

REPORT ON THE IMMUNIZATION AND VACCINE-RELATED IMPLEMENTATION RESEARCH ADVISORY COMMITTEE (IVIR-AC) MEETING

Veyrier du Lac, France, 1 – 2 February 2017

Immunization, Vaccines and Biologicals (IVB)



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Abbreviations

BCG	Bacille Calmette–Guérin
BMGF	The Bill and Melinda Gates Foundation
CFR	Case-fatality rate
CDC	Centres for Disease Control
COI	Cost-of-Illness
CONSORT	Consolidated Standards of Reporting Trials
CEA	Cost-Effectiveness Analysis
DALY	Disability Adjusted Life Year
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
HIC	High Income Country
HPV	Human papilloma virus
Hep B	Hepatitis B
Hib	<i>Haemophilus influenzae</i> type b
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
PCV	Pneumococcal Conjugate Vaccine
PRIME	Papillomavirus Rapid Interface for Modelling and Economics
QUIVER	Quantitative Immunization and Vaccines related Research
SAGE	Strategic Advisory Group of Experts
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
Swiss TPH	Swiss Tropical and Public Health Institute
UNICEF	United Nations Children’s Fund
VPD	Vaccine-preventable disease
WASH	Water, Sanitation and Hygiene
WHO	World Health Organization
WPR	WHO Western Pacific Region

Executive Summary

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

Session 1: Non-specific effects (NSE) of vaccines

Introduction

Between February 2016 and January 2017, the WHO Secretariat convened three consultations of the same group of experts to review NSE hypotheses that researchers have advanced, possible research questions that are related to these hypotheses, and trial designs that could effectively address such questions. In June 2016, IVIR-AC reviewed the ongoing work and acknowledged the progress made towards the refinement of priority research questions and the outlined trial designs. At the February 2017, the Committee was presented with two proposed trial designs developed through the ad-hoc expert consultations.

Recommendations

- IVIR-AC endorsed the value of definitive evidence to confirm or refute the existence and magnitude of the impact of non-specific effects of vaccines on susceptibility to severe childhood infection in low and middle income countries, especially attributable mortality, and the potential follow-on implications for national immunisation schedules.
- IVIR-AC agreed that the two proposed trials emerging from the three ad-hoc expert consultations in 2015 and 2016 were the best options among the possible research questions and trial designs considered. Further development of these proposals will require careful consideration of the balance between feasibility and required sample size to exclude an impact on childhood mortality of public health importance, taking into consideration that the very implementation of a clinical trial is likely to reduce mortality in all arms.
- IVIR-AC noted that the required size and location of the trials will make them technically challenging and expensive to implement. If the trials are implemented, it is important to select sites carefully, with respect to both site and investigative team capacity and generalizability of trial findings. This will require a high level of coordination with national authorities and local stakeholders.
- IVIR-AC will review and comment on the two proposed protocols while they are being finalised.

Session 2: Tools to operationalize the WHO recommendations on the licensed dengue vaccine

Introduction

IVIR-AC agreed that the dengue seroprevalence survey guidelines, modelling using age-specific incidence data and transmission intensity map are useful tools. However, IVIR-AC affirmed the importance of maximising the efficiency of implementation of seroprevalence surveys, and further assessment should be given to opportunities to do so. These two activities should be well coordinated to inform the others.

Recommendations

The survey guidelines should be modified or expanded to take into account issues relevant to feasibility and value for effort expended such as:

- Ensuring serologic criteria used by serosurveys are as comparable as possible to those used in the clinical trials of vaccine.
- Greater clarity with respect to criteria for high, medium and low prevalence strata.
- Better definition is needed for the required level of assay sensitivity and specificity to enable an informative assessment of seroprevalence in each stratum.
- More detailed consideration of the influence of covariates other than age and school attendance is needed.
- Given the lack of capacity for neutralisation assays in many settings, identifying laboratory capacity to process neutralisation assays (validation purposes) for serum collections obtained in other countries would be valuable.
- The ethical implications of an opt-out approach for participation as well as the feasibility and utility of disclosing and explaining results to individual participants should be considered in accordance with usual practices for serosurveys and the situation in country.

To improve efficiencies, the following should be considered:

- The validity of salivary samples as an alternative to serum has been shown for some viral infections such as measles and rubella. Consideration of salivary samples, both as a means to increase study participation, and/or their collection simultaneously with serum to allow further studies of validity is potentially worthwhile in the context of this substantial global effort.
- Similar opportunities to enhance efficiency may arise from simultaneous opportunistic collection of residual blood samples from diagnostic laboratories, or existing biobanks from previous seroprevalence studies on other pathogens, in the same age groups. Comparable findings from opportunistic residual and purposive sampling have been found for measles in a high-income country setting and this may be an appropriate option in regions with adequate access to laboratory testing.
- Efficiency will also be improved if the blood samples taken can also be used to address questions for other pathogens (e.g. as part of the assessment of measles elimination) or stored for future use, but this also has ethical implications for consent procedures.

While the value of the global dengue transmission map is appreciated, there is potential for misinterpretation of the map predictions that may be counter-productive to informed decision-making. To minimise the risk, the following steps should be taken:

- The map should be pilot tested to ensure the comprehension and interpretation is sufficiently clear, including consideration of appropriate disclaimers before it is made publicly available.
- The methods tab text needs more detail. This tab could also be adapted to show a more specific explanation of the data limitations for each of the selected outputs.
- Hover text should be incorporated over the map that reveals the source of information for each estimate (eg. local surveys, extrapolation from other settings).
- The benefits and limitations of the map for different potential uses should be made clear, e.g. identifying data gaps, informing national decisions, informing vaccination decisions by individuals.
- The use of traffic light colour schemes on the map should be avoided as they may be misconstrued.
- The limited granularity in the map may create challenges in interpretation because of spatial heterogeneity in seropositivity within each geographical unit. This should be clearly caveated, and the impact of such heterogeneity on impact predictions should be explored in modelling.
- When new data are obtained, how close the previous predictions were to these data should be shown, along with how the results are changed by the new data.

- Showing potential vaccine impact can be useful, but this should be done only when such estimates are deemed to be sufficiently robust.
- There is a need to deliberately collect/collate data on African countries.

In addition, IVIR-AC would appreciate a more detailed description of the machine learning approach for producing the map. The Committee also recommends working with other groups doing similar work, as well as cross-validation with serosurveys as they become available.

THEME: Research to conduct impact evaluation of vaccines in use

Session 3: Measles mortality model

Introduction

The methods used were reviewed by QUIVER (former IVIR-AC) in 2011. Since then several major methodological innovations have been incorporated, including (i) adding explicit age structure to estimates of cases (so that model outcomes can be fitted to age-specific case data that are now collected by WHO), (ii) changing the function relating the proportion of susceptibles in the population to the annualised attack rate to better approximate the threshold nature for herd effects, and (iii) Stochasticity in the new model is now represented as binomial, rather than Gaussian as in the original model.

Recommendations

- IVIR-AC agreed that the updated data providing information on the age stratification of measles cases is an improvement, but cautioned that input data remain subject to reporting biases such as underreporting in outbreak situations, underreporting of subclinical, atypical cases and misdiagnosis, and that there are important within-country heterogeneities.
- Work to validate the functional form used by the current model to relate susceptibility to the annualised attack rate by comparing it to a fully dynamic SIR model is valuable and if not done, a justification for this should be articulated. The impact of incorporating age specificities in the functional form should be explored.
- There is a need to take into account additional coverage variables, including the association between MCV1, MCV2 and SIA coverage, as well as the duration of high MCV coverage.
- CFRs are likely to change over time, and should be explicitly taken into account when updated information becomes available.
- It is important to understand and communicate the reasons for the differences between estimates of global measles burden by WHO and other groups. A systematic comparison of measles disease burden models would be helpful.
- Data limitations that affect the ability to fit models to age-specific case data from India, especially those related to between region heterogeneity, should be explored.

Session 4: Hepatitis B vaccine impact model comparison study

Introduction

The WHO Global Hepatitis Programme (GHP) and the Immunization, Vaccines and Biologicals (IVB) departments decided to collaborate to request IVIR-AC to compare the methodological approaches that have been used to estimate the Hepatitis B surface Antigen (HBsAg) prevalence in children 5 years of age, and sought the comments from IVIR-AC. The impact model comparison study should be done on the basis of epidemiological and service coverage estimates in terms of model structure and design, assumptions, data inputs. The objective is to identify and understand the most influential drivers of variation of the model estimates.

Recommendations

- IVIR-AC agreed with the overall plan and approach to reviewing and synthesising results from hepatitis B models with calibrated data sets and to leave aside disease progression for another comparative modelling exercise.
- The review should be expanded to include models set in high-income countries that could still be applied to LMIC settings, and static models, partly to ensure that the number of models is sufficient to draw conclusions. To this effect, the date range could also be gradually expanded to encompass a longer period than currently proposed (2009 – 2017). The feasibility of engaging researchers with models published over 10 years ago seems questionable, but may need to be investigated if the number of included models would otherwise be insufficient.
- Changes in hepatitis B prevalence beyond 5 years old should be included as a secondary outcome.
- The research question for which each model was developed should be included in the data extraction form.
- For pooled models, further methodological thinking is needed concerning objective criteria for assessing and weighing the models and on using jack knife methods to examine robustness for excluding models.
- Through systematic literature reviews and a call for interest relevant modelling groups should be identified and be brought together.
- Stratified analysis based on country epidemiology (very low, low, intermediate and high endemicity) categories may be useful.

Session 5: Typhoid vaccine impact and economic models

Introduction

Currently WHO Strategic Advisory Group of Experts (SAGE) on immunization recommends vaccinating high-risk groups and populations against typhoid in the context of other control strategies. However, there is limited vaccine uptake at the moment. Conjugate vaccines with longer duration of protection compared to previous vaccines, and which appear to be immunogenic in infants, have recently become available though not widely licensed. Modellers at the Yale School of Public Health and the University of Antwerp have developed a vaccine impact model and cost-effectiveness analysis. This work has value in informing updated to the typhoid vaccine policy recommendations by SAGE in October 2017.

Recommendations

IVIR-AC appreciated the clear and transparent description of the typhoid modelling work, such as presentation of the model structure and fit to data. The epidemiological modelling work is sophisticated and well done, but both transmission modelling and economic evaluation aspects were noted to have data limitations at the moment. In particular, there were concerns over use of older data (eg. WHO-CHOICE costs from 2004), extrapolation of Zanzibar cost data to the Kenya setting, failure to acknowledge differential costs between urban and rural settings, and use of private sector user charges as a direct proxy of opportunity costs.

Key areas that should be improved include the following:

- Findings from the model should be considered in the context of other available typhoid vaccines (besides the conjugate vaccine) and non-vaccine interventions to control typhoid such as access to improved water, sanitation and hygiene (WASH) facilities. IVIR-AC noted the apparent lack of appropriate data for the latter analyses in the model. Further analysis may be more descriptive than quantitative recognising the potential challenge to interpret the direct impact of each intervention on disease reduction in a quantitative model.
- The impact of antibiotic use and antibiotic-resistant strains of typhoid should be considered, and if it is not included, its likely impact should be discussed.
- More realistic vaccine prices (besides \$1/dose) should be used, including in the base case.
- The use of 1-3xGDP/capita fixed cost-effectiveness thresholds should be avoided as they are not recommended by WHO for priority setting for country level decision-making.
- Data on hospitalisation rates, hospitalisation costs and age-specific case fatality rates (CFRs) should be improved, particularly for the 54 country modelling.
- The role of chronic carriers and asymptomatic/mild infection on disease transmission should be further investigated. If indirect (herd) protection is found not to have an important effect on cost-effectiveness, then this would justify future use of a static model for cost-effectiveness analyses on typhoid fever vaccination. This is partly because a static model is more transparent and adaptable to end-users.
- Uncertainty ranges around parameters should genuinely reflect model and parameter uncertainty since they are crucial to the value of information analysis.
- The use of malaria cost data to estimate the cost of managing typhoid could be an underestimation of the cost implications.

The vaccine impact and cost-effectiveness models should continue to be improved as data on varying level of disease burden in different settings, transmission, vaccine effectiveness and health care costs become available.

Session 6: Reporting guide for observational influenza vaccine effectiveness studies

Introduction

Observational studies can be used to inform uptake of influenza vaccines in National Immunization Programmes. However, such studies are susceptible to bias. Examples of such bias include the finding of a recent meta-analysis that the effectiveness of influenza vaccine against all-cause mortality is greater than its effectiveness against influenza-specific endpoints of hospitalisation for pneumonia and influenza-like illness (ILI). The proposed reporting guide for observational influenza vaccine effectiveness (VE) studies will be helpful to researchers and reviewers.

Recommendations

- IVIR-AC recognizes the value and supports the aim to develop a reporting guide for observational studies of influenza VE. IVIR-AC focal points have been identified to assist with further development.

- IVIR-AC recommends that development of this reporting guide not be construed as requirements for publication, although stratification of priorities (i.e., essential, desired and encouraged) may be appropriate.
- The guide should consider how to address potential sources of bias, such as health-seeking behaviour and confounding for both risk of ILI and likelihood to be vaccinated. The guide may indicate approaches to adjustment for such bias. Estimates of VE should also be accompanied with analysis of antigenic matching of the circulating strains, vaccine formulations, availability and access insofar as possible, and acknowledged in limitations if relevant data are unavailable.
- As a first step, the guide should focus on reporting VE studies, it may then also consider implications for enhancing test-negative study designs based on investigators' study aims and available data.
- IVIR-AC recognizes potential to extend comparable and appropriately adapted recommendations for VE studies for vaccines against other diseases. Collaboration with other groups developing guidelines (e.g. STREngthening the Reporting of OBServational studies in Epidemiology (STROBE)) may be helpful in that regard.

Introduction

Dr. R. Breiman opened the fifth 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 appraise guidance documents including methods to estimate disease and economic impact of vaccines.
- To advance techniques to assess cost-effectiveness of vaccines.
- To develop behavioural research to facilitate optimal and timely acceptance of vaccines.
- To define how disease and post-marketing surveillance should be conducted.

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.

Session 1: Non-specific effects (NSEs) of vaccination

Introduction

In April 2014, SAGE considered that non-specific effects (NSE) of vaccines on all-cause mortality warrant further research. SAGE recommended that IVIR-AC be tasked with providing advice on which priority research questions need to be addressed to inform policy decisions, and what kinds of studies and study designs would provide answers to these questions. SAGE outlined some considerations for IVIR-AC to include in their deliberations—namely, the assessment of the use of high quality randomized controlled trials where feasible (noting the substantial ethical and methodological challenges involved), with sufficient power to explore sex differences, and a priori defined and standardized immunological endpoints designed to answer the specific NSE question.

Between February 2016 and January 2017, the WHO Secretariat convened three consultations of the same group of experts to review NSE hypotheses that researchers have advanced, possible research questions that are related to these hypotheses, and trial designs that could effectively address such questions. In June 2016, IVIR-AC reviewed the ongoing work and acknowledged the progress made towards the refinement of priority research questions and the outlined trial designs. At the present meeting, the Committee was presented with two proposed trial designs developed through the ad-hoc expert consultations.

Review

General considerations. An initial presentation reviewed leading NSE hypotheses and how they have evolved over the last 20 years. Overall, it would be impossible to test all potential NSE hypotheses and questions with higher potential to impact immunization policies need prioritization. Given the anticipated size of potential trials and thus the required investment, it is desirable that additional public health gains of carrying out such trials are considered, such as the assessment of immunization schedules informed by new immunological and epidemiological evidence.

BCG administration at birth or deferred at 14 weeks of age. The proposed study is an individually randomized trial, which should preferably be placebo-controlled to protect randomisation. Its primary objectives are to measure mortality and severe morbidity in the first 14 weeks of life. With mortality as the primary outcome, the indicative sample size for both arms is 49,000 infants (when 90% power, a 0.80 risk ratio between two arms, and 2% mortality are assumed).

Administration of additional measles vaccine dose at 12–16 weeks of age. The proposed study would also include switching the administration of the third DTP or pentavalent vaccine (DTP/HepB/Hib) dose between ages 10 weeks and 9 months. It is an individually randomised, placebo-controlled, double blind trial and its primary objectives are to measure mortality and severe morbidity from 14 weeks to 2 years of age. With mortality as the primary outcome, the indicative sample size for the 4 arms is 110,000 infants (same assumptions for sample size estimation as for previous trial).

Discussion

A first point of discussion highlighted the importance to make the proposed studies relevant and avoid wasting resources. In particular, one should make sure that the research questions are relevant to policy and that appropriate design, methods and analyses are employed. A second point related to the feasibility to achieve the estimated sample size within a reasonable time period. For instance, infrequent institutional attendance of expecting mothers to prenatal health clinics may

slow enrolment in the proposed BCG trial and managing a study across multiple sites and countries (to expand the eligible birth cohort) would add operational challenges. A careful estimation of the needed sample sizes is necessary in the further development of the trials.

It was further discussed the advantage to tackle both the NSE issue and policy relevance of alternative immunization schedules. Also, IVIR-AC Members asked clarifications and offered suggestions on the several details of the proposed trials, which are reflected in the recommendations.

Questions to be addressed

- Does IVIR-AC have any comments on the proposed protocol drafts and future plans?

Summary and recommendations

Introduction

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Recommendations

- IVIR-AC endorsed the value of definitive evidence to confirm or refute the existence and magnitude of the impact of non-specific effects of vaccines on susceptibility to severe childhood infection in low and middle income countries, especially attributable mortality, and the potential follow-on implications for national immunisation schedules.
- IVIR-AC agreed that the two proposed trials emerging from the three ad-hoc expert consultations in 2015 and 2016 were the best options among the possible research questions and trial designs considered. Further development of these proposals will require careful consideration of the balance between feasibility and required sample size to exclude an impact on childhood mortality of public health importance, taking into consideration that the very implementation of a clinical trial is likely to reduce mortality in all arms.
- IVIR-AC noted that the required size and location of the trials will make them technically challenging and expensive to implement. If the trials are implemented, it is important to select sites carefully, with respect to both site and investigative team capacity and generalizability of trial findings. This will require a high level of coordination with national authorities and local stakeholders.
- IVIR-AC will review and comment on the two proposed protocols while they are being finalised.

Session 2: Tools to operationalize the WHO recommendations on the licensed dengue vaccine

Introduction

The prophylactic, tetravalent, live attenuated dengue vaccine CYD-TDV (Dengvaxia[®]) has recently been licensed by multiple countries in Asia and Latin America. The age indication varies by licensing country but most commonly is for individuals aged 9 to 45 years and living in endemic areas. Regional public sector programmes are occurring in Brazil and the Philippines.

The vaccine has shown moderate vaccine efficacy in Phase III trials. Vaccine efficacy varied by serotype, serostatus and disease severity. No elevated risk for severe adverse events or other safety signals for non-dengue endpoints were observed. However, in the third year of the trials, an elevated risk of hospitalisation due to dengue in vaccinated 2-5y old individuals was identified. This increased risk diminished in years 4 and 5. Such increased risk was not seen consistently among older age groups. One hypothesis for this observation is that the vaccine acts like a silent natural infection and hence primes yet unexposed individuals (a high proportion of the 2-5y old participants were seronegative at time of vaccination) to experience a more severe secondary-like infection when exposed after vaccination. Other potential factors include young age and delayed infection through short term protection.

A model comparison study assuming that the vaccine acts like a silent natural infection predicted that Dengvaxia, if introduced in a three dose schedule at 9 years of age, will likely reduce the burden of dengue disease by 10-30% in settings where more than 70% of vaccine recipients have previously been exposed to dengue. Where the proportion of seropositive individuals at vaccination was lower than 30% most models predicted a negative impact of vaccination.

In April 2016 this evidence was reviewed by SAGE and a vaccine position paper was published subsequently in July 2016. In this position paper WHO recommends that countries should consider introduction of Dengvaxia only in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease; seroprevalence should be approximately 70% or greater in the age group targeted for vaccination, and the vaccine is not recommended when seroprevalence is below 50% in the targeted age group. Vaccine introduction should be part of a comprehensive dengue control strategy.

National level decision makers now face the difficulty of translating these recommendations into practise, as representative seroprevalence data on high spatial resolution that is needed to adequately address the spatial heterogeneity of dengue transmission are generally not available today.

An expert consultation held in June 2016 concluded that seroprevalence is the best currently available indicator for identifying target populations to vaccinate. However, if no serological information is available from administrative units being considered for vaccination, efforts need to be made to estimate the likely seroprevalence in those regions. This session assesses a guide to best practices for dengue seroprevalence surveys for identifying target populations and a prediction model to infer dengue seroprevalence from surveillance data.

Review

A technical working group on generic dengue serosurvey design was established in July 2016 and a first draft is currently in circulation. The group proposes a school-based multi stage survey to estimate age-specific dengue seroprevalence in children. The essential age range to sample is the most likely target group for vaccination, e.g. 9-14 year old children. To minimise the risk that a past dengue outbreak obscures an otherwise generally lower transmission intensity and hence seroprevalence the working group recommends to also sample younger children, in particular in settings with irregular dengue epidemics. Including older children could provide additional information on dengue burden, but is considered optional from the working group perspective.

Countries should potentially classify administrative units into three strata of low, moderate and high expected seroprevalence. Sampling of the targeted strata (e.g. high only, or moderate and high) should be performed separately in each desired seroprevalence and age strata. First, a number of administrative units should be sampled for inclusion. Second, within each unit a number of schools should be sampled for inclusion. Third, a number of children should be included in each school.

A sample size calculator has been developed by the group. The sample size accounts for the multi stage design effect. The target precision should be such that the confidence interval half-width of the stratum and age specific seroprevalence estimate is 5 to 7% but no more than 10%. Seropositivity should be determined by indirect IgG ELISA and the group recommends that a subset of samples are validated by PRNT because of the low specificity of the ELISA in the context of co-circulating flaviviruses or flavivirus vaccination. The working group recommends a simple analyses that takes into account weighting, stratification and clustering to yield stratum and age specific seroprevalence estimates including associated uncertainty intervals. Furthermore, a regression model could increase the precision of the estimates of individual strata analyses.

Another group presented on the use of surveillance data to infer estimates of seroprevalence where such is absent. While data on dengue incidence is generally biased by differences in reporting and hence unreliable, the age distribution of cases can be used to infer the force of infection and hence seroprevalence, assuming that the likelihood for reporting is age-independent.

The approach has been validated against seroprevalence estimates from serological data in settings where both surveillance data and serodata were available. The predictive ability of the surveillance data model was in good agreement with the serodata. Also, predictions from all notified dengue cases and a dataset restricted only to those with Dengue Haemorrhagic Fever were similar.

A web interface has been created to allow selection of regions from a world map in order to obtain among other measures estimates of seropositivity of specific age groups. This map currently only holds prediction for a handful of settings where robust surveillance data has been made available to the group. Future plans include the incorporation of predictions from more countries and the extrapolation of these results via a geospatial model to achieve global coverage.

Discussion

IVIR-AC remarked that the Phase III trial used a neutralisation assay to determine seropositivity. While this is unfeasible for the serosurveys this limitation in comparability should be noted. Furthermore, both sensitivity and specificity of the proposed ELISA test are suboptimal and so a subset of samples should be validated using PRNT. Drawing blood from children may face relatively high refusal rates which need to be considered in the sample size and the communication strategy. A saliva assay, if feasible, may offer a less invasive alternative and also would require validation.

The development of more precise guidance on how to stratify regions into low, moderate and high burden was encouraged. Ideally this would be a systematic approach based on existing surveillance data. The prediction model could be employed as a tool to enable such categorisation from surveillance data.

Further IVIR-AC members suggested that the collection of additional covariate data including information on mobility could help reducing bias in the estimates. Similarly, the use of collected samples and the collection of additional samples to address additional questions relevant to public health should be explored. Alternatively, residual blood samples may offer sufficiently good seroprevalence data at minimal additional costs.

IVIR-AC suggested that the approach to predict seroprevalence from age-stratified surveillance data is useful in the absence of serological data. The presented maps would benefit from additional and more recent data, including unpublished sources. Consideration of previous approaches to estimate the global burden of dengue could be valuable to enhance input data quality and quantity. However, with the addition of surveillance data continued cross validation with serological data is needed.

The methodology for extrapolation of these findings to regions without surveillance data is still in development and hence was not featured in the discussion. However, IVIR-AC suggested that the web interface would benefit from additional information on the predicted impact of Dengvaxia at the chosen age of introduction in the selected region.

Questions related to generic guidance on dengue seroprevalence surveys:

- Are the methods for generic guidance adequate to address data needs for targeting vaccination with feasibility/affordability?
- What could be the role of regression modeling in informing vaccination policy for areas that have not been directly sampled?
- How do we deal with the issue of spatial heterogeneity in designing vaccine programs?

Questions related to Global Dengue Transmission:

- Are the methods of the tool appropriate for use of available serological and age specific surveillance data to help identify populations potentially suitable for vaccination?
- How can the user interface be improved to support decision-making?
- How do we deal with the issue of spatial heterogeneity in designing vaccine programs?

Summary and recommendations

Introduction

IVIR-AC agreed that the dengue seroprevalence survey guidelines, modelling using age-specific incidence data and transmission intensity map are useful tools. However, IVIR-AC affirmed the importance of maximising the efficiency of implementation of seroprevalence surveys, and further assessment should be given to opportunities to do so. These two activities should be well coordinated to inform the others.

Recommendations

The survey guidelines should be modified or expanded to take into account issues relevant to feasibility and value for effort expended such as:

- Ensuring serologic criteria used by serosurveys are as comparable as possible to those used in the clinical trials of vaccine.
- Greater clarity with respect to criteria for high, medium and low prevalence strata.
- Better definition is needed for the required level of assay sensitivity and specificity to enable an informative assessment of seroprevalence in each stratum.
- More detailed consideration of the influence of covariates other than age and school attendance is needed.
- Given the lack of capacity for neutralisation assays in many settings, identifying laboratory capacity to process neutralisation assays (validation purposes) for serum collections obtained in other countries would be valuable.
- The ethical implications of an opt-out approach for participation as well as the feasibility and utility of disclosing and explaining results to individual participants should be considered in accordance with usual practices for serosurveys and the situation in country.

To improve efficiencies, the following should be considered:

- The validity of salivary samples as an alternative to serum has been shown for some viral infections such as measles and rubella. Consideration of salivary samples, both as a means to increase study participation, and/or their collection simultaneously with serum to allow further studies of validity is potentially worthwhile in the context of this substantial global effort.
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- Efficiency will also be improved if the blood samples taken can also be used to address questions for other pathogens (e.g. as part of the assessment of measles elimination) or stored for future use, but this also has ethical implications for consent procedures.

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- The use of traffic light colour schemes on the map should be avoided as they may be misconstrued.
- The limited granularity in the map may create challenges in interpretation because of spatial heterogeneity in seropositivity within each geographical unit. This should be clearly caveated, and the impact of such heterogeneity on impact predictions should be explored in modelling.
- When new data are obtained, how close the previous predictions were to these data should be shown, along with how the results are changed by the new data.

- Showing potential vaccine impact can be useful, but this should be done only when such estimates are deemed to be sufficiently robust.
- There is a need to deliberately collect/collate data on African countries.

In addition, IVIR-AC would appreciate a more detailed description of the machine learning approach for producing the map. The Committee also recommends working with other groups doing similar work, as well as cross-validation with serosurveys as they become available.

Session 3 Measles mortality model

Introduction

Global and country-specific measles cases and mortality are estimated using a model developed by Pennsylvania State University. The model is used to track progress towards global measles elimination targets. The methods used were reviewed by QUIVER (former IVIRAC) in 2011. Since then several major methodological innovations have been incorporated, including (i) adding explicit age structure to estimates of cases (so that model outcomes can be fitted to age-specific case data that is now collected by WHO); (ii) changing the function relating the proportion of susceptibles in the population to the annualised attack rate to better approximate the threshold nature for herd effects and (iii) Stochasticity in the new model is now represented as binomial, rather than Gaussian as in the original model.

Review and discussion

A full dynamic SIR model was not used because available case numbers are only available on an annualised basis and hence such a model would need additional assumptions about within-year seasonality. However, the shape of the function appears to approximately the relationship predicted by an SIR model.

The model estimates measles cases and then uses a constant (over time) case-fatality risk (CFR) to estimate deaths. However, the Bill & Melinda Gates Foundation (BMGF) is funding a group at the Harvard School of Public Health to update a systematic review of measles CFR. Preliminary results from their work suggests that measles CFRs have changed over time.

The model appears to reproduce age-specific measles case data from high-burdened countries except for India. However, the age distribution of cases in India may not be reliable due to reporting biases.

Besides this model, several other groups publish measles burden estimates, including the Child Health Epidemiology Reference Group (CHERG) and the Institute for Health Metrics and Evaluation (IHME). All these groups show similar levels of decline in measles mortality over 10-year periods from the 2000s to the 2010s, but estimate absolute figures for measles cases differ slightly. CHERG estimates use data from this model though restrict to under 5 mortality (versus under 10 as this model generates), and have not used updated census population data in their most recent estimate (accounting for an additional 20,000 deaths. Finally, they must envelope the measles deaths within the total estimated deaths.

Questions to be addressed

- Does the committee have any comments/suggestions on further improvements or refinements in updating this model, given the known limitations in the data?

Summary and recommendations

Introduction

The methods used were reviewed by QUIVER (former IVIR-AC) in 2011. Since then several major methodological innovations have been incorporated, including (i) adding explicit age structure to estimates of cases (so that model outcomes can be fitted to age-specific case data that are now

collected by WHO), (ii) changing the function relating the proportion of susceptibles in the population to the annualised attack rate to better approximate the threshold nature for herd effects, and (iii) Stochasticity in the new model is now represented as binomial, rather than Gaussian as in the original model.

Recommendations

- IVIR-AC agreed that the updated data providing information on the age stratification of measles cases is an improvement, but cautioned that input data remain subject to reporting biases such as underreporting in outbreak situations, underreporting of subclinical, atypical cases and misdiagnosis, and that there are important within-country heterogeneities.
- Work to validate the functional form used by the current model to relate susceptibility to the annualised attack rate by comparing it to a fully dynamic SIR model is valuable and if not done, a justification for this should be articulated. The impact of incorporating age specificities in the functional form should be explored.
- There is a need to take into account additional coverage variables, including the association between MCV1, MCV2 and SIA coverage, as well as the duration of high MCV coverage.
- CFRs are likely to change over time, and should be explicitly taken into account when updated information becomes available.
- It is important to understand and communicate the reasons for the differences between estimates of global measles burden by WHO and other groups. A systematic comparison of measles disease burden models would be helpful.
- Data limitations that affect the ability to fit models to age-specific case data from India, especially those related to between region heterogeneity, should be explored.

Session 4: Hepatitis B impact model comparison study

Introduction

WHO has conducted comparisons of PCV, rotavirus, HPV, malaria and dengue models in collaboration with technical consultants under guidance of QUIVER. In 2015, IVIR-AC requested that WHO develop guidelines for such model comparisons. An overview of existing comparisons was presented and key questions were highlighted around:

- (i) What the objective of the comparison is,
- (ii) How models should be identified (e.g. through a systematic review) and selected for inclusion,
- (iii) What outcome measures should be examined,
- (iv) Whether modellers should be asked to run new simulations in order to understand the drivers of uncertainty, and
- (v) Whether models need to be externally or internally validated.

A brief framework to take these questions into account in a model comparison process was presented.

A systematic review of existing comparisons of vaccine models was presented to IVIR-AC in 2016, covering both comparisons not involving new simulations (mostly traditional systematic reviews) and those involving new simulations. The number of vaccine model comparisons has risen dramatically since the first paper in 1992, but only six of the 121 eligible articles involved new simulations. The most common comparisons were for HPV, influenza, and PCV vaccines and most of them only looked at cost-effectiveness rather than effectiveness outcomes. The majority of comparisons not involving new simulations focused exclusively or mainly on high-income countries. Comparisons involving new simulations more often focused on low- and middle-income countries, because four of the six articles were coordinated by WHO. However, comparisons involving new simulations often selected models to include using non-systematic criteria such as convenience samples (e.g. models known to the coordinators), while those not involving selected models more often used systematic criteria for searching and inclusion.

The next step will be to complete the literature review, highlight key areas for future work, draft guidelines, and convene a working group to finalise guidelines in this area.

Review

It was commented that systematic reviews of models with no new simulations were still useful to understand the state of the art and document the different assumptions around parameters and model structure. For cost-effectiveness studies, differences tend to be driven by vaccine price, disease burden, and vaccine effectiveness. Quantitative comparisons are most useful but also require a large number of papers (>15) in order to carry out robust subgroup analyses. Also, reviews have marketing value, so there may be a need for reviews conducted by groups representing different interests or funding sources. Not all reviews reach the same conclusions, and not all emphasise that cost-effectiveness conclusions are conditional on vaccine price, although this is important. Therefore, guidelines in this area would be useful, although there is a need to ensure that they would be strictly enforced by journal editors. Model comparisons with new simulations may be enhanced by making source code open-access, as this would enable groups to generate results without having to contact the original developers.

Developing guidelines for the field would be useful, particularly to establish basic organising principles for model comparisons. It was suggested that the model would need to be weighted for quality before being included in a comparison; this could be done using Approximate Bayesian Computation or Sequential Monte Carlo approaches, which can simultaneously be used for calibration and sensitivity analysis. Different aspects of the models (e.g. epidemiological or economic) may need different assessment criteria.

Discussion

IVIR-AC will be asked to guide the selection of the expert panel to develop the model comparison guidelines, taking into consideration the need to include:

- (i) Previous people who have done model comparisons,
- (ii) Journal editors, and
- (iii) Key organisations who are interested in model comparisons.

Involving funders may be useful so that investigators do not simply avoid journals with stricter guidelines.

Guidelines for both kinds of model comparisons (with and without new simulations) were generally found to be useful. Systematic reviews should ideally present objective quantitative indicators (e.g. the proportion of models that were cost-effective based on a particular threshold) as well as narrative conclusions that may be influenced more by the authors' subjective assessments. The guidelines may be useful in fields outside of vaccines as well, although there are vaccine-specific issues that may require field-specific guidelines. The guidelines should also take into account other relevant guidelines in the field, such as CONSORT.

It was questioned whether WHO was moving in the direction of having systematic criteria for the inclusion of models in future comparisons or IVIR-AC evaluations, as it was not always obvious why particular models were chosen. Gavi is also involved in model comparisons and would find guidelines useful, particularly if they presented both minimal criteria and gold standards for comparisons.

It was also clarified that sometimes model selection was made based on historical criteria, such as particular models being of interest to SAGE working groups. Additionally, the trend in more recent model comparisons has been towards open calls and more detailed comparisons involving new simulations.

It was felt that model harmonisation should be carried out to understand the drivers of variability between models, rather than to converge on a single point estimate or recommendation; as such, a term like "explaining dissonance" may be more helpful. There is also a need to distinguish between different drivers of uncertainty: model, parameter, and methodological uncertainty as well as uncertainty from generalising to other settings. Models may also differ in outcome measures used e.g. DALYS versus QALYs or year of results.

There is a danger in imposing standards that are too prescriptive to the point that they are not used. Guidelines should aim to create a consistent vocabulary for the process, establish guidelines for documenting the process of model comparison, and help people to understand the consequences of using approaches that may be less resource-intensive but more prone to bias.

Open-source code was found to be a good idea and consistent with the current trajectory for promoting the publication of data from trials. However, there need to be safeguards to protect the intellectual contribution of the original modellers so as not to discourage the development of complex models. The CRAN initiative (in which R code is made available through online repositories,

with appropriate credit to the originators) may provide an example. This seems to be an independent issue that may require a separate discussion. Apart from open-source code, a framework for registering models similar to clinicaltrials.gov may be useful.

Model weighing would be useful, particularly to prevent one group from dominating if they publish a number of poor quality models. There are lessons that may be learnt from other processes to evaluate models based on forecasting ability e.g. CDC's influenza modelling challenge prize. Ideally, the dataset used to fit the model should be separate from the validation dataset. Also, many models have problems not only with model structure, but with the data to which the models are fitted. There is a need to involve both subject experts and modellers in the process. In previous WHO modelling comparisons, there was a divergence between groups that had been modelling vaccination for a long time, and other groups that were relatively new to the field and could benefit from discussion with others.

A separate issue is to inform the use of models by decision makers to support decision-making. Here there may be a preference for multiple models that are not too similar. Funding agencies may also need suggestions about how they can structure interactions between funders, users, and model developers.

Model selection based on a systematic review is a good method to avoid selection bias, but it may miss models that are still in development or are unpublished. Hence it should ideally be supplemented by an open call.

Questions to be addressed

- Does IVIR-AC have any comments and/or feedback on the proposed plans for the comparative study of hepatitis B impact models?

Summary and recommendations

Introduction

The WHO Global Hepatitis Programme (GHP) and the Immunization, Vaccines and Biologicals (IVB) departments decided to collaborate to request IVIR-AC to compare the methodological approaches that have been used to estimate the Hepatitis B surface Antigen (HBsAg) prevalence in children 5 years of age, and sought the comments from IVIR-AC. The impact model comparison study should be done on the basis of epidemiological and service coverage estimates in terms of model structure and design, assumptions, data inputs. The objective is to identify and understand the most influential drivers of variation of the model estimates.

Recommendations

- IVIR-AC agreed with the overall plan and approach to reviewing and synthesising results from hepatitis B models with calibrated data sets and to leave aside disease progression for another comparative modelling exercise.
- The review should be expanded to include models set in high-income countries that could still be applied to LMIC settings, and static models, partly to ensure that the number of models is sufficient to draw conclusions. To this effect, the date range could also be gradually expanded to encompass a longer period than currently proposed (2009 – 2017). The feasibility of engaging researchers with models published over 10 years ago seems questionable, but may need to be investigated if the number of included models would otherwise be insufficient.

- Changes in hepatitis B prevalence beyond 5 years old should be included as a secondary outcome.
- The research question for which each model was developed should be included in the data extraction form.
- For pooled models, further methodological thinking is needed concerning objective criteria for assessing and weighing the models and on using jack knife methods to examine robustness for excluding models.
- Through systematic literature reviews and a call for interest relevant modelling groups should be identified and be brought together.
- Stratified analysis based on country epidemiology (very low, low, intermediate and high endemicity) categories may be useful.

Session 5: Typhoid vaccine impact and economic models

Introduction

WHO recommends vaccinating high-risk groups and populations against typhoid in the context of other control strategies. However there is limited vaccine uptake at the moment. A conjugate vaccine with longer duration of protection compared to previous vaccines has recently become available. The Pennsylvania State University and the University of Antwerp have been constructing a vaccine impact model and cost-effectiveness analysis in order to inform recommendations updated SAGE recommendations that are expected in October 2017.

The model is a dynamic SIR model with compartments for primary and secondary (subclinical) infections as well as chronic carriage. Transmission is possible via both short-term (i.e. food and environment) and long-term (i.e. water-borne) cycles. It is able to reproduce weekly case data by age from Vellore in 2000-2012.

Several strategies for use of the conjugate vaccine are evaluated, including routine vaccination at 6 months and a range of catch-up strategies at different age ranges. The magnitude of indirect protection is influenced by the role of chronic carriers. When fitted to data from cluster randomised trials in Kolkata and Karachi, chronic carriers are responsible for about 25-50% of transmission in Kolkata but close to 0% in Karachi. Parameters fitted to the Kolkata data were used in subsequent modelling because the data from Karachi were contaminated by high levels of migration.

The cost-effectiveness of vaccination was then evaluated at five settings with incidence and cost data from inpatient and outpatient hospitalisations: Kolkata, Delhi, Dong Thap, Kibera and Lwak. A health care provider perspective was used with vaccine prices at £1/dose, using a range of cost-effectiveness thresholds. Routine vaccination alone was cost-saving in two sites (Delhi, Dong Thap), cost-effective at 1xGDP/capita at two sites (Kolkata, Kibera) and cost-effective at 3xGDP/capita at one site (Lwak). However, some form of catch-up was found to be the optimal strategy at 1-3xGDP/capita. In sensitivity analysis using random forest analysis, key influential parameters were found to be the number of doses and probability of hospitalisation.

Future steps are to run the model for 54 Gavi countries with different strategies, vaccine coverage, doses and time horizons. Incidence, hospitalisation and cost data will be obtained from the literature and databases such as WHO-CHOICE. A systematic review and meta-regression will be conducted to estimate CFRs for each country. Value of information analysis will be used to identify countries and parameters associated with large decision uncertainty at different cost-effectiveness thresholds.

Review and discussion

When fitting the model to age-dependent incidence data, only the reproduction number and overall reporting rate were varied, assuming no age-dependencies. However, the sensitivity of blood culture was assumed to be age dependent, based on the amount of blood that could be collected at different age groups.

Costs in Delhi were over 10 times higher than in Kolkata due to use of private hospital charges. Costs from the two Kenyan sites were actually obtained from Zanzibar due to the unavailability of Kenyan costs.

There were concerns that the final cost-effectiveness conclusions in the 5 country analysis were too optimistically expressed, given that hospital costs may be over-estimated, vaccine costs were low and cost-effectiveness thresholds were high.

It would be ideal to include other public health interventions such as WASH as comparators, but the efficacy of such interventions is extremely poor so the information value of such an analysis would be questionable.

The cost-effectiveness analysis including the expected value of information analysis will be completed in time to be discussed for SAGE recommendations and Gavi investment strategy conclusions in 2017. Models will be updated as data from trials and field studies become available over the next few years.

Questions to be addressed

- IVIR-AC members were asked to provide feedback on the overall objective and plan for future work.

Summary and recommendations

Introduction

Currently WHO Strategic Advisory Group of Experts (SAGE) on immunization recommends vaccinating high-risk groups and populations against typhoid in the context of other control strategies. However, there is limited vaccine uptake at the moment. Conjugate vaccines with longer duration of protection compared to previous vaccines, and which appear to be immunogenic in infants, have recently become available though not widely licensed. Modellers at the Yale School of Public Health and the University of Antwerp have developed a vaccine impact model and cost-effectiveness analysis. This work has value in informing updated to the typhoid vaccine policy recommendations by SAGE in October 2017.

Recommendations

IVIR-AC appreciated the clear and transparent description of the typhoid modelling work, such as presentation of the model structure and fit to data. The epidemiological modelling work is sophisticated and well done, but both transmission modelling and economic evaluation aspects were noted to have data limitations at the moment. In particular, there were concerns over use of older data (eg. WHO-CHOICE costs from 2004), extrapolation of Zanzibar cost data to the Kenya setting, failure to acknowledge differential costs between urban and rural settings, and use of private sector user charges as a direct proxy of opportunity costs.

Key areas that should be improved include the following:

- Findings from the model should be considered in the context of other available typhoid vaccines (besides the conjugate vaccine) and non-vaccine interventions to control typhoid such as access to improved water, sanitation and hygiene (WASH) facilities. IVIR-AC noted the apparent lack of appropriate data for the latter analyses in the model. Further analysis may be more descriptive than quantitative recognising the potential challenge to interpret the direct impact of each intervention on disease reduction in a quantitative model.
- The impact of antibiotic use and antibiotic-resistant strains of typhoid should be considered, and if it is not included, its likely impact should be discussed.

- More realistic vaccine prices (besides \$1/dose) should be used, including in the base case.
- The use of 1-3xGDP/capita fixed cost-effectiveness thresholds should be avoided as they are not recommended by WHO for priority setting for country level decision-making.
- Data on hospitalisation rates, hospitalisation costs and age-specific case fatality rates (CFRs) should be improved, particularly for the 54 country modelling.
- The role of chronic carriers and asymptomatic/mild infection on disease transmission should be further investigated. If indirect (herd) protection is found not to have an important effect on cost-effectiveness, then this would justify future use of a static model for cost-effectiveness analyses on typhoid fever vaccination. This is partly because a static model is more transparent and adaptable to end-users.
- Uncertainty ranges around parameters should genuinely reflect model and parameter uncertainty since they are crucial to the value of information analysis.
- The use of malaria cost data to estimate the cost of managing typhoid could be an underestimation of the cost implications.

The vaccine impact and cost-effectiveness models should continue to be improved as data on varying level of disease burden in different settings, transmission, vaccine effectiveness and health care costs become available.

Session 6: Reporting guide for observational influenza vaccine effectiveness studies

Introduction

Randomised controlled trials (RCTs) provide the key evidence, including vaccine efficacy, needed for vaccine licensure. However, by design those studies favour relatively frequent disease endpoints to avoid unfeasibly large sample size requirements. As a result RCTs that led to the licensure of influenza vaccines have almost exclusively focussed on the prevention of lower respiratory illness. However, information is of limited value for decisions for or against the inclusion of influenza vaccines into national immunisation schedules, which primarily aim to limit the burden of severe illness and mortality.

Observational studies can address this evidence gap. However, those are more susceptible to biases. Examples for such bias include the finding of a recent meta analyses that the effectiveness of influenza vaccine against all-cause mortality is greater than its effectiveness against the more influenza specific endpoint of hospitalisation for pneumoniae and influenza like illness.

Review & Discussion

Helped by the recent increasing use of electronic health records the test negative study design offers a relatively robust and low cost method to estimate vaccine effectiveness and is increasingly used for influenza vaccines. However, interpretability and compareability of studies is hindered by inconsistencies in study design, reporting and analyses.

WHO has an interest in improving study transparency to enable adequate assessment. The STROBE reporting guideline for observational studies can be built upon but Influenza specific adaptations are needed. Also, STROBE guidelines are not necessarily met by all reports.

To help consensus in the public health community about the effectiveness of influenza vaccines WHO suggests to develop and publish recommendations for the reporting of influenza vaccine effectiveness studies and test negative designs in particular. A stepwise approach to increase transparency is suggested. In the first instance a guide of reporting standards based on STROBE would be developed. Support from IVIR-AC is sought and an official WHO publication would be the desired output. A second step would see the development of data reporting transparency guidelines.

Question to be addressed

Does the IVIR-AC have any comments/feedback to the presented plans for the development of the reporting guide?

Summary and recommendations

Introduction

Observational studies can be used to inform uptake of influenza vaccines in National Immunization Programmes. However, such studies are susceptible to bias. Examples of such bias include the finding of a recent meta-analysis that the effectiveness of influenza vaccine against all-cause mortality is greater than its effectiveness against influenza-specific endpoints of hospitalisation for

pneumonia and influenza-like illness (ILI). The proposed reporting guide for observational influenza vaccine effectiveness (VE) studies will be helpful to researchers and reviewers.

Recommendations

- IVIR-AC recognizes the value and supports the aim to develop a reporting guide for observational studies of influenza VE. Robert Breiman, Mitchell Weiss and Wilfred Ndifon will be IVIR-AC focal points to assist with further development.
- IVIR-AC recommends that development of this reporting guide not be construed as requirements for publication, although stratification of priorities (i.e., essential, desired and encouraged) may be appropriate.
- The guide should consider how to address potential sources of bias, such as health-seeking behaviour and confounding for both risk of ILI and likelihood to be vaccinated. The guide may indicate approaches to adjustment for such bias. Estimates of VE should also be accompanied with analysis of antigenic matching of the circulating strains, vaccine formulations, availability and access insofar as possible, and acknowledged in limitations if relevant data are unavailable.
- As a first step, the guide should focus on reporting VE studies, it may then also consider implications for enhancing test-negative study designs based on investigators' study aims and available data.
- IVIR-AC recognizes potential to extend comparable and appropriately adapted recommendations for VE studies for vaccines against other diseases. Collaboration with other groups developing guidelines (e.g. STRENGTHENING the Reporting of OBSERVATIONAL studies in Epidemiology (STROBE)) may be helpful in that regard.

Session 7 Closed session

Rabies modelling consortium

The SAGE working group on rabies is due to present draft recommendations to SAGE in October 2017, particularly in view of WHO targets to reduce global rabies deaths to zero by 2030. Multiple modelling streams involving vaccine business plans, demand projections and impact evaluations are needed, so a number of modelling groups working on these issues will come together at a meeting in Bangkok in April 2017. Three IVIR-AC members (Mary Amuyunzu, Yot Teerawattananon and Marc Brisson) will review the modelling material and potentially attend the meeting.

Haemophilus influenzae and Streptococcus pneumoniae burden of disease

A group of institutions have been working since 2006 on generating estimates for WHO of the burden of disease due to *H. influenzae* and *S. pneumoniae*. The estimates have recently been updated, and two IVIR-AC members (Peter McIntyre and Philippe Beutels) have been involved in reviewing the methods. The modellers have been able to address all the major comments from the IVIR-AC reviewers. However, minor concerns remain around incorporation of model uncertainty and the impact of pneumococcal vaccination that are difficult to address. IVIR-AC's recommendation is to use the most conservative estimate from the modelling work.

Malaria vaccine costing tool

A tool for estimating delivery costs of malaria vaccines has been developed by PATH and WHO. It will be discussed at the 20-21 September IVIR-AC meeting.

Multi-model comparisons

Marc Brisson has been leading on developing guidelines for multi-model comparisons. A systematic review of existing multi-model comparisons has been completed and will be written up for publication. The next step is to produce a commentary paper with appropriate guidelines in collaboration with IVIR-AC members as well as other experts with experience of comparative modelling and/or guideline development. A draft of this will be presented at the 20-21 September IVIR-AC meeting.

WHO will consult internally about future multi-model comparisons that need to be conducted. One possibility is on rotavirus vaccine impact modelling set in low and middle income countries, given the growing availability of post-vaccine introduction data that need to be interpreted. Influenza vaccine models are a further possibility, but will represent a very large undertaking given the vast literature and variety of vaccine target groups, modelling methods and settings that have been considered.

Annex 1: Agenda

Annotated IVIR-AC Agenda 2017

Wednesday, 1 February 2017

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
08.30-09.00	Registration			
09.00-09.30	Welcome	Introduction and Charge of the Committee		R. Breiman
<u>THEME: Research to minimize barriers and improve coverage of vaccines currently in use</u>				
09.30-11.00	Session 1: Non-specific effects (NSE) of vaccines	<ul style="list-style-type: none">- Introduction and context by P. Fine (10 min)- Summary of ad-hoc expert consultation on clinical trials for NSE held in January 2017 by R. Breiman (20 min)- IVIR-AC reviewers' comments (each 5 min)- Discussion (50 min)	<ul style="list-style-type: none">- Does IVIR-AC have any comments on the proposed protocol drafts and future plans?	<p>IVIR-AC members: M. Brisson Y. Teerawattananon</p> <p>WHO focal point: A. Vicari</p>
11.00-11.30	Coffee break			

THEME: Research to conduct impact evaluation of vaccines in use

11.30-13.00	Session 2: Tools to operationalize the WHO recommendations on the licensed dengue vaccine	<ul style="list-style-type: none"> - Introduction and context by K. Vannice (10 min) - Generic guidance on dengue seroprevalence surveys to target vaccination by N. Dean (10 min) IVIR-AC reviewer's comment (5 min) Discussion (20 min) 	<p><i>Questions related to generic guidance on dengue seroprevalence surveys:</i></p> <ul style="list-style-type: none"> - Are the methods for generic guidance adequate to address data needs for targeting vaccination with feasibility/affordability? - What could be the role of regression modeling in informing vaccination policy for areas that have not been directly sampled? - How do we deal with the issue of spatial heterogeneity in designing vaccine programs? <p><i>Questions related to Global Dengue Transmission:</i></p> <ul style="list-style-type: none"> - Are the methods of the tool appropriate for use of available serological and age specific surveillance data to help identify populations potentially suitable for vaccination? - How can the user interface be improved to support decision-making? - How do we deal with the issue of spatial heterogeneity in designing vaccine programs? 	<p>IVIR-AC members: D. Burke P. Beutels</p> <p>WHO focal point: K. Vannice</p>
		<p>Global Dengue Transmission Map by N. Ferguson and D. Cummings (15 min)</p> <p>IVIR-AC reviewer's comments (5 min)</p> <p>Discussion (25 min)</p>		

13.00-14.00	<i>Lunch</i>
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14.00-15.30	Session 3: Measles mortality model	<ul style="list-style-type: none">- Introduction and context by M. Patel (5 min)- Measles mortality model by M. Ferrari (20')- Subject expert reviewer's comments – A. Hinman (5min)- IVIR-AC reviewers' comments (each 5 min) Discussion (50 min)	<ul style="list-style-type: none">- Does the committee have any comments/suggestions on further improvements or refinements in updating this model, given the known limitations in the data?	<p>IVIR-AC members: P. McIntyre M. Amuyunzu</p> <p>WHO focal points: M. Patel</p>
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15.30-16.00	<i>Coffee/tea break</i>
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16.00-17.30	Session 4: Hepatitis B vaccine impact model comparison study	<ul style="list-style-type: none"> - Introduction and context by Y. Hutin (10 min) - Presentation of plans of comparative modeling study by M. Brisson (20 min) - IVIR-AC reviewers' comments (each 5 min) Discussion (50 min) 	<ul style="list-style-type: none"> - Does IVIR-AC have any comments and/or feedback on the proposed plans for the comparative study of hepatitis B impact models? 	<p>IVIR-AC members: P. Beutels G. Kang</p> <p>WHO focal point: Y. Hutin</p>
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17.30	Cocktail	<i>Venue TBD</i>
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Thursday, 2 February 2017

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
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THEME: Research to conduct impact evaluation of vaccines in use (continued)

09.00-10.30	Session 5: Typhoid vaccine impact and economic models	<ul style="list-style-type: none"> - Introduction and context by A. Bentsi-Enchill (5 min) - Transmission and impact model for typhoid vaccination by V. Pitzer (10 min) - Cost-effectiveness analysis for representative settings by V. Pitzer (10 min) - Next steps on extending CEA and expected value for information by J. Bilcke (10 min) - IVIR-AC reviewers' comments (each 5 min) - Discussion (45 min) 	<ul style="list-style-type: none"> - Are the models presented appropriate for global transmission/impact and CEA considerations? - Have all relevant scenarios and/or sensitivity analyses been adequately incorporated to guide SAGE policy questions and decisions of TCV use? - Are the methods proposed for EVI analysis robust? What if any, further analysis is recommended or required? 	<p>IVIR-AC members: Y. Teerawattananon D. Burke</p> <p>WHO focal point: A. Bentsi-Enchill</p>
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10.30-11.00 **Coffee/tea break**

11.00-12.30	Session 6: Reporting guide for observational influenza vaccine effectiveness studies	<ul style="list-style-type: none"> - Introduction and context by J. Ortiz (10 min) - Presentation of plans for the development of the reporting guide by J. Ortiz (20 min) - IVIR-AC reviewers' comments (each 5 min) - Discussion (50 min) 	<ul style="list-style-type: none"> - Does the IVIR-AC have any comments/feedback to the presented plans for the development of the reporting guide? 	<p>IVIR-AC members: W. Ndifon M. Weiss</p> <p>WHO focal point: J. Ortiz</p>
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12.30-13.30 ***Lunch***

CLOSED SESSION

13.30-15.00	Discuss written reports with new studies and updates of on-going studies reviewed by IVIR-AC	<ul style="list-style-type: none">- Hib/Sp disease burden estimates- Epidemiological and cost-effectiveness modelling for rabies vaccines- Malaria vaccine costing
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15.00-15.30 ***Coffee/tea break***

15.30-17.00	Discussion and write up of final IVIR-AC recommendations
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17.00 ***Meeting closure***

Annex 2: List of participants

Meeting of the Advisory Committee on Immunization and Vaccines-related Implementation Research (IVIR-AC)

Centre de Conférences Les Pensières, Veyrier du Lac, France
1-2 February 2017

Draft list of participants

Advisory Committee Members

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

Philippe Beutels, Associate Professor, Health Economics, Health Economics and Modeling Infectious Diseases Unit, University of Antwerp, Centre for the Evaluation of Vaccination, Universiteitsplein 1, Antwerp 2610, **Belgium**

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

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

Donald Burke, Dean of the Graduate School of Public Health and UPMC Jonas Salk Chair of Global Health, University of Pittsburgh, Pittsburgh, Pennsylvania, 15261, **United States of America**

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

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

Peter McIntyre, Director, National Centre for Immunization Research & Surveillance, University of Sydney, Cnr Hawkesbury Road and Hainsworth Street, Westmead, **Australia**

Wilfred Ndifon, Chair, Career Development Research, African Institute for Mathematical Sciences, 5 Melrose Rd, Muizenberg 7945, Cape Town, **South Africa**

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