local context.

A subgroup of the IVIR-AC should be convened to continue on the efforts of the SAGE working group on vaccine hesitancy, to build on their framework including proposed questionnaires that will create country and district level capacity for identification of potential issues with non-vaccination, promotion of community-focused research, and translation of findings into sound vaccine policy.

Questions to be addressed

- What kind of evaluation and methods are required to understand and respond to the root causes of non-vaccination?
Summary and recommendations

To understand the root causes of non-vaccination, IVIR-AC suggests promoting and supporting community research studies linked to effective vaccine policy and media communications.

IVIR-AC recognizes that there are a variety of disparate factors related to non-vaccination, relating to political, ethnic, tribal or religious-based active barriers for immunization for all children living in a certain area (like in the FATA region of North West Pakistan and Boko Haram-held territory in Nigeria), concerns about adverse events regarding specific vaccines, and individual non-acceptance of vaccines. These factors require different strategies to improve coverage.

IVIR-AC observed that the WHO VPD burden and impact assessment framework should be populated by evidence from community studies on determinants, and acknowledged both the value and limitations of global answers to local problems with regard to non-vaccination.

The outcomes of the deliberations of the SAGE meeting in October 2014 and that will focus on vaccine hesitancy should help guide the way forward on the broader set of non-vaccination implementation research issues for the IVIR-AC sub-group.

An IVIR-AC sub-group should be established to work on research protocols (designs and instruments), considering when and how these may be used. IVIR-AC members M. Amuyunz-Nyamongo, S. Sow and M. Weiss volunteered to join the sub-group and report back to the IVIR-AC meeting in 2015.
12. Integration of immunization services with delivery of other health programmes/interventions

Introduction

IVIR-AC aims to identify research questions to support the integration of immunization services with other health programmes/interventions. At its June 2014 Ad-Hoc meeting, it was highlighted that challenges for integration arise from the limited capacities of health systems in many developing countries. Integration requires strong planning and management to achieve desired service delivery efficiencies. Given the high degree of country specificity, it was felt that providing a menu of solutions and strategies for integration was the best direction for the future.

IVIR-AC was presented with an overview of the global landscape and evidence-base for integration resulting from a comprehensive literature review carried out by CDC. The published information on immunization and integration cite a variety of delivery models, multiple challenges, and frequently do not measure the impact of integration on vaccine coverage. Priorities for future research involve questions of quality, cost savings, efficiencies, contextual factors, and optimization of delivery.

Despite the weak evidence base, the need for integration is central in key global immunization frameworks and strategies such as GVAP (Objective #4) and the Global Action Plan for Pneumonia and Diarrhoea (GAPPD). The opportunity and risks of integration are acknowledged to be country specific, and it was highlighted that in many countries where human resources are severely constrained, integrated service delivery is inevitable.

As a common starting point it was considered useful to use WHO’s (2008) working definition of integration as “the management and delivery of health services so that clients receive a continuum of preventive and curative services, according to their needs over time and across different levels of the health system”.

Recognizing the immediate need to support the implementation of GAPPD given its impact on child mortality, as well as achievement of MDG#4, and its linkage with new vaccine introduction, there was consensus that identification of research issues and specific questions that would accelerate integration in this context should be prioritized.
IVIR-AC was presented with a current WHO supported pilot project in Mazabuka District, Zambia to understand the impact of integration of immunization delivery with other essential GAPPD interventions. The project focuses on retraining of healthcare workers in the study district and on improving the supply of necessary commodities to reduce severity of disease and increase coverage of key interventions for local achievement of GAPPD milestones. IVIR-AC was invited to provide technical support to the project team in order to produce relevant and quality evidence on the impact of integration and lessons learned for further implementation of similar studies/efforts.

Review

The literature review by CDC was comprehensive, and identified significant gaps and variability in the evidence on integration. The perspectives of decision-makers need to be better incorporated and detailed data on current strategies and work capacities is needed to inform both integration research and its implementation. Identifying desired additional activities and suitable scopes of work for health workers is essential to maintaining quality. Better coordination within and outside of the health sector at local, regional and global levels will likely maximize efficiencies and the benefits from integration.

It is essential for future research and evaluations to include pre and post estimates of coverage. These measurements should be a requirement in all future assessments of integration within immunization systems. It is important to learn from previous programs of integration; there are important benefits and unintended consequences that may better inform future efforts (e.g. reduction in ORS coverage with integrated delivery of other CDD treatments).

Research should inform how to leverage points of contact with the EPI system as opportunities for delivering other interventions. The ultimate goal is to develop a menu rather than a recipe and a helpdesk for technical assistance rather than a training program on integration.

Discussion

The spectrum of integration from “bundling” of commodities (i.e. vitamin A, ITNs, and deworming) to be co-administered at the time of vaccination, to more comprehensive approaches to disease control aiming to scale up other interventions not temporally associated with vaccination but important to the overall disease control objective (particularly in cases where vaccines are only partially effective e.g. PCV, Rotavirus, HPV) was discussed and debated. Given the breadth of this issue, and that other programmes also may have learnings to share, IVIR-AC voiced the need to focus and clearly define the scope for priority action.

WHO partners at PAHO have shared their experiences and tools for evaluating and implementing integration of delivery of health interventions. In the future, researchers should collaborate to adapt the menu of choices and strategies for integration with immunization programs to other contexts. Understanding of existing health systems would inform which interventions should and should not be integrated with immunizations in different countries and contexts.
The potential for negative impact on immunization delivery and EPI systems should not be ignored. Concerns of overloading systems and sustainability of integrated approaches were raised by committee members. This underscores the need to characterize interventions based on complexity and resource requirements (e.g. expertise, space, time, etc.) to promote integration where improvements in health outcomes and efficiencies are likely to occur.

Particular opportunities that may be considered “low-hanging fruit” for integration should be the focus for research efforts (e.g. GAPPD integration with PCV and RV vaccines). Determining process and outcome indicators for measuring successful integration may be particularly valuable for reducing child mortality in many settings, and enable further implementation of integrated GAPPD approaches.

In the short term, IVIR-AC identified the planned implementation of GAPPD interventions in Mazabuka District, Zambia as an opportunity to provide technical support to the development of an assessment methodology covering intervention and control districts and using a quasi-experimental design. IVIR-AC members Rachel Feilden and Yot Teerawattananon agreed to assist the evaluation team with the development and revision of methods and assessment tool and of sharing an updated tool for use in other countries.

Questions to be addressed
• What are priority research questions to support the integration of delivery of vaccines with other health interventions?

Summary and recommendations
IVIR-AC observed that the question is no longer whether to integrate but how, when and where to integrate.

To study the integration of immunization services with other health interventions, IVIR-AC identified the need for standardization of research tools and protocols to be applied locally, by antigen and schedule, and to determine how to communicate the evidence on integration to decision-makers, programme managers, health workers and the community. However, IVIR-AC cautioned that integration must not compromise the quality of successful immunization programs, and that documenting this should be an integral part of implementation research activities.

In line with the recommendations from the IVIR-AC Ad Hoc meeting in June 2014⁷, IVIR-AC recommended to use the presented proposal project on “Evaluation of GAPPD interventions: example for Mazabuka District in Zambia” as a case study. IVIR-AC members Rachel Feilden and Yot Teerawattananon agreed to assist with reviewing the assessment tool that is being developed for Zambia (and which is intended to be used in other countries) and report back to IVIR-AC at the 2015 meeting.

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⁷ To establish a sub-group to propose elements of the menu of solutions on the integration of care with immunization programs; adherence to a two year time line with a selective approach to proposed integration at service delivery and management levels; and identification of a network of social scientists in different disease areas including country managers.
IVIR-AC observed the need to document and learn from the experiences of other ongoing disease programs integrating immunization activities to inform research and implementation.
13. Missed opportunities for vaccination

Introduction

IVIR-AC reviewed the evidence on missed opportunities for immunizations (MOI) to identify knowledge gaps and research priorities. Missed opportunities are defined by WHO as any contact with a health service that did not result in an eligible child or woman receiving the needed vaccines. Requests were made for more comprehensive systematic reviews on the evidence available on MOI in women and children focusing on LMICs, and better understanding of the impact that MOI may have on coverage.

Magnitude of Missed Opportunities

A systematic literature review was performed by an Agence de Médecine Préventive (AMP) investigator on MOI in LMICs, focusing on women of child-bearing age and children. The final review included 57 qualitative results, and 61 quantitative results that reported prevalence. Data were highly heterogeneous and not equally distributed regionally, which prevented meta-analysis. Only 11 studies specifically addressed missed opportunities in relation to vaccines.

Reasons for MOI were categorized by practices, perceived contraindications, immunization organization, logistics of supply, and economic barriers. For both women and children the most important reasons for MOI were perceived contraindications, practices related to asking for immunization histories at visits, and logistics that prevented access. Economic barriers were not mentioned as reason for not getting vaccinated. Reasons for MOI among women also included attitude of provider and self-perceived need for vaccines, however women were not included in many studies. The review determined that MOI exist in LMICs with similar prevalence in comparison to rates from 20 years ago.

These findings are limited due to few studies, difficulty in comparing findings, and inability to estimate effects of particular determinants on the prevalence of MOI. The link between MOI and vaccine coverage is unknown making the importance of these findings uncertain. This emphasizes the need for better vaccination records, outreach, and systems strengthening.

Investigators at LSHTM aimed to estimate how vaccine coverage and timeliness could be improved by identifying opportunities to give overdue vaccines while receiving other immunizations or while seeking medical care. These modeling efforts attempt to better answer the question of how MOI may impact coverage, focusing only on DTP and measles vaccines. Survey data were available from 94 countries, but analysis was restricted to 58 countries based on a requirement of recorded date of vaccination for at least 40% of doses given. Dates of vaccination were necessary because opportunities
were defined based on timeliness of vaccination in relation to schedule. The model estimated that if all probable opportunities for DTP vaccine were taken, median DTP3 coverage may increase from 81% to 89%, with larger gains expected in the AFRO region. The model also estimated that 7% to 15% of vaccinated children could improve the timeliness of receiving their measles immunization by taking opportunities.

Many model assumptions were made and data sources were limited. Furthermore the difficulty in defining missed opportunities made it very complex to estimate of increased coverage from taking such opportunities; including contraindications for vaccination during illness were not included. Despite limitations, the link between MOI and coverage is clear, particularly in the AFRO region.

**Studies of Missed Opportunities**

PAHO methodologies for evaluation of MOI as a roadmap for updating protocols to address missed opportunities were presented. The project aimed to improve questionnaires to capture reasons for MOI. After literature reviews and revisions, pilot studies were conducted in the Dominican Republic to test the methodologies for identifying determinants of low vaccination coverage due to system factors, health knowledge, and attitudes of parents and providers.

The results of these pilot projects inspired revision of the protocols for research methods related to MOI. Five major steps were outlined: planning the assessment, implementation, analysing and interpreting, presenting the results and taking action. The steps describe a pathway for identification of the problem, training, piloting, and adapting of tools for data collection, analyses and interpretation, presentation of the results, and taking action based on the PAHO developed “Best Buys” Manual for MOI. This manual includes a systematic review of strategies for addressing MOI, monitoring MOI with local level guidelines, and an element of validation with field experts and EPI managers.

When piloted in the PAHO region reasons for MOI remained the same as 20 years ago: health providers do not ask for cards, do not know schedules and are informed by false contraindications; parents are unaware of their child's need for vaccinations at the point of contact with the health system; and persistent systems issues such as stock outs contribute to missed opportunities. Validation of the Manual of Best Buys for MOI is needed to understand how to apply and adapt methods for other settings and regions.

**Review**

The topic of MOI is not new to IVIR-AC, and nothing has changed in the past 20 years according to the evidence presented. There is an opportunity for applying the PAHO developed protocols and manual to the African region, with potentially larger gains according to the presented model estimates. The reasons for MOI in terms of healthcare practices are similar across all LMICs (i.e. false contraindications, logistical issues), but local factors such as poverty and geography may make access more influential to coverage than MOI.
The link between MOI and coverage is important to understand in different contexts. Countries with weak EPI systems are likely to have very different reasons for having low coverage than those with strong EPI systems. From the research presented it appears that strong EPI systems and health systems settings may benefit from interventions to address MOI, while countries with weak EPI/health systems may benefit more from addressing infrastructure, capacity and access issues for vaccinations.

The work from PAHO shows that there is adequate evidence and information to begin implementing what has been learned thus far. Future efforts should focus on continuing these methodologies and piloting studies in areas where EPI systems are working well. It is important to identify these settings within AFRO before devoting resources to MOI research.

Discussion

WHO and IVIR-AC are committed to moving forward with the work on MOI in the PAHO region and adapting and piloting these methods for the AFRO region. In the adaptation, there is potential for adding research questions to address missed opportunities for other interventions within the immunization system to quantify gains to be made via integration.

A consultant should be identified to continue this work and then present the adapted protocols and data available on MOI in African settings to IVIR-AC. This will enable better site selection within AFRO region for piloting the adapted protocols and maintain communication with IVIR-AC on implementation research conducted.

The models presented by LSHTM made many assumptions in trying to get an idea of MOI influence on vaccine coverage, and some committee members felt that the available data are too limited and assumptions made are too extensive to make any meaningful conclusions. The models rely on DHS and MICS survey data, which do not contain information on providers or availability of EPI services. This limits the quality of the data, particularly for this purpose. The nature of the survey data focuses on facilities, further limiting our use and interpretation of the findings.

The statement that economic barriers were not highly mentioned in the literature review on reasons for MOI in LMICs was concerning. Due to the facility focus of the data in the review, the populations surveyed were likely to have less economic burden than others who may not access to health facilities. Reaching populations outside of health facilities is essential to coverage estimates and determining reasons for MOI in LMICs.

Reliance on vaccination cards for measuring coverage and missed opportunities limits data quality and availability. Many women do not carry cards when seeking treatment for health problems unrelated to immunization, cards are lost over time, or the information provided by cards is inaccurate. These constraints highlight the need to improve registries and record keeping, and move towards electronic registry systems for vaccinations (and other health records). Opportunities for mobile phone technologies and electronic systems are exciting and this topic is gaining traction as funders observe mobile phones penetrating LMICs at rapid speeds.
Question to be addressed

- What are the key next steps in terms of research in this area?

Summary and recommendations

IVIR-AC observed that the fundamental question for evaluating missed opportunities is the impact on overall immunization coverage, and thus impact assessments must be carried out to measure this outcome.

Studies of missed opportunities should include documentation of reasons for the missed opportunity, strategies to address these reasons, and measurement of impact (including on overall immunization coverage) with robust methodology.

IVIR-AC suggested that these types of studies should be implemented rapidly in the African region using an adapted version of the protocols and tools from the experiences in Latin America. Rather than establishing a sub-group, IVIR-AC suggested that a consultant be identified to implement this work in collaboration with PAHO colleagues and the AFRO office to ensure the context that would inform adaptation, and report back to the IVIR-AC meeting 2015.
14. Non-specific effects (NSE) of vaccines research agenda

Introduction

SAGE convened a working group to review available evidence on non-specific effects (NSE) of vaccines and deliberate any necessary changes to policy to be made. SAGE concluded that at this time there were not sufficient available evidence to support any change in immunization policy for measles, DTP, or BCG; and current schedules for BCG and Measles demonstrate some evidence of benefit to all-cause mortality in children under-five. SAGE encouraged further investigation of NSE to be conducted via high quality RCTs adequately powered to understand potential differences in sex, and refinement and standardization of methods to conduct such research. IVIR-AC reviewed the evidence to identify priority research questions that may help to inform policy and decision-making.

A systematic review on the available evidence of immunological NSE was conducted for humans under-five years of age. Of the 10,000 initial results, only 80 were eligible for inclusion; 48% of the articles involved BCG and 70% involved children. None of the studies were specifically designed to answer questions of NSE, but data could be extracted which measured such non-specific immunologic endpoints following vaccination.

Twenty-four studies on BCG vaccine involving children under-five were included, from which 89 different parameters were looked at in varying capacities. The variety in the data made forming conclusions extremely difficult. None of the studies looked at sex differences in immunologic NSE after vaccination. The review was inconclusive on the nature or impact of NSE. Findings highlight the need to understand the underpinnings of the immune response and the need for high quality data on immunological endpoints from studies specifically designed to answer questions of NSE due to vaccinations. Future technologies may enable better measurement and understanding of immunologic endpoints related to vaccination.

An epidemiologic review was conducted to determine if administration of vaccines in infancy is associated with an effect on under-five mortality, and any difference in effect according to sex, age at vaccination, number of doses, administration with vitamin A or other vaccines, and sequence of vaccines. The review identified 73 articles mostly from Africa, with a large majority from one site in Guinea-Bissau. The review consisted of evidence from both RCTs and observational studies with high risk of bias. Findings indicate that BCG and measles vaccination may reduce the risk of all-cause mortality; but the impact of DTP on all-cause mortality could not be determined. The difficult landscape of data prevented further conclusions from being made.
From the reviews presented the following messages were formulated: RCTs should be conducted (rather than observational studies) to understand NSE of vaccines; RCTs should be designed to measure both mortality and immunological end points, and powered to detect differences in sex, age, and vaccine sequence (i.e. potential effect modifiers). Future research efforts should be conducted by a wider pool of investigators in a variety of populations and settings.

**Review**

The comprehensive reviews show a lot of variety in quality of data frustrating both investigators and conclusions. The efforts and resources devoted to this topic may never lead to changes in policies, and therefore the enormous amount of work should be contextualized in the broad landscape of priorities in vaccines, immunization programs, and public health. To conduct research that may be conclusive, designs for RCTs may be pose ethical questions not only for control groups but also if schedules are varied without data on safety or efficacy. Pursuit of this work should prioritize the identification of immunological parameters to be measured.

The need for this discussion and area of research was further questioned. If the need for further efforts in the area of NSE is decided upon, then the focus should be determining the best methods and design to obtain objective and rational results. If such studies deliver negative results about NSE of vaccinations, there would need to be a plan in place to deal with such repercussions and inform changes in vaccine policy.

**Discussion**

As combination vaccines become more widely available, studying the sequence of vaccinations may be less important than studying interactions between vaccinations in terms of NSE.

Many limitations and biases in studies of NSE exist due to the selection of individuals that have only received certain immunizations or none at all. Additionally, confounding effects (e.g. health status, living conditions, hygiene, socio-economic status, etc.) may play a significant role in outcomes of NSE and on the associations between antigens (i.e. DTP) and all-cause mortality.

Although prioritization of NSE was questioned, the commitment of groups working in this field has made discussion of this topic very relevant in the field of immunizations. IVIR-AC members acknowledge the need to continue reviewing the available evidence on NSE, and to better direct future research agendas and efforts.

It is important to maintain focus on how NSE research and findings may impact policy and implementation. Although influence of NSE on mortality may be discovered through rigorous studies in the future, IVIR-AC and decision-makers must understand if and how these findings will change implementation of immunizations in terms of schedules, sequences, and use.

Major points of action and continued refinement of research priorities and potential designs should be further discussed by a NSE task force with IVIR-AC presence and participation.
Committee members developed potential research questions from the NSE presentations:

- Is any evidence suggestive that schedule should be changed?
- Is there a better ordering of vaccines?
- Do particular antigens cause more NSE or more harmful NSE than others? Are any such antigens in WHO recommended vaccines?
- What study designs will allow for evaluation of different schedules and doses while still maintaining efficacy and having a valid comparison group?

**Question to be addressed**

- What are the priority research questions to inform policy?

**Summary and recommendations**

IVIR-AC reviewed the epidemiologic and immunologic data presented to SAGE and concurs with the SAGE view that these data do not provide a basis to adjust policy. IVIR-AC cautioned that the epidemiological data reviewed consists mainly of observational studies and a few RCTs with high risk of bias; immunological data were derived from studies not specifically designed to assess the issue of non-specific effects of vaccines.

IVIR-AC will work to guide the development of standard protocols and implementation of high quality prospective studies (including RCTs where feasible), as observational studies are unlikely to provide conclusive evidence. At a minimum, studies should mimic RCT circumstances and should be sufficiently powered to assess whether there are gender differences related in regards to non-specific effects of vaccines.

Immunological analysis should become an essential part of future RCTs with clear methodology describing the outcomes being measured, their temporal relation to immunization and how results can be interpreted.

Future NSE studies should consider inclusion of not only mortality but also morbidity outcomes.

IVIR-AC supports the proposal to establish a multi-disciplinary team with IVIR-AC participation to review the evidence and identify research questions. The priority research questions will continue to be refined by IVIR-AC informed by the deliberations from the proposed ad-hoc expert groups.

IVIR-AC members M. Brisson and B. Gessner volunteered to lead a sub-group to implement the work described above and to report back to the IVIR-AC meeting 2015.
Introduction

As the immunization landscape becomes increasingly complex coverage surveys must also become more complex to adequately measure relevant indicators. Three main household surveys relevant to measuring coverage of immunization exist: Demographic and Health Survey (DHS), Multiple Indicator Cluster Survey (MICS), and EPI Surveys. The need to reduce information bias in survey data has initiated a revision of the methods for coverage surveys, particularly within the EPI guidelines. A WHO team presented the revisions of coverage survey methodologies and guidelines.

The ideal measure of coverage is precise district level estimates, however these numbers can be difficult and expensive to obtain and usually have variable quality. In cases of resource constraints the guidelines under development provide methods for classifying coverage as high or low at district level, while making reasonably precise estimates at provincial level, and very precise estimates at national level. These methods aim to ensure sample size requirements are both manageable and affordable and that coverage estimates are reliable.

The revised guidelines require probability sampling; clusters with similar numbers of households are randomly selected and all households are visited to obtain information from all eligible persons in the selected clusters. This will reduce reliance on field worker selection of households. Collaboration with census departments for sharing of maps, data and population lists may be required. Importantly, this will require weighted analysis to be conducted increasing the statistical expertise needed for conducting and analysing surveys.

Another revision to the survey guidelines will increase the effort to obtain more accurate estimates of vaccination status by examining multiple records: both home-based cards and health facility records of vaccination, (where available). This will provide additional documented data essential to making robust estimates of coverage and may highlight key issues in EPI systems (i.e. low card retention).

The team presenting these revisions emphasized the importance of assessing whether a household survey should be conducted as the immunization landscape and surveys entail additional complexities; in certain situations it may be beneficial to use resources in different ways and leverage DHS or MICS results as they become available.

15. Coverage Surveys
Updated guidance documents will be distributed to country level partners on: data checks and management, standard analysis, adaptation of methods, and interpretation of results. This documentation is aimed at ensuring adoption of revised methods and understanding of the protocols recommended by WHO.

The revised coverage survey guidelines are being piloted in different settings to better understand and explain differences in cost and quality between methodologies. The revised protocols aim to decrease selection bias, decrease reliance on maternal recall, increase likelihood for adequate power, increase rigor, and increase quality; however, these changes will likely be accompanied by increased costs.

Review

The methods presented significantly advance quantitative methods and structuring of survey research. The revision recommending the use of sampling frames is detailed and helpful, however the additional need for statistical expertise may pose limitations for use in many LMICs. The enhancement of data collected by incorporating clinic based records (in addition to home-based cards) should be carefully contextualized; many settings may have less reliable facility records than individual vaccination cards. This reemphasizes the potential for electronic immunization records that are linked to birth registries as an accurate real time tool for estimating coverage.

The revisions will likely improve the quality of survey results; however getting countries to use improved methodologies for surveys may be difficult. Also, we should try to better understand the criticisms of previous methods. Perhaps the problems with survey data are caused by failure to carry out current methods correctly, rather than flawed methodologies that should be revised.

Discussion

The requirement for weighted analysis poses risks for countries with limited capacity of statistical expertise required to do such activities. However the complexities of the EPI system and immunization world are making this element of coverage surveys inevitable.

Moving towards more sophisticated methods without understanding the issues in implementation of old methods for coverage surveys may be harmful. Such understanding would enable better training and use for revised methods. Risk for new methods being implemented poorly would result in poor quality data at a higher cost.

The quality and availability of facility based immunization records is varied in LMICs. In certain settings utilizing facility based records may not be feasible at present, but the recommendation may highlight needs for improved record keeping. Situations may arise in which facility based records and home records do not agree, and protocols should be developed to address them.

In some locations in sub-Saharan Africa the prevalence of vaccination cards is only 2%. Using these records for estimating coverage is pointless in such settings; however measuring card prevalence may better pinpoint core issues of immunization systems in a location.
Moving towards electronic systems and smart phone based vaccination cards seems to be the way forward as technology penetrates LMICs. PAHO is beginning work on electronic registers now. These systems should be thought of as long-term solutions rather than ways to better estimate coverage and health indicators currently. Although electronic registries might be further down the pipeline, other technologies can be incorporated to improve quality of data such as GPS and GIS auto checks that record time of interviews and houses visited.

Surveyors could leverage the point of contact with community members to obtain further and more refined information. Incorporation of qualitative and open-ended questions could help identify root causes of low coverage and hard to reach populations.

There was debate about whether healthcare workers or separately trained interviewers should conduct surveys. The revised methods recommend avoiding health or EPI staff who may unwittingly influence the way respondents reply to some questions, particularly to those relating to reasons for not being immunized. Discussion of the pilot in Bangladesh and fieldwork in Nigeria highlighted the importance of supervising interviewers, regardless of who the individuals are. The importance of supervision for surveyors should be emphasized. The previous advice to choose the best interviewers to be supervisors was erroneous due to different skill requirements between the two occupations, and the revised guidelines address how to select and train suitable supervisors.

Interpretation of results from new methods in comparison to those of old methods is not clearly defined at this point. There is a need to understand how results can be assessed together to monitor trends and improvements in coverage.

**Questions to be addressed**

- Are the revised methods useful to address existing shortcomings?

**Summary and recommendations**

IVIR-AC agreed that the revised method for coverage surveys is the proper way forward, but that statistical expertise will be required to implement the survey in the field.

IVIR-AC identified the need for incorporating GPS technology to keep up with real time information and to improve the quality of survey sampling.

To identify the unreached, IVIR-AC recognized the need for qualitative studies and piloting of surveys in hard-to-reach settings such as in rural and urban areas of Bangladesh and Zimbabwe.

IVIR-AC identified the concern of interpreting the new survey data in comparison with the data collected from previously used methods. Difficulties in monitoring progress and comparing cross-sectional data across methods and time must be addressed.
16. Gavi perspective on implementation research

Introduction

The mission of Gavi/The Vaccine Alliance includes monitoring and evaluation and this scope of work will likely require increasing investments overtime. Gavi aims to demonstrate the impact of vaccinations and refine modeling efforts to fill the gaps in evidence. Currently, their work on impact includes modeling, assessments, and surveillance, with hopes for filling gaps and better connecting these three areas of work in the future. The Gavi advisory board oversees evaluations of systems and programmes that contain elements of implementation and impact research. This scope of work has particular relevance and linkages to the IVIR-AC ToR, and Gavi presented opportunities for collaboration and communication with the committee.

Gavi presented their work through the lens of WHO vaccine research and areas of engagement. In particular: minimizing barriers, monitoring, evaluating impact and optimizing and developing policy for immunizations were cited as areas with the strongest linkages between the IVIR-AC and Gavi scopes of work.

Minimizing barriers to vaccines was presented as one of the more critical components of research for Gavi, particularly in terms of increasing coverage and equity. Monitoring efforts of Gavi are currently focused on assessing the quality of coverage data and using better methods for assessing coverage and demographic surveys as well as improving and utilizing modeling efforts to assess disease burden and vaccine impact. Gavi is currently advocating for more resources to utilize for impact evaluations for their next period of investments.

Key points and guidance for IVIR-AC and Gavi collaboration come from standardization of information and protocols, leveraging evidence synthesis and reviews from IVIR-AC, engagement in earlier stages of work, and identification of key research needs, particularly in terms of data collection.

Implementation research opportunities with collaboration from the IVIR-AC may be better leveraged by Gavi in the future for assessment of impact of Gavi supported vaccines. The area of impact modeling presents unique opportunities for Gavi and IVIR-AC to better understand the broad effect of vaccines and immunization programs on development, and utilize these modeling efforts to streamline funding for collection of key parameters and indicators. Validation of model abilities to accurately measure trends in disease burden and vaccine impact is essential to the Gavi mission and continued investments. In the future it would be helpful for models to capture indirect effects of immunizations and to assess the impact of multiple interventions or vaccinations within a Gavi country.
Opportunities for IVIR-AC to partner with Gavi and potentially obtain support exist within implementation research. Gavi recognized the need to fill critical data gaps and standardize guidance for collecting such measurements, which IVIR-AC may play a role in. IVIR-AC may also be essential for improving model estimates of burden and impact as well as estimating ROI for Gavi supported vaccines in the future. However better coordination between the opportunities and scopes of work of IVIR-AC and Gavi is needed to maximize the expertise and funding available. Transparency and communication of protocols, key knowledge gaps, and modeling efforts should also be improved between Gavi and IVIR-AC. Gavi staff explained their current position within a fundraising period and hoped for feedback and collaboration with IVIR-AC in their future strategic investment period of 2016-2020.

Discussion

IVIR-AC members were extremely pleased by the Gavi presentation, and stated that there are concrete areas where collaboration between the two parties is important. A coherent dialogue between IVIR-AC, Gavi, and other partners should be continued to better focus support and optimize opportunities between multiple organizations.

Gavi staff explained that linkages with IVIR-AC and other groups are critical from their side and they are committed to continue to engage through dialogue. Efficient use of meeting time is important to Gavi, and a standing session for communication was recommended.

Timelines should be better aligned between Gavi discussions and investment and IVIR-AC meetings and recommendations. Members identified this as a problem at present, and communication may help to improve the fit and collaboration between IVIR-AC and Gavi. Aligning timelines may also contribute to reduce unproductive duplications of work and to increase efficiencies within vaccine research and implementation research.

IVIR-AC members recognized the importance of Gavi as a partner, but discussed the need to think more broadly within the field of immunizations and various other organizations that contribute to the scope of work. Priorities should therefore be decided not only based on the Gavi mission, but also on the drivers of coverage and equity for all vaccines in all settings (not just Gavi eligible countries). Expanding frameworks to answer and direct research questions based on Gavi perspectives and vaccination programs more broadly was suggested.

Evaluation of the sustainability of Gavi investments, especially as countries approach graduation or graduate is extremely important to maintaining gains in vaccine coverage and programs. Better mechanisms for collecting evidence and understanding the impact of Gavi support and vaccine programs in such countries should be prioritized by Gavi and IVIR-AC.

Future priorities should include understanding the direct return on investment and the broad economic impact of vaccines. Measuring the societal impact of vaccines, immunization programs, and EPI infrastructure is essential for continued investment and efforts. The impact of immunizations on the broader health system is not well understood and should also be incorporated into future evaluations and research.
Both Gavi and IVIR-AC should benefit from collaboration and communication by identifying particular areas of work where partnership would have significant added value, and other projects that are not relevant within one another’s scopes of work. This will enable IVIR-AC to act as a hub of information and expertise as presented in the WHO VPD and impact assessment framework that Gavi and other partners can look to for expertise and guidance.

Questions to be addressed

What are the suggested research questions to improve process of the impact estimates/investment overall?

Summary and recommendations

IVIR-AC observed that the session was a product of many discussions related to WHO and GAVI Secretariat to create a consistent plan for communication in order to optimally utilize IVIR-ACs capacity.

IVIR-AC agreed that the WHO VPD burden and impact assessment framework should be used to coordinate and leverage work from IVIR-AC and by using resources available in existing GAVI investments to fill the critical gaps in implementation research.

IVIR-AC noted that GAVI’s impact evaluation is important and should be used globally if the quality is ensured through an independent review process.

If GAVI seeks advice (like review of models of interest to [or sponsored by] GAVI) from IVIR-AC, GAVI staff are encouraged to engage IVIR-AC (via its Secretariat) from the start so that the Committee can provide early and pivotal commentary, rather than reviewing close to final stages of work, when it is not feasible to address critical concerns. IVIR-AC would provide to the WHO Secretariat its technical opinion on work presented and leave official endorsement to the WHO.
Annex 1: Agenda
### Annotated IVIR-AC Agenda 2014 – Salle A, WHO headquarters

**THEME**: Research to conduct impact evaluation of vaccines in use  
**Wednesday, 17 September 2014**

<table>
<thead>
<tr>
<th>Time</th>
<th>What will be presented?</th>
<th>What are the questions?</th>
<th>AC reviewers and WHO focal points</th>
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<tr>
<td>08.30</td>
<td>Registration</td>
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<tr>
<td>09.00</td>
<td>• Welcome</td>
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<td>• R. Breiman</td>
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<td></td>
<td>• Introduction and Charge of the Committee and new members</td>
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<tr>
<td>09:30-10:30</td>
<td>Draft framework to streamline impact activities</td>
<td>• Is the proposed framework useful?</td>
<td>IVIR-AC members:</td>
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<td>• What are the emerging gaps by information presented?</td>
<td>• J. Edmunds</td>
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<td>WHO focal point:</td>
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<td>• AM. Henao Restrepo</td>
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<td>10:30-11:00</td>
<td>Coffee/tea break</td>
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<td>11:00-12:00</td>
<td>SAGE April 2015 will discuss how models can help to understand pertussis resurgence and determine optimal vaccination strategies</td>
<td>What are the best modelling approaches to address policy questions defined by SAGE regarding pertussis vaccines?</td>
<td>IVIR-AC members:</td>
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<td>• Summary of existing pertussis impact models presented by S. Flasche</td>
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<td>• P. McIntyre</td>
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<td>• P. Beutels</td>
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<td>• P. Duclos</td>
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<td>12:00-13:00</td>
<td>Lunch</td>
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<td>Time</td>
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| **Session 3: Meningitis A impact assessment** | • Introduction overview presentation on approach for meningitis A impact evaluation by MP Preziosi (WHO)  
• Meningitis A modeling presented by C. Trotter | • Is the proposed approach adequate to assess meningitis A vaccination?                                      | IVIR-AC members:  
• J. Edmunds  
WHO focal point:  
• MP. Preziosi |
| 13:00-14:00 |                                                                                         |                                                                                                           |                                  |
| **Session 4: Impact evaluation of Hep B vaccines** | • Introductory overview of progress to date and next steps by WHO secretariat  
• Preliminary model progress and results of systematic review on vaccine effectiveness presented by A. Apolloni | • Is the proposed approach adequate to assess hepatitis B vaccination?                                       | IVIR-AC members:  
• P. Beutels  
• F. de La Hoz (TC)  
WHO focal point:  
• X. Riveros Balta |
| 14:00-15:00 |                                                                                         |                                                                                                           |                                  |
| 15:00-15:30 | **Coffee/tea break**                                                                     |                                                                                                           |                                  |
| **Session 5: Decade of Vaccine Economics (DoVE)** | • To present DoVE methods of:  
  – Health impact model  
  – Costing, financing and funding gap model  
  – Return on investment estimation model presented by S. Ozawa | • Is the proposed approach adequate?  
• Do the individual model components meet the state-of-the-art modelling requirements? | IVIR-AC members:  
• M. Brisson  
• E. Sinanovic(TC)  
WHO focal point:  
• K. Senouci |
| 15:30-17:00 |                                                                                         |                                                                                                           |                                  |
| 17:15      | **Cocktail**                                                                            |                                                                                                           |                                  |
**THEME: Research to conduct impact evaluation of vaccines in use (continued)**

*Thursday, 18 September 2014*

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<tr>
<td>09:00-10:00</td>
<td><strong>Session 6: HPV Cost-effectiveness tool (PRIME)</strong>&lt;br&gt;- Introduction of PRIME model design, methods and assumptions by M. Jit</td>
<td>• Does IVIR-AC consider PRIME to be a suitable model to use as a demonstration tool and to provide a conservative estimate of the cost-effectiveness of vaccinating girls prior to sexual debut in LMICs?&lt;br&gt;• If there is opportunity to develop PRIME further, what areas of extension/development to PRIME would IVIR-AC consider most useful?</td>
<td>IVIR-AC members:&lt;br&gt;- Y. Teerawattananon&lt;br&gt;- E. Sinanovic (TC)&lt;br&gt;WHO focal point:&lt;br&gt;- R. Hutubessy</td>
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<td>10:00-10:30</td>
<td><strong>Session 7: Typhoid disease burden, impact and economic assessment</strong>&lt;br&gt;- Overview of global typhoid vaccine policy, strategy for prevention and control, overall objectives of the typhoid modelling and economic analyses presented by I. Khan. &lt;br&gt;- Disease burden estimates presentation by I. Khan</td>
<td><strong>Disease burden</strong>&lt;br&gt;• Is the proposed approach robust as a base case?</td>
<td>IVIR-AC members&lt;br&gt;- G. Kang&lt;br&gt;- Y. Teerawattananon</td>
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<td>10:30-11:00</td>
<td><em>Coffee/tea break</em></td>
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<td><strong>Session 7 continued</strong></td>
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<td>11:00-12:30</td>
<td>• Mathematical models, and evaluation of vaccination strategies and their impact presented by I. Longini</td>
<td><strong>Transmission models</strong>&lt;br&gt;- What are the specific scenarios or sensitivity analyses on impact estimates that are required?&lt;br&gt;- Are the current model structures appropriate for global impact modelling?</td>
<td>• J. Edmunds&lt;br&gt;• Y. Teerawattanong&lt;br&gt;&lt;br&gt;<strong>COI/CEA</strong>&lt;br&gt;- The variation in the cost of illness by geographic regions is not captured. How best could this be addressed?</td>
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<td>12:30-13:30</td>
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<td><strong>Lunch</strong></td>
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<td><strong>THEME:</strong></td>
<td><strong>Research to minimize barriers and improve coverage of vaccines currently in use</strong></td>
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<td><strong>Session 8:</strong></td>
<td>Reasons for non-acceptance in endemic and outbreak/unsecure and political unrest situations</td>
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<td>13:30- 14:30</td>
<td>• Application on polio and influenza vaccine experiences in Africa and Asia.&lt;br&gt;• Presentation M. Weiss on non-vaccine acceptance</td>
<td>• What kind of evaluation and methods are required to understand the root causes?</td>
<td><strong>IVIR-AC members</strong>&lt;br&gt;- B. Gessner&lt;br&gt;- R. Feilden&lt;br&gt;&lt;br&gt;<strong>External experts:</strong>&lt;br&gt;- J. Okeibunor (AFRO)&lt;br&gt;&lt;br&gt;<strong>WHO focal point:</strong>&lt;br&gt;- M. Schuster</td>
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### Session 9: Integration of care for pneumonia and diarrhoeal diseases.

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<tr>
<td>14:30 – 15:30</td>
<td>• Overview of research questions on integration by M. Watkins (CDC)</td>
<td>• What are priority research questions to support the integration of delivery of vaccines with other health interventions?</td>
<td>IVIR-AC members</td>
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<td>R. Feilden</td>
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<td>T. Goodman</td>
</tr>
<tr>
<td>15:00-15:30</td>
<td>Coffee/tea break</td>
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<tr>
<td>15:30-16:00</td>
<td>Session 9 continued</td>
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<td></td>
<td>Session 10: Missed opportunities for vaccination</td>
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<tr>
<td>16:00-17:00</td>
<td>• Magnitude of missed opportunities:</td>
<td>• What are the key next steps in terms of research in this area?</td>
<td>IVIR-AC members</td>
</tr>
<tr>
<td></td>
<td>− Systematic review literature by S. Sridhar (AMP)</td>
<td></td>
<td>S. Sow</td>
</tr>
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<td></td>
<td>− Analysis of data coverage surveys by C. Sanderson (LSHTM)</td>
<td></td>
<td>M. Kigasia</td>
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<tr>
<td></td>
<td>− Studies of missed opportunities in Latin America by M. Velandia (PAHO)</td>
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<tr>
<td>17:00</td>
<td>Adjourn</td>
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<tr>
<td>17:30</td>
<td>Organized dinner</td>
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</tbody>
</table>
THEME: Research to minimize barriers and improve coverage of vaccines currently in use (continued)

Friday, 19 September 2014

<table>
<thead>
<tr>
<th>Time</th>
<th>What will be presented?</th>
<th>What are the questions?</th>
<th>AC reviewers and WHO focal points</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:30-09:30</td>
<td>Session 11: Non-specific effects (NSE) of vaccines research agenda</td>
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<tr>
<td>08:30-09:30</td>
<td>Overview of evidence and SAGE recommendations regarding research for NSE presented by A. Pollard and J. Higgins and WHO Secretariat</td>
<td>What are priority research questions informing policy?</td>
<td>IVIR-AC members: G. Kang, S. Sow, WHO focal point: X. Riveros Balta</td>
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</tbody>
</table>

THEME: Research to improve methods for monitoring of immunization programmes

<table>
<thead>
<tr>
<th>Time</th>
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<tbody>
<tr>
<td>09:30-10:30</td>
<td>Session 12: Coverage surveys</td>
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<tr>
<td>09:30-10:30</td>
<td>To present suggested revision of sampling, questionnaire construction, analysis and presentation of results presented by T. Burton (WHO)</td>
<td>Are the revised methods useful to address existing shortcomings?</td>
<td>IVIR-AC members: G. Kang, F. De La Hoz, WHO focal point: T. Burton</td>
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<tr>
<td>10:30-11:00</td>
<td>Coffee/tea break</td>
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<tr>
<td>11:00-12:00</td>
<td>Session 13: WHO pertussis burden modelling</td>
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<tr>
<td>11:00-12:00</td>
<td>Estimation of model parameters based on expert elicitation survey and IVB pertussis burden estimates and model used presented by T. Burton</td>
<td>Does the proposed model provide reliable burden of pertussis estimations?</td>
<td>IVIR-AC members: P. McIntyre, P. Beutels, WHO focal point: P. Duclos</td>
</tr>
<tr>
<td>12:00-13:00</td>
<td>Lunch</td>
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<tr>
<td>Time</td>
<td>What will be presented?</td>
<td>What are the questions?</td>
<td>AC reviewers and WHO focal points</td>
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<tr>
<td>Session 14: GAVI perspective on implementation research</td>
<td>Present GAVI plans on implementation research</td>
<td>What are the suggested research questions to improve process of the impact estimates/investment overall?</td>
<td>IVIR-AC member: M. Kigasia</td>
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<tr>
<td>13:00-14:00</td>
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<td>WHO focal point: R. Hutubessy</td>
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</tbody>
</table>

END OF OPEN SESSIONS

CLOSED SESSION - Recommendation session

<table>
<thead>
<tr>
<th>Time</th>
<th>Session recommendations</th>
<th>Draft list of recommendations for WER and SAGE presentation chair</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:00-15:00</td>
<td>Discuss session recommendations</td>
<td>Draft list of recommendations for WER and SAGE presentation chair</td>
</tr>
<tr>
<td>15:00-15:30</td>
<td>Coffee/tea break</td>
<td>Draft list of recommendations for WER and SAGE presentation chair</td>
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</tbody>
</table>

CLOSED SESSION - Recommendation session continued

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<th>Time</th>
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</tr>
</thead>
<tbody>
<tr>
<td>15:30-17:00</td>
<td>Review update reports of previous sessions e.g. malaria vaccine impact models, measles eradication models etc.</td>
<td>Draft list of recommendations for WER and SAGE presentation chair</td>
</tr>
<tr>
<td>17:00</td>
<td>Meeting closure</td>
<td>Draft list of recommendations for WER and SAGE presentation chair</td>
</tr>
</tbody>
</table>
Annex 2:
List of Participants

Advisory Committee Members

Dr. Mary Amuyunzu-Nyamongo, Executive Director and co-founder, African Institute for Health and Development (AIHD), Nairobi, Kenya

Philippe Beutels, Associate Professor, Director, Centre for Health Economics Research and Modeling Infectious Diseases (CHERMID), Vaccine & Infectious Disease Institute, University of Antwerp, Universiteitsplein 1, Antwerp 2610, Belgium

Robert F. Breiman (Chair), Director, Emory Global Health Institute, Emory University, 1599 Clifton Road, Suite 6.101, Atlanta, GA 30322, United States of America

Marc Brisson, Associate Professor, Department of social and preventive medicine, Faculty of Medicine, Laval University, Canada

Donna Burke, Dean of the Graduate School of Public Health and UPMC Jonas Salk Chair of Global Health, University of Pittsburgh, 130 De Soto Street, Pittsburgh, Pennsylvania, 15261 United States of America (unable to attend)

John Edmunds, Head, Department of Infectious Diseases and Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom of Great Britain & Northern Ireland

Rachel Feilden, FBA Health System Analysts, Tellisford Mill, Tellisford, Bath Somerset BA2 7RL, United Kingdom of Great Britain & Northern Ireland

Fernando de la Hoz Restrepo, General Director, Colombian National Institute of Health, Bogotá D.C., Colombia (via teleconference)

Brad Gessner, Scientific Director, Agence de Médicine Préventive (AMP), Paris, France

Gagandeep Kang, Head, Department of Gastrointestinal Sciences, Christian Medical College, Ida Scudder Road, 632004 Tamil Nadu, Vellore, India

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Edina Sinanovic, Senior Lecturer in Health Economics, Health Economics Unit, University of Cape Town, South Africa (via teleconference)

Samba Ousmane Sow, Director General, Center for Vaccine Development-Mali (CVD-Mali), CNAM, Ministère de la Santé, CNAM-ex-Institut Marchoux, Bamako, Mali
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

Mitchell Weiss, Professor & Head, Swiss Tropical & Public Health Institute (Swiss TPH), Socinstrasse 57, CH-4002 Basel, Switzerland

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Julian Higgins, Professor of Evidence Synthesis, School of Social and Community Medicine, University of Bristol, United Kingdom of Great Britain & Northern Ireland (via teleconference)

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Margaret Watkins, Epidemiologist, Global Immunization Division, Centers for Disease Control and Prevention, Centre for Global Health, Atlanta, GA 30333, United States of America

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Adriansjah Azhari, Head, Research and Development Division, Bio Farma, Bandung 40161, West Java, Indonesia

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Hope Johnson, Head, Programme Outcomes and Impact, Monitoring and Evaluation Policy & Performance, GAVI Alliance Secretariat, c/o UNICEF, Palais des Nations, Genève 10 CH-1211, Switzerland

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Anthony H. Burton, Systems Analyst, Expanded Programme on Immunization, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

Thomas Cherian, Coordinator, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

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Karen Hennessey, Routine Immunization Officer, Expanded Programme on Immunization Plus, Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland
Ana Maria Henao-Restrepo, Group Leader, Implementation Research and Economic Analysis, Initiative for Vaccine Research, World Health Organization, Switzerland

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

Hamid Jafari, Director, Polio Operations and Research, World Health Organization, Geneva, Switzerland

Jeremy Lauer, Economist, Costs, Effectiveness, Expenditure and Priority Setting, World Health Organization, Switzerland

Marie-Pierre Preziosi, Medical Officer, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

Ximena Riveros, Technical Officer, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

Holly Schuh, Intern, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

Melanie Schuster, Medical Officer, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

Kamel Senouci, Technical Officer, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

Nataliya Shapovalova, Technical Officer, Health Systems and Innovation, World Health Organization, Switzerland