

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

Advisory Committee Meeting
Geneva, 9-11 June 2015



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Abbreviations

aP	acellular pertussis vaccine
BCG	Bacille Calmette–Guérin
BMGF	The Bill and Melinda Gates Foundation
CFR	Case-fatality rate
CDC	Centres for Disease Control
COI	Cost-of-Illness
CEA	Cost-Effectiveness Analysis
DALY	Disability Adjusted Life Year
DoVE	Decade of Vaccine Economics
DTP	Diphtheria–tetanus–pertussis
EPI	Expanded Programme of Immunization
Gavi	The Vaccine Alliance (Global Alliance on Vaccines and Immunizations)
GVAP	Global Vaccine Action Plan
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B vaccine
HCC	Hepatocellular carcinoma
HIC	High Income Country
HPV	Human papilloma virus
Hep B	Hepatitis B
Hib	Haemophilus influenzae type b
IPV	Inactivated polio vaccine
IVAC	International Vaccine Access
IVB	WHO Department of Immunization, Vaccines and Biologicals
IVIR-AC	Immunization and Vaccine-related Implementation Research Advisory Committee
IVR	Initiative for Vaccine Research

LMICs	Low and middle income countries
NIP	National Immunization Programs
NSE	Non-specific effects
OPV	Oral polio vaccine
PCV	Pneumococcal Conjugate Vaccine
PRIME	Papillomavirus Rapid Interface for Modelling and Economics
QUIVER	Quantitative Immunization and Vaccines related Research
ROI	Return on Investment
SAGE	Strategic Advisory Group of Experts
Swiss TPH	Swiss Tropical and Public Health Institute
UNICEF	United Nations Children’s Fund
WASH	Water, Sanitation and Hygiene
WHO	World Health Organization
WPR	WHO Western Pacific Region
wP	whole cell pertussis vaccine

1. Executive Summary

THEME: Research to minimize barriers and improve coverage of vaccines currently in use

Session 1: Research methods for community vaccine acceptance studies

Study designs are needed for research to assess the impact of community factors affecting vaccine uptake and coverage.

Presentation of an antenatal influenza vaccination study in Pune, India, indicated prospects for developing a generic protocol for community study to discuss issues related to acceptance and demand for this vaccine at other sites. Antenatal immunization, however, has many features that distinguish it from routine infant immunization, requiring additional research for other vaccines.

A comprehensive framework to guide the conduct of research on community uptake of vaccines was recommended to facilitate the design of community studies on a range of vaccines and settings. An IVIR- AC subgroup has been set up to provide leadership capacity to develop such a comprehensive framework.

A plan is needed for validating the impact of community interventions on hesitancy in at risk communities in the general population and decisions to prioritize vaccination in professional communities.

The comprehensive framework should facilitate development of vaccine-specific strategies and research designs based on an underlying chain-of-causality dynamic model of the processes and behaviours.

Assessment of the effectiveness of community interventions to improve vaccine acceptance is needed to ensure that research outcomes may contribute to programmatic actions.

Session 2: Non-specific immunological effects of vaccines

IVIR-AC appreciates the scope and value of the reviews that have been conducted of non-specific effects of vaccines, and re-affirms the conclusions of the Oxford meeting on this topic.

IVIR-AC reiterates SAGE conclusions that there is insufficient evidence for a schedule change. However, the available findings warrant further research exploration in this area.

There is scepticism about some of the large effect sizes (up to 50%) reported in some studies linking vaccination (by vaccines such as measles and BCG) to reductions in all-cause mortality.

The link between immunological readouts and epidemiological endpoints has not been clearly established. The relevance of the work to public health outcomes such as changes to vaccine schedules needs to be highlighted. Immunological studies could be incorporated in clinical trials so that their relevance to clinical/epidemiological endpoints can be understood.

Clinical trials do not need to be delayed until the completion of immunological studies. Rather studies that include evaluation of the non-specific effect of vaccination should be conducted in parallel and where appropriate with the immunological studies nested within the clinical trial. Nevertheless, available data from immunological studies should be used to determine key times for sample collection in clinical trials. IVIR-AC reiterates SAGE conclusions that further observational studies are not likely to inform public health decision-making and thus emphasizes the importance of randomized trials.

IVIR-AC can be involved in setting research questions and designing the appropriate methodology for clinical trials to investigate epidemiological outcomes. Two IVIR-AC representatives will be included in groups which may be formed in the near future to consider next steps for designing epidemiological studies to explore non-specific clinical effects of vaccines. Others with appropriate expertise should also be identified and engaged in such consultations.

The distinction between a vaccine's specific and non-specific effects needs further delineation as there are different pathways involved, and the latter may not correlate with immunological responses to vaccination.

Consideration should be given to developing mechanistic models of non-specific immune response to vaccination, and to link them to between-host epidemiological models.

Failure to collect appropriate samples during ongoing clinical trials of vaccines is problematic, particularly in trials with a randomized design. Consideration is needed on whether the trial design could answer questions around non-specific vaccine effects. If so, collection of the appropriate specimens should be ensured; such specimens could be bio-banked pending available resources and specific study design for future investigation.

There is no a priori reason not to include other vaccines besides DTP, measles and BCG. Additional vaccines that could be considered for investigation into immunological pathways include other live-virus vaccines, mucosal vaccines, protein-polysaccharide conjugates, or newer vaccines such as those against malaria or dengue. However, such additional study pathways should be driven by clinical, laboratory or epidemiologic evidence for non-specific immunological effects.

THEME: Research to conduct impact evaluation of vaccines in use

Session 3: Polio vaccine modelling

IVIR-AC agreed that models, such as the one presented at the meeting, which explore the long-term implications of current polio vaccination strategies, and considering silent poliovirus transmission, are valuable. IVIR-AC takes note of the work in progress and recommends that the Polio Group continues funding modelling work such as the current model to investigate silent transmission of poliovirus, assuming that the issues highlighted below are incorporated.

The current model is useful but there is a need to explore strengthening some of its simplifying assumptions, particularly concerning waning mucosal immunity and vaccine-derived poliovirus. Also of priority is the incorporation of IPV into the model, alongside OPV which is already in the model, as IPV is increasingly a part of national EPI programmes around the world, and is scheduled to replace OPV in 2016.

There is a need to explore whether the experience in Israel, demonstrating widespread shedding of poliovirus in a setting where IPV was used routinely (without use of OPV) is relevant for other settings. Prolonged silent circulation of polio in the setting of IPV-only may have very different dynamics from that in settings of OPV-end game eradication.

The model could be used to identify the parameters and assumptions that have the greatest impact on model uncertainty, so that these can be prioritised for future research funding.

Further work to understand the kinetics of vaccine waning and its implications on vaccine strategies across different polio models is needed. IVIR-AC members were nominated to represent IVIR-AC in a polio modelling meeting in Seattle on 1 July 2015.

An important outcome from any modelling work is to inform future policy decisions such as the addition of adult boosters to the immunization schedule.

Session 4: Decade of Vaccine Economics (DoVE)

IVIR-AC recognizes the ambitious scope of the present DoVE work, and the limited time and resources still available to investigators to complete it. IVIR-AC also appreciates that the DoVE team returned to update the committee on the status of DoVE and to report their responses to last year's comments.

IVIR-AC members reported continued concern over the internal and external validity, uncertainty, transparency and nature of extrapolation of the work to define the economic impacts of immunization programmes. Many of these concerns have been raised at previous IVIR-AC meetings.

IVIR-AC appreciates that some of these issues are beyond the remit or remaining timelines of the DoVE investigators to address. Hence, it is strongly recommended that any publications of the DoVE work is accompanied by clear statements about the appropriate use of the results at global, regional and country level. Since donors and decision-makers often want country level and vaccine-specific estimates, a clear statement about aspects for which the model cannot be used needs to be given prominence.

There were concerns about the face validity of some of the grades given to the health impact models that are used as inputs to the DoVE work. It is recommended that these are graded independently of the model developers or the DoVE team. IVIR-AC is willing to assist with this if needed.

IVIR-AC supports efforts by the GAVI Alliance (GAVI) to communicate uncertainty in model outcomes to decision-makers.

For future work of this nature, it is recommended that investigators involve members of IVIR-AC from earliest stages of scoping out and drawing up terms of references of the work to maximize the value of committee recommendations to the ultimate products. Committee recommendations are less useful if the study and report are essentially completed by the time the recommendations can be provided.

Session 5: Impact evaluation of hepatitis B vaccines

IVIR-AC appreciates the value of the new work done in response to last year's recommendations.

There are 3 important policy questions concerning EPI schedules that the model should address:

- Early administration of a birth dose (which the current model addresses)
- Whether or not EPI schedules should include a birth dose at all. The current model does not address this issue, which IVIR-AC considered the key policy question related to infant hepatitis B vaccine schedules. Consequently, the model should be assessed to determine if this question can be addressed.
- The choice of whether a DPT booster dose given from age 9–15 months should be delivered as standard pentavalent (DTP–Hib –Hep B)) or as quadrivalent (DTP–Hib)

A question related to presentation is whether there is any advantage to providing single component HPB at any visit other than a birth visit rather than multivalent (usually pentavalent) vaccines.

Further clarifications of assumptions and findings seem necessary on the following issues:

- Main reasons why the annual rate of hepatitis B virus carrier clearance was estimated (through Markov Chain Monte Carlo) to be substantially different in different countries;
- What would be the potential impact of changes in HepC epidemiology;

-
- Main reasons for deviations between the modelled post-vaccination anti-HBc estimates and the observed anti-HBc data, especially for children in China.

The cost and benefit of improving the current hepatitis B vaccination programme, i.e. with both the current (imperfect) vaccination schedule and an optimized schedule, could be highlighted in a way that is relevant for decision-makers. Since the force of infection in the model is unaffected by changing demographics (in the absence of vaccination), it may be possible to reduce model complexity by keeping the population static until disease outcomes are projected. The next step for IVIR-AC after the model is completed is to consider cost-effectiveness issues around a broader package of maternal and child interventions.

Session 6: Pertussis impact modelling comparison

IVIR-AC appreciates the plan for phase 1 of the comparison of pertussis models from Australia, England & Wales and the United States of America, which is meant to be a rapid assessment on the relative contributions of vaccine formulations, waning immunity, vaccine coverage and schedule to observed pertussis resurgence in these countries. If successful, phase 2 offers further opportunities to test whether existing models are sufficiently robust to changes in factors such as demographics, spatial heterogeneity, immunity and contact matrices across multiple settings.

In many countries using aP vaccine in the national immunization programme, aP vaccine is used in the private sector which represents a variable proportion of infant immunizations, so these complexities will need to be reflected when the models are extended to low and middle income settings.

Pertussis surveillance and laboratory capacity are still extremely poor in LIMCs particularly in Africa), and beyond the scope of the model comparison exercise to address. The committee noted that data are expected to be forthcoming through ongoing studies and follow-on analysis of maternal influenza trials, and strongly endorses the identification or further opportunities to add pertussis markers (primarily PCR on respiratory specimens) to studies such as GAVI- or the BMGF- supported vaccine impact studies.

There were concerns that the opportunistic process by which the 3 models were identified may not have included all relevant parameters or modelling approaches. The feasibility of taking into account other models and parameters identified through a literature review and/or open call should be assessed, focusing on the main results of the different models for phase 1, and if they are interested to include them in phase 2.

Session 7: Dengue vaccine modelling comparison exercise

IVIR-AC appreciated the process of identifying the participating models (such as having an open call and clear inclusion criteria) and the general plan for the comparison exercise. The participating models were generally appropriate given the policy question involved. Not all the models may eventually be suitable to inform SAGE processes, but their relative strengths and weaknesses will become clear during the process of model comparison.

Data and models relevant to dengue vaccines in Africa are lacking and need to be prioritised in the future.

Considerations about the safety of dengue vaccines need to be addressed in addition to questions about impact or efficiency. The model comparison needs to prioritize exploring whether there is potential for vaccination to increase the risk of disease in subgroups, such as groups defined by age or by prior immunity.

Model outputs need to include infection. The influence of different vaccine coverage levels on infection prevalence should be explored. The infection prevalence at equilibrium should also be identified.

Models should report their level of spatial stratification, incorporation of vectors, as well as temporal changes and assumptions about efficacy of vector control and case management.

Results of both phase 1 and phase 2 of the model comparison process should be reported to prevent over- harmonization in phase 2.

Both the pertussis and dengue model comparison exercises highlight the need for guidelines on best practice for conducting model comparison exercises to guide further work in this field.

THEME: Research to improve methods for monitoring of immunization programmes

Session 8: Development of guidance for the collection, assessment, and use of immunization data

IVIR-AC appreciated this work not only for the value of guidance it may provide for programme management but also for acquiring data that serve the interests of advocacy.

The aims, scope, and anticipated products of the work should be made more explicit and clearer at the outset, indicating the documents, tools for field managers and interactions the work aims to encourage.

Strategic aims may be usefully informed by prior relevant planning documents, e.g. the Global Framework for Immunization Monitoring and Surveillance and the Global Immunization Vision and Strategy.

The committee recognized a danger of overloading field workers with data collection responsibilities. Documentation for field workers on collecting and using their data should be brief, and should include practical advice informed by a bottom-up approach to ensure the relevance of recommendations.

For redesigning Health Management Information Systems (MIS) and for integrating an immunization MIS with a primary health care MIS, the approach should be process-driven and tailored to the particular context and needs of a specific health system.

Use of qualitative methods should be encouraged to explain vaccine acceptance and features of both more and less well-functioning programmes.

Further consideration of enhancing capacity for use of electronic data collection methods is needed. Paper-based tools for acquiring and using data are being replaced by electronic strategies that offer many advantages, such as data cleaning and opportunities to verify data sources and avoid double counting.

A single work plan will not be suitable for application in every country, given financial and infrastructure constraints. It is therefore important to develop a set of options as templates for contexts and settings, and to thereby enable national planning to develop an optimal system in each country.

Session 9: Proposed analysis of EPI surveys

IVIR-AC appreciated the work done since comments given by the committee last year.

The work was felt to be of value for identifying potential missed opportunities for vaccination, although it was not designed to indicate solutions to missed opportunities. A clear definition and an algorithm for identifying all missed opportunities are needed. It was agreed that early doses are unlikely to be ineffective and considering them invalid for the purpose to identifying missed opportunities is not a useful approach.

Correlation between the proportions of missed, as opposed to utilised, opportunities for vaccination catch- up and vaccination coverage should be explored.

- Development of methods for missed opportunities for vaccination should include:
- Assessment of the degree to which decreases in missed opportunities will translate into improvements in vaccination coverage;
- Reasons for missed opportunities;
- The degree to which evaluations need repeated to reflect temporal and geographic variations.

IVIR-AC welcomed the plans of the team working on revising EPI coverage survey methodology to update COSAS, the software designed for analysis of such data, to run on current operating systems and accommodate the new statistical features of the methodology.

2. Introduction

Dr. R. Breiman opened the fourth 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.

3. Research methods for community vaccine acceptance studies

Introduction

In 2012, WHO released a position paper on influenza vaccination stating that pregnant women should have the highest priority for seasonal influenza vaccination in countries considering the initiation or expansion of influenza immunization programs. Despite this recommendation, maternal influenza immunization has not been incorporated into routine immunization programs in many low-resource countries. In follow-up, IVR has engaged with the Swiss TPH to development of tools to assist developing countries in making decisions with regard to maternal influenza introduction.

Review

Based on a prior study of pandemic influenza vaccine acceptance and use, a generic protocol to research community acceptance has been developed by the Swiss TPH, aiming to examine prospects and problems for vaccinating pregnant women for influenza in low-resource countries. These findings will thereby be used to enhance prospects for implementing policy to vaccinate pregnant women for influenza in low resource countries.

The background to this work has been detailed elsewhere. The protocol outlines an approach based on options for design and instrumentation to assess awareness, hesitancy, confidence and anticipated use among women of child-bearing age, who are potential vaccine candidates, and their spouses or partners who may influence or be involved in the decision-making process. The protocol also includes options for assessing awareness, priority, policy and the perceived community views of health care personnel in settings with a recognized public health priority for influenza vaccination.

The implementation of a pilot study has been planned at the Indian site. Involvement of potential partners is being further explored for expanding interests of adapting and implementing the generic protocol at other sites (e.g., Thailand, Kenya and possibly others) and generalizing the interests in community studies for influenza vaccination implementation to other vaccines.

A delay in acceptance or refusal of vaccination despite availability of vaccine has been observed in Pune, India. The relevance of confidence building in the health sector was regarded as critical result of the work undertaken so far. There is a clear need for community level experiences to inform global policy making and adapted implementation of local practice.

A further piloting of the study protocol is planned where vaccination rates among active clinical partners will be compared to routine immunization as it previously existed in the country. The approach of improving awareness and promote adherence in the intended study will be consistent with the recommendations of the SAGE Working Group on Hesitancy.

Discussion

In the ensuing discussion among IVIRAC members, the adaptation of generic protocols to local contexts was suggested to improve coverage.

It was highlighted that at national level, immunization teams may be more interested in practical interventions rather than gathering data for research, which should be reflected in the roll out of the study. The costs and long duration of the roll out through large scale studies were seen as potential bottlenecks. In particular, experiences gathered for maternal immunization that are generalizable to other vaccines were regarded as helpful. The group requested that the benefits resulting from the piloting and roll out of the study protocol should be practical and communicated to programme managers.

Structural issues such as poverty and disconnected communities should be taken into account in the study and comparison groups should be used in the study. The outcome, stated as reducing hesitancy or increasing immunization coverage, should be clearly identified. Feasibility of implementation should also be evaluated.

Generally, it was deemed important to assess drivers or blockage of uptake through implementation research that should be led by implementers.

GAP and GAVI should comment on the priority of this topic to help close the gap of maternal immunization at larger scale.

Questions to be addressed

- What are the key issues in a generic protocol to research community acceptance of vaccines to facilitate implementation?
- How should the process of adaptation and implementation of a generic protocol to research community acceptance of vaccines proceed most effectively?

Summary and recommendations

- Study designs are needed for research to assess the impact of community factors affecting vaccine uptake and coverage.
- Presentation of an antenatal influenza vaccination study in Pune, India, indicated prospects for developing a generic protocol for community study to discuss issues related to acceptance and demand for this vaccine at other sites. Antenatal immunization, however, has many features that distinguish it from routine infant immunization, requiring additional research for other vaccines.
- A comprehensive framework to guide the conduct of research on community uptake of vaccines was recommended to facilitate the design of community studies on a range of vaccines and settings. An IVIR- AC subgroup has been set up to provide leadership capacity to develop such a comprehensive framework.

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- A plan is needed for validating the impact of community interventions on hesitancy in at risk communities in the general population and decisions to prioritize vaccination in professional communities.
 - The comprehensive framework should facilitate development of vaccine-specific strategies and research designs based on an underlying chain-of-causality dynamic model of the processes and behaviours.
 - Assessment of the effectiveness of community interventions to improve vaccine acceptance is needed to ensure that research outcomes may contribute to programmatic actions.

4. Non-specific immunological effects of vaccination

Introduction

Researchers have advanced that vaccines can have beneficial or detrimental effects on child mortality other than those on the target disease. These effects are similarly referred to as non-specific effects (NSE), heterologous or off-target.

After considering systematic reviews of epidemiologic and immunologic studies, SAGE concluded in April 2014 that no change to the recommended immunization schedules was necessary. However, SAGE also recommended that IVIR-AC be tasked to prioritize research questions and to propose the study designs that can answer those questions. SAGE asked to focus research on questions that can inform immunization policy.

In September 2014, IVIR-AC committed to guiding the development of standard protocols and the implementation of high quality prospective studies (included randomized control trials where feasible). To this end, IVIR-AC proposed the creation of ad-hoc expert groups and two members volunteered to follow up on those efforts.

A meeting of an ad-hoc expert group was convened on 1–2 February 2015 in Oxford, United Kingdom, to discuss non-specific immunological effects. In particular, this meeting treated four topics:

- Biological plausibility for heterologous effects;
- How high dimensional immune and systems biological analysis may link immunological findings to epidemiological observations;
- Studies that may define the mechanisms underlying non-specific immunological effects of vaccination in children; and
- Opportunities to define the mechanism underlying the non-specific immunological effects of vaccines in interventional studies in children.

IVIR-AC was presented with the summary and the conclusions from this meeting and discussed its conclusions.

Review

The ad-hoc expert group first considered the systematic epidemiologic and immunologic reviews prepared for the SAGE meeting of April 2014. Overall, the experts agreed with SAGE that the available evidence did not support a change in either the choice of vaccines or the timing or sequence of immunizations routinely administered to children. It was nonetheless reiterated that further research is warranted on the NSE on the immune system. The ad-hoc expert group thus delved into the evidence gaps relevant to the NSE of vaccines and highlighted a number of key considerations for future studies.

Innate, adaptive, and developmental immune responses are very complex. The challenge is to highlight the links of non-specific immune responses to epidemiological outcomes through a high dimensional immune and systems biological analysis. The identification of clear, precise immunological markers that correlate with clinical outcomes would provide the best basis with which to inform policy. As current data are mainly cross-sectional, the experts agreed on the need of longitudinal information. Furthermore, future studies should examine cause-specific mortality as well collect detailed information on morbidity. Consideration should be given to exposure to different pathogens and the microbiome in different settings and individuals. Important variables include the effect of immune maturation, actual variation in vaccine delivery in any given setting, and the order of dose administration with different vaccines. This would help to generalize findings to a real world context, as long as study protocols are consistent across different sites. The consideration of immunological markers is relevant because in-depth study of the immune system will likely identify a range of plausible mechanisms.

The case for investment in new methods and approaches was discussed, broadly dividing the topic into animal and human studies. Animal studies could generate hypotheses that are relevant to the human setting or in testing hypotheses originating from human data. As the effects being induced in animal models should reflect the human scenario, non-human primates as opposed to murine models should be used. Potential challenges are the difficulty in defining outcomes based on human epidemiological data on all-cause mortality, the lack of an established systems approach in animals, and mimicking human mucosal infection in animal models. Human studies may focus on either adults or infants. Pathogen challenge models to replicate infection acquisition could be tested in adults. Also, the effect of the order of vaccine delivery and interference by vaccines, such as the whole-cell pertussis vaccine, can readily be examined in large adult studies. In infants, studies underway should be leveraged to examine non-specific immunological effects, if immunological data can be correlated with clinical outcomes. These studies could build an increasing breadth of data that may inform larger studies, including large scale epidemiological studies. In-vitro studies are not likely to be useful for informing policy decisions.

High dimensional immune and systems biological analysis may link immunological findings to epidemiological observations. Although non-specific changes in conventional immunological parameters (such as antibody levels and cellular responses) can be measured, they provide little mechanistic insight into the relatedness of vaccination to an epidemiological outcome. Studies on yellow fever and influenza vaccination have uncovered the key mechanisms behind the related vaccine effects, while other studies have examined the roles specific molecular pathways play in susceptibility. Thus, systems biology can describe how biological networks are mechanistically related

to well-defined epidemiological outcomes such as infectious disease susceptibility. The systems approach may also be able to incorporate complex considerations such as multiple vaccine antigens administered simultaneously.

When designing studies for NSE, the ad-hoc expert group highlighted four issues:

- 1) identification of endpoints (for example, viral or bacterial disease);
- 2) complexity of multiple antigens given at one time;
- 3) immunization schedule order and initial set-point, and;
- 4) type of biological measurements.

To address these issues, mechanistic studies should guide what material should be collected at what times in future larger epidemiological studies and bank the immunological samples. These mechanistic studies would most readily be carried out in small cohorts of adults or in animals where multiple samplings at different times are feasible.

Interventional studies in children could also offer the opportunity to define the mechanism underlying immunological NSE of vaccines. Findings from the epidemiological systematic review suggest focusing on interventional studies involving BCG, measles, and DTP vaccines, as evidence for other vaccines is currently lacking. The two components of a mechanistic hypothesis that will address in priority are the extent to which a vaccine induces an immunological parameter in the context of external influences (e.g., natural infections) and to which it induces or protects against heterologous effects akin to the specific protective effect of a vaccine. A framework of opportunities for interventional studies in children is shown in Table 1.

Table 1: Framework of opportunities for interventional studies in children

Study design	Examples
Vaccine versus no vaccine	BCG versus no BCG in settings of low disease burden Early versus delayed BCG Early measles vaccine versus at 9 months of age
Vaccine comparison	Acellular versus whole-cell pertussis vaccines
Vaccine order	Third dose of DTP before or after measles vaccine BCG before or after the first dose of DTP

The heterogeneity between different settings, such as local causes of mortality, genetics, and background of infections, needs to be accounted for in study design and analyses and may require the realization of multi-site studies. Feasibility issues (e.g. frequency of the non-targeted outcome, logistical challenges and assay affordability) need particular consideration in each setting. Immunological case-control studies could be nested into large epidemiological studies that collect biobanks. Finally, confounding factors should be considered and carefully measured, including status at time of vaccination, exposure since vaccination, socio-economic factors, sex, and vitamin A administration.

Overall, the ad-hoc expert group concluded that no consistent immunological data in children is currently available to explain possible NSE of vaccines on all-cause mortality. Studies are proposed in adults and animal models to examine mechanistic links.

These links are able to inform future application of systems biology approaches in children, which should eventually relate to distinct epidemiological outcomes. Immunological assays may be applied in interventional studies directed toward elucidating the mechanism of the effect of an immunization attribute or nested within observational studies directed at closely evaluating outcomes of interest.

Discussion

IVIR-AC members highlighted that insufficient evidence on NSE of vaccines exists for use in policy decisions. A volume of information indicates rather large biological effects, but some members consider them implausible. The underlying goal of future research should be to optimize vaccination schedules that, if beneficial NSE existed, could have a greater impact than current schedules. Consequently, prioritised research questions need to drive the next steps, especially the design and implementation of both immunological and epidemiological studies.

With regard to immunological NSE of vaccination, the scientific knowledge of immunological pathways is limited to provide relevant answers. For instance, immunological markers can be measured after the administration of a vaccine: while they may be different than in not vaccinated persons, no data exist to establish any clinical relevance of such findings. For this reason, immunological research to address key immunization policy questions needs to be nested in well-designed vaccine trials or epidemiological studies. This type of research could lead to a better mechanistic understanding of immunological processes and how they relate to vaccination. Uncertainties remain regarding the type of sample to collect, the adequate biological markers to measure, and the timing of such measurements.

Whether mechanistic effects influence epidemiological results remain unknown. It was suggested that the first step should be to assess whether immunological NSE of vaccines actually exist. Then, to assess whether these immunological effects have epidemiological effects and, if so how both are linked. Only if the effects are held up at population level, an implication for immunization policies and vaccination schedules can be concluded.

Doubt was expressed on the usefulness of studies in adults and animals to impact immunization policies. In particular, the correlation with real life clinical outcomes was questioned for studies in humans if these studies are done in RCTs or nested trials. Questions on systems analyses related in particular to the links between immunological and epidemiological findings and policy changes.

As a generic biological question is addressed, some IVIR-AC members did not consider legitimate limiting studies to BCG, DTP, and measles vaccines. Expanding research question to other vaccines, such as pneumococcal, influenza and dengue, seem to offer advantages.

Similarly, mortality as the sole endpoint was questioned. Mortality based on hospitalization records could be assessed in high-income countries, but it is hardly measurable in other settings. In some places, the limited number of deaths will make an appraisal of the outcome or impact impossible. Conversely, a large effect could be observed in endpoints other than mortality. Also, key findings needs to refer to clinical and population-based outcomes. Endpoints in alternative to mortality should thus be searched for.

The need to consider two pathways for NSE was expressed. A pathway should look at the NSE of vaccines per se, while another at the NSE of infection or disease that the vaccine is preventing. Concern was expressed that, if immune responses to vaccine are assessed rather than infection or disease that the vaccine is preventing, what is happening as a result of the infection will be missed. This issue may be most relevant if the effects on mortality are mainly due to effects of the infection and not the vaccine (i.e. direct effect of vaccine vs. indirect effect of infection/not having infection). Additionally, the direct effects of one infection can modify susceptibility to a different infection.

Overall, the discussion highlighted the many unknowns in the field and the different positions about what currently available data mean. While additional immunological research is desirable and could be informative, the role of WHO and its advisory bodies is to guide research that can closely inform key immunization policy questions. SAGE recommended that IVIR-AC guide the definition of research questions that can inform immunization policy. Upcoming challenges are to prioritise research questions, to identify methods best suited to address them, and the corresponding research team to involve.

Question to be addressed

- IVIR-AC to comment on the conclusions of the Oxford meeting
- Propose next steps

Summary and recommendations

- IVIR-AC appreciates the scope and value of the reviews that have been conducted of non-specific effects of vaccines, and re-affirms the conclusions of the Oxford meeting on this topic.
- IVIR-AC reiterates SAGE conclusions that there is insufficient evidence for a schedule change. However, the available findings warrant further research exploration in this area.
- There is scepticism about some of the large effect sizes (up to 50%) reported in some studies linking vaccination (by vaccines such as measles and BCG) to reductions in all-cause mortality.
- The link between immunological readouts and epidemiological endpoints has not been clearly established. The relevance of the work to public health outcomes such as changes to vaccine schedules needs to be highlighted. Immunological studies could be incorporated in clinical trials so that their relevance to clinical/epidemiological endpoints can be understood.
- Clinical trials do not need to be delayed until the completion of immunological studies. Rather studies that include evaluation of the non-specific effect of vaccination should be conducted in parallel and where appropriate with the immunological studies nested within the clinical trial. Nevertheless, available data from immunological studies should be used to determine key times for sample collection in clinical trials. IVIR-AC reiterates SAGE conclusions that further observational studies are not likely to inform public health decision-making and thus emphasizes the importance of randomized trials.

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- IVIR-AC can be involved in setting research questions and designing the appropriate methodology for clinical trials to investigate epidemiological outcomes. Brad Gessner and Marc Brisson will act as IVIR-AC representatives to be included in groups which may be formed in the near future to consider next steps for designing epidemiological studies to explore non-specific clinical effects of vaccines. Others with appropriate expertise should also be identified and engaged in such consultations.
 - The distinction between a vaccine's specific and non-specific effects needs further delineation as there are different pathways involved, and the latter may not correlate with immunological responses to vaccination.
 - Consideration should be given to developing mechanistic models of non-specific immune response to vaccination, and to link them to between-host epidemiological models.
 - Failure to collect appropriate samples during ongoing clinical trials of vaccines is problematic, particularly in trials with a randomized design. Consideration is needed on whether the trial design could answer questions around non-specific vaccine effects. If so, collection of the appropriate specimens should be ensured; such specimens could be bio-banked pending available resources and specific study design for future investigation.
 - There is no a priori reason not to include other vaccines besides DTP, measles and BCG. Additional vaccines that could be considered for investigation into immunological pathways include other live-virus vaccines, mucosal vaccines, protein- polysaccharide conjugates, or newer vaccines such as those against malaria or dengue. However, such additional study pathways should be driven by clinical, laboratory or epidemiologic evidence for non-specific immunological effects.

5. Polio vaccine modelling

Introduction

Eradication of poliomyelitis is among the top priorities in global public health and has cost multiple billion dollars. Eradication efforts have reduced the burden of polio from being one of the most concerning diseases of the 19th and 20th century to 33 wild type cases in the first six month in 2015. All those cases were wild polio type 1 and were reported from Pakistan and Afghanistan. In the same period 8 cases of circulating vaccine derived polio virus type 1 have been reported from Madagascar and 1 case of circulating vaccine derived polio virus type 2 has been reported from Nigeria. The last case of wild polio virus type 2 was reported in 1999 and the risk of the type 2 component of OPV now likely outweighs the benefits.

Objective 2 of the polio endgame plan calls for the introduction of at least one dose of IPV into all routine immunisation schedules globally by the end of 2015. Then, in a worldwide synchronised manner, starting in April 2016 the currently used trivalent OPV will be replaced by bivalent OPV which no longer includes the type 2 component. Complete withdrawal of OPV is envisaged for the end of this decade.

A major concern for the eradication efforts is silent transmission of polio. The vast majority of polio infections are asymptomatic. IPV induces strong protection against polio disease, however, low levels of immunity in the intestine allowing asymptomatic infection transmission. Hence there is a risk that after the envisaged discontinuation of OPV and the switch to IPV a potential relapse in transmission would not be detected by symptomatic surveillance, as seen in Israel in 2013 where wild polio type 1 was detected in sewage samples first in the South but then in most of the country without any notifications of paralytic cases.

A progress report on the development of a series of transmission dynamic models that evaluate determinants of silent polio circulation during the eradication endgame was presented to IVIR-AC. Before introduction of IPV and while scaling up OPV coverage factors including waning immunity, high transmission intensity, suboptimal vaccine coverage and transmissibility of vaccine derived polio are potential risk factors for silent transmission. The objective of the presented transmission dynamic models is to identify key model dynamics before assumptions are realistically relaxed.

The deterministic, age structured, dynamical transmission model is differentiating between wild type polio infection and vaccine derived polio infection where the two compete for infection of a host and between first and consecutive infections. No polio subtypes are currently considered. In this deterministic setting eradication is defined as a wild polio virus prevalence smaller than 1. Silent circulation is defined as no eradication with less than 1 cumulative first infections that lead to paralytic polio with the last

12 months. The model illustrates that the combined effect of high transmissibility of wild polio virus and a long delay between the start of regular OPV campaigns and elimination of paralytic polio interact with waning immunity to increase the likelihood of prolonged silent circulation of polio.

Review

The presented model assumes that following polio infection via exposure through transmission or vaccination individuals are initially immune to then become susceptible again. While the susceptibility to re-infection is assumed to be less than the susceptibility of naïve individuals, intermediate stages of waning immunity with time or further reduced susceptibility following consecutive infections are not considered. While there is little evidence to help making an informed choice on a finer structured waning approach the assumption on waning immunity may play a key role in the potential for silent transmission and IVIR-AC members encouraged to study the sensitivity of the model results to a relaxation of this assumption.

The model considers natural infection with wild polio virus and infection with vaccine derived polio virus via transmission or vaccination. In the light of the plan to globally introduce at least a single dose of IPV for all children by the end of 2015 IVIR-AC members encourage inclusion of IPV vaccination in this framework.

Discussion

The IVIR-AC committee agrees on the importance and relevance of the model development process as outlined. The project is still in its early stages and exploring the impact of relaxation of model assumptions to increase its epidemiological plausibility is keenly anticipated.

Sequence data from paralytic polio cases can be useful to establish transmission chains and to approximate the number of unnotified case in between. It could also be used to help determining the minimal amount of complexity that is required to capture the polio endgame dynamics (e.g. between country transmission).

Questions to be addressed

- Review of the hypothesis of silent circulation phase transition and the related model design and assumptions for polio end game strategies.

Summary and recommendations

- IVIR-AC agreed that models, such as the one presented at the meeting, which explore the long-term implications of current polio vaccination strategies, and considering silent poliovirus transmission, are valuable. IVIR-AC takes note of the work in progress and recommends that the Polio Group continues funding modelling work such as the current model to investigate silent transmission of poliovirus, assuming that the issues highlighted below are incorporated.
- The current model is useful but there is a need to explore strengthening some of its simplifying assumptions, particularly concerning waning mucosal immunity and vaccine-derived poliovirus. Also of priority is the incorporation of IPV into the model, alongside OPV which is already in the model, as IPV is increasingly a part of national EPI programmes around the world, and is scheduled to replace OPV in 2016.

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- There is a need to explore whether the experience in Israel, demonstrating widespread shedding of poliovirus in a setting where IPV was used routinely (without use of OPV) is relevant for other settings. Prolonged silent circulation of polio in the setting of IPV-only may have very different dynamics from that in settings of OPV-end game eradication.
 - The model could be used to identify the parameters and assumptions that have the greatest impact on model uncertainty, so that these can be prioritised for future research funding.
 - Further work to understand the kinetics of vaccine waning and its implications on vaccine strategies across different polio models is needed. IVIR-AC members were nominated to represent IVIR-AC in a polio modelling meeting in Seattle on 1 July 2015.
 - An important outcome from any modelling work is to inform future policy decisions such as the addition of adult boosters to the immunization schedule.

6. 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 over a 2011-2020 period.

The DoVE project was presented at earlier IVIR-AC meetings in June 2014 and September 2014 meeting.

Review

The objectives of the DoVE project is to develop models for the Global Vaccine Action Plan (GVAP) which estimates impact of the “Decade of vaccines” in 94 low-and middle income countries in terms of:

- 1) Cost, Financing & Funding Gap (CFF) of National Immunization Programs (NIPs)
- 2) Cost of Illness (COI) averted
- 3) Return of Investment (ROI)

COI and ROI models focus on 10 antigens for which there are reliable health impact inputs. CFF are modeled for 18 antigens. The DoVE project models results across 2011-2020 for 73 GAVI countries plus 21 countries included in the GVAP. The model is built up by country, by year, by antigen and/or vaccine. Sensitivity analyses are conducted using Monte Carlo simulations across models to derive 95% uncertainty ranges around key parameters for disease burden and immunization program cost components (see methods documents for details).

The DoVE team at the International Vaccine Access (IVAC) team at the Johns Hopkins Bloomberg School of Public Health provided the historical background and scope of the DoVE project. The project which will end in September 2015 is funded by BMGF while the impact modelling work is co-convened by BMGF and Gavi while the CFF of NIPs work is guided by the GVAP Costing & Financing Steering Committee with members from BMGF, Gavi, UNICEF and WHO. The project has a global and regional focus for stakeholders such as BMGF, Gavi secretariat and the WHO African Task Force on Immunization and is not intended for country level decision making use.

The IVAC team presented an update of their responses to the IVIR-AC recommendations from 2014. Specifically the team presented how they have dealt with the concerns of the Committee with regard to how the models deal with marginal costs and benefits scale linearly with vaccination coverage, sensitivity and uncertainty analysis and increased transparency and clarity regarding all the methods to provide a stronger basis for a broad range of stakeholders to understand the strengths and limitations of the DoVE project. A disease model comparison exercise across diseases models (e.g. LIST/TriVac for Hib/PCV, Rota; WHO/PRIME for HPV) was organized in May 2015 by BMFG-Gavi.

In terms of identified gaps and future work IVIR-AC guidance was requested to provide guidance on how to grade the quality of inputs and assumptions in models; standardization on how to conduct disease model comparisons to more adequately determine the validity of model projection; guidance on sensitivity and uncertainty; approaches for missing data and extrapolations; approaches to project future financing of immunizations and how to deal with non-linearly scale costs with increasing coverage, changes in vaccination schedules and/or new vaccine introductions.

Discussion

It was emphasized that the DoVE project has an ambitious scope of interest hence is a major effort put together for the GVAP. The reviewers had concerns with regard to the internal and external validity, uncertainty, transparency and nature of extrapolation of the work to define the economic impact models as were raised at previous committee meetings. Currently both Gavi and WHO bringing modelling groups together through model comparison exercises to assess individual models which may be relevant to the multi vaccine model developed by DoVE.

Question to be addressed

- Agree on appropriateness on update DOVE study and how the group dealt with specific IVIR-AC 2014 recommendations

Summary and recommendations

- IVIR-AC recognizes the ambitious scope of the present DoVE work, and the limited time and resources still available to investigators to complete it. IVIR-AC also appreciates that the DoVE team returned to update the committee on the status of DoVE and to report their responses to last year's comments.
- IVIR-AC members reported continued concern over the internal and external validity, uncertainty, transparency and nature of extrapolation of the work to define the economic impacts of immunization programmes. Many of these concerns have been raised at previous IVIR-AC meetings.
- IVIR-AC appreciates that some of these issues are beyond the remit or remaining timelines of the DoVE investigators to address. Hence, it is strongly recommended that any publications of the DoVE work is accompanied by clear statements about the appropriate use of the results at global, regional and country level. Since donors and decision-makers often want country level and vaccine-specific estimates, a clear statement about aspects for which the model cannot be used needs to be given prominence.

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- There were concerns about the face validity of some of the grades given to the health impact models that are used as inputs to the DoVE work. It is recommended that these are graded independently of the model developers or the DoVE team. IVIR-AC is willing to assist with this if needed.
 - IVIR-AC supports efforts by the Gavi to communicate uncertainty in model outcomes to decision-makers.
 - For future work of this nature, it is recommended that investigators involve members of IVIR-AC from earliest stages of scoping out and drawing up terms of references of the work to maximize the value of committee recommendations to the ultimate products. Committee recommendations are less useful if the study and report are essentially completed by the time the recommendations can be provided.

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 the global and country level impact of HBV vaccine and develop a communication and data sharing platform for HBV immunization.

In September 2014 a static model, designed to assess the global impact of HBV vaccines under different vaccination strategies over the next decades, was presented to IVIR-AC. 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. IVIR-AC found the work 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).

The results of a dynamic transmission model that uses the same transition rates as the previously presented static model but also includes predictions on the indirect effect of HBV vaccination programmes were presented to IVIR-AC. The model includes predictions for China, Gambia and South Korea. The model uses MCMC to fit the force of infection to pre vaccination sero-survey data in those three countries. This is used to calibrate the dynamical model on its endemic equilibrium. One of the main sources of uncertainty in the model is the prediction of demographic changes in these countries for the next decades. The demographic predictions were chosen to be similar to those provided by the UN. Progression rates to hepatocellular carcinoma (HCC) and cirrhosis were estimated from literature reviews. The model predictions were validated against post vaccination Anti-HBc sero-survey data and against the post vaccination HCC incidence estimates from the GLOBOCAN 2012 project. The model predicted the data generally well. Anti-HBc prevalence in China in 2000 was consistently overestimated but within the prediction intervals of the model. The model predicts that there is little difference in the expected public health impact of a schedule with 3 doses given within the EPI schedule and in combination with a birth dose if compared to a schedule with 2 doses given within the EPI schedule and in combination with a birth dose. Assuming that the efficacy of a birth dose decreases from 40% to 10% if given more than 48 hours after birth, timely administration of such birth dose is estimated to

prevent 150 cases and 16 cases of HCC in South Korea and Gambia respectively until 2050. No measurable difference in impact of timely administration of a birth dose is predicted for China.

Review

The presented model is well developed. The analysis is based on extensive systematic reviews to inform parameterisation which presents a strength of this work. The presentation and the accompanying documentation were accessible and transparent. The model is yet to incorporate a comparison between the impact of HBV vaccination with and without a birth dose. The presented comparison of timely versus untimely birth dose may present a vague proxy but the committee would like to see the actual comparison with a no birth dose programme to be able to estimate the impact of the birth dose.

Discussion

The model estimates that administration of a birth dose within 48h after delivery will avert 150 cases of HCC in South Korea and 16 in the Gambia until 2050 if compared to the same routine schedule but with delayed administration of the birth dose. No such benefit is predicted for China. It is unclear why China would not benefit from timely administration of the birth dose.

Currently the South Korean infant immunisation schedule doesn't include a birth dose of HBV. The question was raised if it is policy in South Korea to use immunoglobulin instead. This would impact the model fitting and predictions and hence may need to be accounted for.

Because of the nature of transmission of HBV one could expect that the force of infection is elevated among the most sexually active age groups. As the model does not take into account of this it may run the risk of underestimation of the force of infection in these age groups and hence their significance in the overall transmission of HBV. However, this elevated force of infection in the sexually most active population is not evident from the anti-HBc data that has been used for parameterisation of the model.

The model results are currently presented as a comparison of a birth dose and either 2 or 3 epi doses or, alternatively, a comparison between timely and delayed administration of the birth dose. A presentation as the benefit of current implementation versus a proposed implementation schedule is encouraged.

The model is parameterised to data from China, South Korea and the Gambia and infers results accordingly. From Taiwan most of the included data sources are also available, however, demographic forecasts are complicated by a lack of demographic data availability. As the demographic forecasts are essential for the model predictions Taiwan hasn't been included in this work yet.

The models are parameterised to fit pre-vaccination data from the three countries. While the post vaccination predictions fit the data observed in the early years after vaccination reasonably well, there is a notable discrepancy in particular among children. This could indicate an overestimation of the force of infection among children. It should be investigated if the drivers for such are due to the population forecasts or the fit of the force of infection to anti HBc-titres.

When fitting the force of infection to anti-HBc data in the static model framework the implicit assumption is that demographic changes in the pre-vaccination era do not impact on the force of infection. IVIR-AC members recommended to assess if in the dynamical forecasting model the force of infection is again not dependent on demographics because then the model could be run without inclusion of complex demographic changes but based on disease rates and only converted to case numbers based on demographic predictions once the simulations are completed.

The models allow the clearance rate of HBV carriage to vary between settings. IVIR-AC members recommended to investigate further the underlying assumptions that necessitates such difference and if a common assumption would result in the models inability to fit the country specific data.

Questions to be addressed

- Are the design of models, methods, data inputs and assumptions suitable to estimate the impact of HBV vaccines?

Summary and recommendations

- IVIR-AC appreciates the value of the new work done in response to last year's recommendations.
- There are 3 important policy questions concerning EPI schedules that the model should address:
 - Early administration of a birth dose (which the current model addresses)
 - Whether or not EPI schedules should include a birth dose at all. The current model does not address this issue, which IVIR-AC considered the key policy question related to infant HBV schedules. Consequently, the model should be assessed to determine if this question can be addressed.
 - The choice of whether a DPT booster dose given from age 9–15 months should be delivered as standard pentavalent (DTP–Hib –Hep B) or as quadrivalent (DTP-Hib).
- A question related to presentation is whether there is any advantage to providing single component HBV at any visit other than a birth visit rather than multivalent (usually pentavalent) vaccines.
- Further clarifications of assumptions and findings seem necessary on the following issues:
 - Main reasons why the annual rate of hepatitis B virus carrier clearance was estimated (through Markov Chain Monte Carlo) to be substantially different in different countries;
 - What would be the potential impact of changes in HepC epidemiology;
 - Main reasons for deviations between the modelled post-vaccination anti-HBc estimates and the observed anti-HBc data, especially for children in China.

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- The cost and benefit of improving the current hepatitis B vaccination programme, i.e. with both the current (imperfect) vaccination schedule and an optimized schedule, could be highlighted in a way that is relevant for decision-makers. Since the force of infection in the model is unaffected by changing demographics (in the absence of vaccination), it may be possible to reduce model complexity by keeping the population static until disease outcomes are projected. The next step for IVIR-AC after the model is completed is to consider cost-effectiveness issues around a broader package of maternal and child interventions.

8. Pertussis impact modelling comparison study

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. A report was issued which was presented to SAGE in April 2014. 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). 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. SAGE identified the conditions necessary for pertussis resurgence and the effective strategies for resurgence prevention as important for modelling research

In September 2014, IVIR-AC reviewed three recent modelling studies from Australia, England and Wales, and the US that supported the hypothesis that wP to aP transitions may be associated with disease resurgence. All three models commonly conclude that a shorter duration of protection inferred by aP if compared to either natural protection or wP induced protection is likely to be one of the key drivers of the observed resurgence.

IVIR-AC found all three models to be of sufficient standard in terms of model structure to help 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). An IVIR-AC sub-group, consisting of IVIR-AC members P. Beutels, P. McIntyre and B. Gessner, was formed to identify specific data needs as an input for various models by conjoining modeler needs with epidemiologic expertise.

In February 2015 a model comparison of these three models was initiated. All models base their contact structure on age-patterns of two-way conversational contacts among UK citizens. Changing demography was only accounted for in the UK and the US model. Historical national DTaP/wp coverage data was used for parameterisation although in the AUS and the US model multiple databases had to be combined or interpolated. Historical notification data was used for model fitting in all models including age-stratification for the UK. For the Australian model the notification data was supplemented by 3 serosurveys. Differences in key model assumptions include vaccine properties (allowed range of immunity induced by natural infection, wP and aP, the duration of protection, and whether the vaccine is modelled as leaky or fully

protective). Furthermore, in the US model previously infected are less infectious during consecutive infections and do not report; in the UK model, once immunity wanes, previously infected are similar to naïve individuals but with a lower probability of reporting notifiable symptoms; in the AUS model consecutive infections are less symptomatic and less infectious while the time since the previous infection determines susceptibility and, if infected again, infectivity.

Plans for further work include two phases. In phase I (~ 6 months) the modelers plan to address: “What are the relative contributions of vaccine formulation (wP vs aP), waning immunity, vaccine coverage and schedule to observed pertussis resurgence in Australia, the UK and US?” within a model comparison of the three models. If successful, phase II (~ 2 years) will seek to address: “Are the existing models sufficiently robust to produce consistent results across multiple settings?” including the evaluation of resurgence potential of pertussis in LMICs that have been consistently using wP but with varying coverage levels and the potential benefit of a booster dose.

Review

At the IVIR-AC meeting in September 2014 members concluded that quality and surveillance of data was identified as the key problem, particularly in LMICs. This problem has since not been addressed but falls outside the scope of what the modelling groups can address themselves.

Differences between the diagnosis of pertussis and actual reporting to national surveillance can lead to surveillance artefacts that may mislead models. The SAGE WG recommended focusing on severe disease outcomes, for example hospitalisation during the first year of life, where variability due to surveillance artefacts is less.

Australia, the US and the UK were identified by the SAGE WG as fulfilling criteria for true resurgence. However, there are notable differences between countries with regards to vaccine uptake, surveillance and vaccine formulation. Given their period of low coverage due to concerns over adverse events the UK scenario may be most applicable to LMICs when assessing the potential of resurgence in a wP program with low coverage.

Discussion

In response to the resurgence of pertussis which led to multiple deaths in particular in infants too young to be immunised the UK introduced a maternal pertussis vaccination programme. The modelling groups have not planned to address the impact and cost effectiveness of such programme. WHO prioritises studies on the optimisation of infant vaccination programmes to understand the drivers of resurgence and prevent it with effective infant programmes.

Spatial heterogeneity, in particular for vaccine uptake and transmission intensity, can aid resurgence. Localised upsurges of pertussis notifications have been observed, for example, in Chile. Currently none of the models incorporate spatial heterogeneity. Data needs to parameterise spatially heterogeneous models substantially exceed data availability, in particular in LMICs. Scenarios that are representing sub-populations assuming that those sub-populations are not connected may be a compromise to address spatial heterogeneities.

In LMICs a mixture of aP and wP vaccines are commonly administered through either the private or public sector. This is further complicated by the potential diversity in protection offered from different aP or wP formulations; although the poorly efficacious pertussis vaccines of the past are no longer administered. Simultaneous use of aP and wP can be included in the models albeit a lack of heterogeneity that likely exists between the groups that choose to vaccinate aP and wP.

In particular for LMICs data availability and data quality remains concerning. Serological studies may help to address the burden of pertussis infection and inform the models. IVIR-AC members strongly encourage assessment of the burden of pertussis disease in LMICs but it was acknowledged that this falls beyond the scope of the model comparison exercise; although it would be important evidence that helps inform the models.

The three models that were endorsed by IVIR-AC in September 2014 were identified through an opportunistic process. No models that were parameterised to data from one of the countries where resurgence was observed was published at that time and hence groups that were known to have developed such were approached. With the exception of the US model no pertussis model that is fitted to the local epidemiology in one of the countries where pertussis resurgence was observed has been published at the time of the IVIR-AC meeting in July 2015. However, IVIR-AC members raised that multiple, structurally different models addressing the resurgence of pertussis without the use of data on resurgence have been published recently. A model comparison to identify the likely drivers for the observed resurgence may benefit from wider inclusion criteria which in turn would introduce greater variability on model assumptions; e.g. differences in mixing patterns. As phase I of the planned model comparison is making explicit use of the existing parameterisation to data on resurgence the broadening of model inclusion criteria is encouraged to be considered after completion of phase I.

Questions to be addressed

- Endorsement for the plan for further work

Summary and recommendations

- IVIR-AC appreciates the plan for phase 1 of the comparison of pertussis models from Australia, England & Wales and the United States of America, which is meant to be a rapid assessment on the relative contributions of vaccine formulations, waning immunity, vaccine coverage and schedule to observed pertussis resurgence in these countries. If successful, phase 2 offers further opportunities to test whether existing models are sufficiently robust to changes in factors such as demographics, spatial heterogeneity, immunity and contact matrices across multiple settings.
- In many countries using aP vaccine in the national immunization programme, aP vaccine is used in the private sector which represents a variable proportion of infant immunizations, so these complexities will need to be reflected when the models are extended to low and middle income settings.

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- Pertussis surveillance and laboratory capacity are still extremely poor in LIMCs particularly in Africa), and beyond the scope of the model comparison exercise to address. The committee noted that data are expected to be forthcoming through ongoing studies and follow-on analysis of maternal influenza trials, and strongly endorses the identification of further opportunities to add pertussis markers (primarily PCR on respiratory specimens) to studies such as GAVI- or the BMGF- supported vaccine impact studies.
 - There were concerns that the opportunistic process by which the 3 models were identified may not have included all relevant parameters or modelling approaches. The feasibility of taking into account other models and parameters identified through a literature review and/or open call should be assessed, focusing on the main results of the different models for phase 1, and if they are interested to include them in phase 2.

9. Dengue vaccine modelling comparison exercise

Introduction

The global burden of dengue virus disease has grown dramatically in recent decades. About half of the world's population is estimated as currently being at-risk for dengue infection. To date vector control measures are the only available measures to limit dengue transmission and subsequent disease. Recently, the live attenuated CYD-TDV dengue vaccine demonstrated safety and efficacy in two large phase III trials in South America and Asia. Vaccine efficacy against symptomatic, virologically confirmed dengue is exceeding 70% against type 3 and 4 dengue virus but is considerably lower in particular against type 2. Vaccine efficacy also varies substantially with previous exposure to dengue: protection against clinical dengue among seropositive individuals was about twice as good at 75% if compared with seronegative individuals.

In March 2015 a WHO SAGE working group was established to review available evidence on safety, the likely long-term public health impact, cost effectiveness and programmatic considerations around the introduction of CYD and to report to SAGE in April 2016 with a proposed policy position. To help inform the evidence on the long-term public health impact and cost-effectiveness of CYD for this recommendation a model comparison exercise has been initiated by WHO.

An open call for participation on “Comparative modelling of dengue vaccine public health impact (CMDVI)” with the objective to understand the potential long-term population impact and cost-effectiveness of dengue vaccines to inform SAGE recommendations was initiated on April 13th 2015. Inclusion criteria were the presence of a transmission dynamic model of dengue that is documented to have been used to examine the potential public health impact of prophylactic vaccination. Overall, 10 groups expressed their interest all of which met the inclusion criteria. The models cover a great variety of structural and parametric differences. Half are agent-based rather than deterministic, most models calibrations include those to Brazil or Thailand, and all models consider 4 dengue serotypes mostly incorporating cross enhancement as a way of interaction of the types. Most models explicitly include a vector population and seasonality of either vector density, biting rate, the incubation period or R_0 . Challenges for the comparison were identified as different approaches to vaccine properties (waning of vaccine protection or vaccine efficacy variation by previous exposure) and the fixed parameterisation of some models to settings outside the commonly used Brazil and Thailand.

The models will use a harmonised vaccine profile chosen to represent the main properties of CYD derived from published results of the Phase III trials as of June 2015. That is that the vaccine efficacy is chosen as measured in the trials and differs by serotype and serostatus. CYD is assumed to induce an average of 5 years of protection and is given at 80% vaccine coverage with 100% completion. Other vaccine profiles with varying assumptions on vaccine efficacy and duration of protection will also be considered. Scenarios will be run for Thailand-like and Brazil-like countries and results reported per 100,000 model population. A three-dose routine introduction at the lower end of the likely respective age of indication is assumed. The modellers will be asked to provide highly stratified outcome data on a 10 years post vaccine introduction time horizon that will allow to evaluate the cost effectiveness of the proposed introduction strategies.

Review

IVIR-AC is endorsing process of this model comparison. In particular the clarity and transparency of the selection criteria and the openness to participation of all groups that met those were welcomed. It was noted that none of the model are parameterised to an African setting which points to a data gap that will need to be addressed. It was acknowledged that addressing this data gap is outside the scope of the model comparison project, however, IVIR-AC encouraged an assessment of the evidence gaps that are highlighted from this exercise, as there are opportunities to leverage funds and to find data reservoirs.

The analysis plan was generally approved. IVIR-AC members suggested to also include dengue infection in the list of outcomes and to compare the pre-vaccination equilibrium infection burden between models to establish a robust baseline for the comparison. It was recommended that the sensitivity of the results to assumed coverage rates and the duration of protection are studied and that the results from both the Phase I and Phase II are included into the final report to limit the risk of over-harmonisation.

Discussion

The model comparison plan encompasses only the harmonisation on the vaccine profile and schedule as well as the setting. This is leaving many part of Dengue epidemiology open to interpretation by the respective groups. IVIR-AC members recommended a stratification of results to address the potential of role various assumptions including spatial heterogeneity and explicit modelling of vectors.

Current efforts to limit the burden of dengue are based on vector control measures and treatment of clinical manifestation of dengue infection. The models will assume that after the introduction of CYD control measures remain unchanged. However, there is scope to also evaluate the impact and cost effectiveness of CYD if vector control is enhanced.

A concern about CYD is that the vaccine efficacy against clinical manifestation of dengue, in particular haemorrhagic fever, may wane rapidly and leave vaccinated individuals at increased risk afterwards. As the follow up in the phase III trials was too short to assess this potential risk IVIR-AC members encouraged the model comparison exercise to investigate this safety concern across models as one of the key priorities.

One of the key assumptions that will drive the cost-benefit assessment of CYD is the vaccine price. It is unlikely that this information will be available in time to inform the model comparison analysis. Hence IVIR-AC member recommended to perform a budget impact analysis and sensitivity analysis on the price of CYD.

The CMDVI has the objective to provide information for SAGE recommendations in 2016 on the use of dengue vaccine and to understand the key features of dengue vaccine models that influence results, in order to improve the standard of modelling and help country-level decision makers interpret the results of modelling evidence they are confronted with. The IVIR-AC committee raised the need to differentiate between the objective and that not all models may be helpful to address both objectives.

Questions to be addressed

- Are the models appropriate given the policy question?
- Endorsement of plans for comparison exercise.
- Review and endorsement on outcomes for the December 2014 meeting.

Summary and recommendations

- IVIR-AC appreciated the process of identifying the participating models (such as having an open call and clear inclusion criteria) and the general plan for the comparison exercise. The participating models were generally appropriate given the policy question involved. Not all the models may eventually be suitable to inform SAGE processes, but their relative strengths and weaknesses will become clear during the process of model comparison.
- Data and models relevant to dengue vaccines in Africa are lacking and need to be prioritised in the future.
- Considerations about the safety of dengue vaccines need to be addressed in addition to questions about impact or efficiency. The model comparison needs to prioritize exploring whether there is potential for vaccination to increase the risk of disease in subgroups, such as groups defined by age or by prior immunity.
- Model outputs need to include infection. The influence of different vaccine coverage levels on infection prevalence should be explored. The infection prevalence at equilibrium should also be identified.
- Models should report their level of spatial stratification, incorporation of vectors, as well as temporal changes and assumptions about efficacy of vector control and case management.
- Results of both phase 1 and phase 2 of the model comparison process should be reported to prevent over- harmonization in phase 2.
- Both the pertussis and dengue model comparison exercises highlight the need for guidelines on best practice for conducting model comparison exercises to guide further work in this field.

10. Development of guidance for the collection, assessment, and use of immunization data

Introduction

Recent calls were heard from the international community for better data quality and the use of data for action. In fact, numerous projects and initiatives using Information and Communications Technology (ICT) are conducted to improve immunization programs, but with little homogeneity.

There is a clear need to better assist member states in collecting, assessing and using immunization data. This implies improving WHO guidance by setting standards, coming up with clear steps for capacity building and enhancing the conduction of operational research on the field.

Review

The background for the framework and guidance document for the collection, assessment, and use of immunization data was presented.

As first step, a common definition for data quality is crucial. Better quality of data matters as long as it improves program performance and ultimately, immunization coverage.

With higher quality of data, three levels of program performance will be impacted: operational decisions, management response and strategic decisions and policy.

Investing in ICT can help in many cases. Numerous pilots and initiatives from diverse stakeholders assessing newly developed tools are ongoing but little is known on how they make real changes. Identifying pros and cons of different existing tools through an information sharing platform was acknowledged as potential lever to move forward.

The shift in data collecting systems needs support by adapted guidance covering the collection and use of immunization data, the assessment and improvement of immunization data quality and the use of ICT.

The role of the WHO in providing guidance on systems, analytics and ICT is highlighted as key but it needs to be more clearly defined as it implies working with many partners and stakeholders.

Operational research was recognised as lagging behind; prioritizing topics and setting an entire research agenda needs to be conducted along with the IVIR AC.

Discussion

Including practical advice to help field workers to report necessary immunization data was recognised as critical topic. However, the scope of this work still needs to be clarified, particularly regarding interactions with existing regional frameworks.

Advice included:

- one should ensure that health care workers are not overloaded with data collection.
- developing this guidance from the bottom up approach
- focusing on the processes to achieve high immunization coverage and on the use of collected data. Two aspects of use should be considered: for advocacy and for managing immunization programs.
- documents should be brief, and understandable to field workers.
- in the developing phase of this guidance, it seems important to include all teams recognised for their ability to conduct the review, including community members.
- qualitative aspects such as vaccine hesitancy should also be recorded.

GAVI recognized the added value of this work to their new strategy aiming to empower countries to implement a data monitoring system and to conduct periodical surveys.

Question to be addressed

- Comments on framework and document
- Identify research gaps

Summary and recommendations

- IVIR-AC appreciated this work not only for the value of guidance it may provide for programme management but also for acquiring data that serve the interests of advocacy.
- The aims, scope, and anticipated products of the work should be made more explicit and clearer at the outset, indicating the documents, tools for field managers and interactions the work aims to encourage.
- Strategic aims may be usefully informed by prior relevant planning documents, e.g. the Global Framework for Immunization Monitoring and Surveillance and the Global Immunization Vision and Strategy.
- The committee recognized a danger of overloading field workers with data collection responsibilities. Documentation for field workers on collecting and using their data should be brief, and should include practical advice informed by a bottom-up approach to ensure the relevance of recommendations.
- For redesigning Health Management Information Systems (MIS) and for integrating an immunization MIS with a primary health care MIS, the approach should be process-driven and tailored to the particular context and needs of a specific health system.
- Use of qualitative methods should be encouraged to explain vaccine acceptance and features of both more and less well-functioning programmes.

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- Further consideration of enhancing capacity for use of electronic data collection methods is needed. Paper-based tools for acquiring and using data are being replaced by electronic strategies that offer many advantages, such as data cleaning and opportunities to verify data sources and avoid double counting.
 - A single work plan will not be suitable for application in every country, given financial and infrastructure constraints. It is therefore important to develop a set of options as templates for contexts and settings, and to thereby enable national planning to develop an optimal system in each country.

11. Proposed analysis of EPI surveys

Introduction

It is estimated that globally over 7 million children started but failed to complete the recommended vaccination schedule during the first year of life. It is a need to better inform national immunization programmes on magnitude of missed opportunities for vaccination.

There is no standardised definition for missed opportunity and therefore comparison over time or between different immunization programmes is very difficult.

WHO has recently updated the Vaccination Coverage Cluster Survey Reference Manual and recommends a set of standard analysis to provide information on missed opportunities.

In the context of a coverage survey, a missed opportunity for vaccination is the failure to administer all vaccines for which the child was eligible (according to the national vaccination schedule) on the date of a clinic visit for vaccination.

Review

The overall aim of this session was to present how data collected for immunization coverage surveys can be used to analyse missed opportunities for vaccination (MOV).

The primary purpose of immunization coverage surveys are to estimate immunization coverage. However, along with national vaccination schedules, they could provide information of timeliness of vaccination and MOV.

Literature reviews suggest that currently over 12 different definitions are used for missed opportunities. It appears as a window of opportunity to initiate a thorough work on MOV, as the WHO is working on two documents related to MOV: the cluster survey reference manual and accompanying tools and the exit interview (clinic visit) guideline. Both approaches offer standard definitions for missed opportunity.

A new Vaccination Coverage Cluster Survey Reference Manual provides:

- Definition for missed opportunities in the context of documented visit for vaccination
- Standard analysis to quantify missed opportunities and potential effect on immunization coverage
- Standard set of codes in common statistical software for above mentioned calculation

MOV measures in the cluster survey reference manual:

- What would valid coverage be if all vaccines for which the child was eligible had been given on each recorded visit date?
- Visit based MOV (crude and valid)
- Child based MOV (crude and valid)

Discussion

Clearly defining MOV was highlighted as key, particularly when considering early and inappropriate vaccine dose.

Attention should be paid on the low accuracy of dates reported on vaccination cards and therefore, this information is not sufficient to understand if MOV have been faced.

Generalizability of MOV results should be done with caution, because it is highly context specific.

In the African region, MOV was recognised as a critical work to conduct; A standardised tool (exit interview after clinical visit) is being developed to assess the magnitude of the problem, as well as its geographical disparities.

Potential issues related to MOV were pointed out:

- An analysis of the correlation between MOV and immunization coverage should be conducted.
- Although intervening on MOV is not possible, intervening on its root causes is the way forward. Causes seem numerous, and evolve with setting and time.
- MOV was finally questioned as if it is a measure to use and include in all immunization datasets.

Question to be addressed

- Comments on the recommendations and work plan

Summary and recommendations

- IVIR-AC appreciated the work done since comments given by the committee last year.
- The work was felt to be of value for identifying potential missed opportunities for vaccination, although it was not designed to indicate solutions to missed opportunities. A clear definition and an algorithm for identifying all missed opportunities are needed. It was agreed that early doses are unlikely to be ineffective and considering them invalid for the purpose to identifying missed opportunities is not a useful approach.
- Correlation between the proportions of missed, as opposed to utilized, opportunities for vaccination catch- up and vaccination coverage should be explored.

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- Development of methods for missed opportunities for vaccination should include:
 - Assessment of the degree to which decreases in missed opportunities will translate into improvements in vaccination coverage;
 - Reasons for missed opportunities;
 - The degree to which evaluations need repeated to reflect temporal and geographic variations.
 - IVIR-AC welcomed the plans of the team working on revising EPI coverage survey methodology to update COSAS, the software designed for analysis of such data, to run on current operating systems and accommodate the new statistical features of the methodology.

Annex 1: Agenda

Tuesday, 9 June 2015

Time	What will be presented?	What are the questions?	AC reviewers and WHO focal points
08.30-09.00	Registration		
09.00-09.30	Welcome <ul style="list-style-type: none">• Introduction and Charge of the Committee		R. Breiman
THEME: Research to minimize barriers and improve coverage of vaccines currently in use			
Session 1: Research methods for community vaccine acceptance studies			
09.30-11.00	<ul style="list-style-type: none">• A generic protocol to research community acceptance of influenza vaccination of pregnant women and a plan for implementation of a pilot study at the Indian site, involvement of potential partners for expanding interests of adapting and implementing the generic protocol at other sites (e.g., Thailand, Kenya and possibly others) and generalizing the interests in community studies for influenza vaccination implementation to other vaccines (M. Weiss)	<ul style="list-style-type: none">• What are the key issues in a generic protocol to research community acceptance of vaccines to facilitate implementation?• How should the process of adaptation and implementation of a generic protocol to research community acceptance of vaccines proceed most effectively?	IVIR-AC members: <ul style="list-style-type: none">• M. Nyamongo WHO focal point: <ul style="list-style-type: none">• P. Lambach
11.00-11.30	Coffee break		
Session 2: Non-specific immunological effects of vaccination			
11.30-13.00	<ul style="list-style-type: none">• Summary and conclusions of February 2015 Oxford Meeting (R. Kandasamy)	<ul style="list-style-type: none">• IVIR-AC to comment on the conclusions of the Oxford meeting• Propose next steps	IVIR-AC members: <ul style="list-style-type: none">• G. Kang• B. Gessner WHO focal point: <ul style="list-style-type: none">• A-M. Henao
13.00-14.00	Lunch		

Time	What will be presented?	What are the questions?	AC reviewers and WHO focal points
THEME: Research to conduct impact evaluation of vaccines in use			
<i>Session 3: Polio vaccine modelling</i>			
14.00-15.30	<ul style="list-style-type: none"> Phase transition for silent circulation relevant for polio end game model (J. Koopman) 	<ul style="list-style-type: none"> Review of the hypothesis of silent circulation phase transition and the related model design and assumptions for polio end game strategies. 	IVIR-AC members: <ul style="list-style-type: none"> D. Burke Y. Teerawattananon Subject expert: <ul style="list-style-type: none"> W. Ndifon WHO focal points: <ul style="list-style-type: none"> R. Sutter
15.30-16.00	<i>Coffee break</i>		
<i>Session 4: Decade of Vaccine Economics</i>			
16.00-17.00	<ul style="list-style-type: none"> Update on DOVE project: progress since IVIR-AC 2014 recommendations, identified gaps and implications for future work (S. Ozawa, by phone) 	<ul style="list-style-type: none"> Agree on appropriateness on update DOVE study and how the group dealt with specific IVIR-AC 2014 recommendations 	IVIR-AC members: <ul style="list-style-type: none"> M. Brisson Subject expert: <ul style="list-style-type: none"> V. Mogasale WHO focal point: <ul style="list-style-type: none"> C. Politi
17.15	<i>Starling hotel – VIP Salon</i>		

Wednesday, 10 June 2015

Time	What will be presented?	What are the questions?	AC reviewers and WHO focal points
THEME: Research to conduct impact evaluation of vaccines in use (<i>cont'd...</i>)			
Session 5: <i>Impact evaluation of hepatitis B vaccines</i>			
09.00–10.30	<ul style="list-style-type: none">Present dynamic hepatitis B model including country results and comparison with static global model (A. Apolloni)	<ul style="list-style-type: none">Review design of models, methods, data inputs and assumptions	IVIR-AC members: <ul style="list-style-type: none">P. BeutelsY. Teerawattananon Subject expert: <ul style="list-style-type: none">E. Mast WHO focal point: <ul style="list-style-type: none">X. Riveros-Balta
10.30–11.00	Coffee break		
Session 6: <i>Pertussis impact modelling comparison study</i>			
11.00–12.15	<ul style="list-style-type: none">Overview of comparison models to identify the relative contribution factors to pertussis resurgencePlan for using standardized set of historical data to understand resurgence using different models (S. Flasche)	<ul style="list-style-type: none">Endorsement of plan for further work	IVIR-AC members: <ul style="list-style-type: none">P. BeutelsP. McIntyre WHO focal point: <ul style="list-style-type: none">P. Duclos
12.15–13.15	Lunch		

Time	What will be presented?	What are the questions?	AC reviewers and WHO focal points
Session 7: Dengue vaccine modelling comparison exercise			
13.15-14.30	<ul style="list-style-type: none"> • Introduction (K. Vannice) • Review of mathematical models (S. Flasche) • Plan for dengue vaccine model comparison exercise (M. Jit) 	<ul style="list-style-type: none"> • Are the models appropriate given the policy questions? • Endorsement of plans for comparison exercise • Review/endorsement on outcomes from the December 2014 meeting 	IVIR-AC members: <ul style="list-style-type: none"> • M. Brisson Subject expert: <ul style="list-style-type: none"> • C. Burgess WHO focal point: <ul style="list-style-type: none"> • K. Vannice
THEME: Research to improve methods for monitoring of immunization programmes			
Session 8: Development of guidance for the collection, assessment, and use of immunization data.			
14.30-15.30	<ul style="list-style-type: none"> • Presentation of overall framework and guidance document (J. Grevendonk) 	<ul style="list-style-type: none"> • Comments on framework and document • Identify research gaps 	IVIR-AC members: <ul style="list-style-type: none"> • R. Feilden • M. Weiss WHO focal point: <ul style="list-style-type: none"> • J. Grevendonk
15.30-16.00	<i>Coffee break</i>		
Session 9: Proposed Analysis of EPI surveys			
16.00-17.00	<ul style="list-style-type: none"> • Presentation of plan to compare MOV results across studies and how to link MOV analysis with coverage data (D. Rhoda) 	<ul style="list-style-type: none"> • Comments on the recommendations and work plan 	IVIR-AC members: <ul style="list-style-type: none"> • R. Feilden • D. Burke WHO focal point: <ul style="list-style-type: none"> • M. Gacic-Dobo
17.00	<i>Adjourn</i>		
17.30	<i>Organized working dinner at Restaurant Vieux Bois (AC members only)</i>		

Thursday, 11 June 2015

Time	Session	What will be presented?
CLOSED SESSION		
09.00-10.00	Discuss written reports with updates of ongoing studies reviewed by IVIR-AC	<ul style="list-style-type: none"> • WHO framework on VPD burden and impact assessments • RTS, S Malaria vaccine impact and cost-effectiveness modelling • Global Framework for Rotavirus Vaccine Implementation Evaluation • Influenza Task Force on data for modelling and impact assessment • Typhoid investment case • Missed opportunities for vaccination in the African region
10.00-10.30	RFP on implementation research of vaccination programs in LMICs	<ul style="list-style-type: none"> • To present Alliance for HPSR/Gavi/UNICEF request for proposals processes and plans
<i>10.30-11.00</i>	<i>Coffee/tea break</i>	
11.00-12.30	Discussion and write up of final IVIR-AC recommendations	
<i>12.30</i>	<i>Meeting closure</i>	

Annex 2:

List of Participants

Advisory Committee Members

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

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