Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC): summary of conclusions and recommendations, 1-2 February 2017

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 of 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.
- 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 public 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 (e.g. 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.