Executive Summary IVIR-AC Recommendations
17-19 September 2014 meeting

THEME: Research to conduct impact evaluation of vaccines in use

Comprehensive WHO VPD burden and impact assessment framework

Questions to be addressed:
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 duplications of work 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

Question to be addressed:
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 for parameterization of 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

Questions to be addressed:
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 the expert solicitation exercise was too broad, the age groups too wide (should be focused on children under-five 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

Question to be addressed:
Is the proposed approach adequate to assess meningitis A vaccination?

• IVIR-AC agreed the dynamic model presented is the appropriate approach to understanding of the long-term impact of current campaigns on future meningitis A vaccination strategies.
• Assumptions of the model may need further sensitivity and uncertainty analysis, such as varying assumptions of duration of 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 better 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 A meningococcal meningitis and the economic impact and benefits of MenAfriVac, as well as of various vaccination strategies for the future.

Impact evaluation of Hep B vaccines

Question to be addressed:
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)**

**Questions to be addressed:**

*Is the proposed approach adequate?*

*Do the individual model components meet the state of the art modeling requirements?*

- IVIR-AC recognized that the ambitious 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 the state-of-the-art modeling requirements, but IVIR-AC acknowledges that this is a massive task because of the scale of the DoVE project. Ideally, 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. 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 should 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 sound basis for 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 including 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)

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?

- IVIR-AC agreed that PRIME is a suitable model to use as a demonstration 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\(^1\) 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 to present sources and ratings of data quality 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 IVIR-AC recommendations in the past on complex infectious disease models there is a need to develop an emulator-interface\(^2\) 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

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?

\(^1\) http://globocan.iarc.fr/Default.aspx

\(^2\) 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 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.
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 Expected Value of Information analysis to determine model drivers and key parameters to direct investments towards in future research.

- IVIR-AC observed that the case fatality rate (CFR) used for burden of disease calculations might be conservative. However, 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 and utilization of care. 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 in settings.

- 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-center 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

Questions to be addressed:
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.
- IVIR-AC recognizes that there are a variety of disparate factors related to non-vaccination, relating to political, such 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, of course, require entirely different strategies to improve coverage.
- IVIR-AC observed that the WHO VPD burden and impact assessment framework would benefit from community studies on determinants, and acknowledged both the value and limitations of global answers to local problems with regard to non-vaccination.
- An IVIR-AC sub-group should be established to work on research protocols (designs and instruments), considering when and how these may be used for implementation research.
- The outcomes of the deliberations of the SAGE meeting in October 2014 should guide the way forward on non-vaccination implementation research issues for the IVIR-AC sub-group.
- 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

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

- IVIR-AC observed that the integration question is no longer whether to integrate but how, when and where to integrate.
- To study integration of care with immunization programs, 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 translate the evidence on integration to community messaging. However, IVIR-AC cautioned that integration should be conducted such that quality of successful immunization programs is not compromised and that documenting this should form an integral part of implementation research activities.
In line with the recommendations from the IVIR-AC Ad Hoc meeting in June 2014\(^3\), 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 observed the need to document and learn from the experiences of other ongoing disease programs integrating immunization activities to inform research and implementation.

IVIR-AC members R. Feilden and Y. Teerawattanon volunteered to join the sub-group on “integration of care” and to provide guidance on appropriate methodology and tools for evaluations to the aforementioned Zambia study and report back to the IVIR-AC 2015 meeting.

**Missed opportunities for vaccination**

**Question to be addressed:**
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 suggests a consultant implement this work in collaboration with PAHO colleagues and the AFRO office to ensure the context would inform adaptation, and report back to the IVIR-AC meeting 2015.

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

**Question to be addressed:**
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 in regards to non-specific effects of vaccines.

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\(^3\) 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

Questions to be addressed:
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

Questions to be addressed:
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.