

**Immunization and Vaccine related
Implementation Research Advisory Committee
(IVIR-AC) recommendations September 2018**

(Final version 11 October 2018)

THEME 1: Research to minimize barriers and improve coverage of vaccines currently in use

Session 1: Global vaccine acceptance and demand

Introduction

The IVIR-AC working group on Vaccine Acceptance and Demand, which was established in March 2018, presented their draft terms of reference for review. The working group presented a draft generic IVIR-AC stakeholder framework for vaccine acceptance and demand. In addition, a project protocol was presented from South Africa guided by the IVIR-AC stakeholder framework to address essential features of vaccination acceptance and demand. Planned testing in South Africa was intended to inform the generic approach of IVIR-AC for HPV and other vaccination programmes in other country settings. Finally, as a tool to guide decision-makers, a draft country level dashboard for HPV was presented, containing information on population demographics, information on the national cervical cancer screening programme, HPV burden and prevalence, vaccination and vaccination impact to inform policy and monitoring.

RECOMMENDATIONS

Terms of reference of the IVIR-AC working group

- The Committee agreed on the presented terms of reference and proposed for the working group to: 1) map the current knowledge base to determine priority research questions, to guide focused support on existing gaps; and 2) establish a model of the determinants of vaccine decision-making, based on existing literature.
- It was proposed that IVIR-AC encourage development of behavioural modelling inspired by behavioural economics, incorporating psychological, cultural and other drivers to explain health behaviour change. IVIR-AC is in a good position to provide input on such studies given the diverse mix of disciplines represented on the Committee (modellers, economists, social scientists, anthropologists, psychologists, epidemiologists, EPI programme managers, etc).
- Ensure linkage with other ongoing projects and partnerships with stakeholders active in this area.

IVIR-AC Framework on vaccine acceptance and demand

- Consideration of equity should be emphasized to acknowledge that coverage problems are most acute in the most difficult to reach populations (e.g. with regard to school-based vaccination programs that miss children who do not attend school or drop out).
- The Framework should explicitly acknowledge variation in contexts and settings (e.g. school-based versus provider-based vaccination programs).

- The Committee recommended exploring quantitative and qualitative methods for understanding decision making, at minimum by providing a conceptual scheme showing the underlying processes (e.g. behavioural choices) about how decisions are made (diagram, or computational representations), which is amenable to quantification of input variables.
- Explore the use of the conceptual framework model to assess features of acceptance and demand and their interaction, and possibly derive input parameters, taking into account stakeholders.

Research protocol

- The Committee noted that the protocol does not include sufficient methods for assessing the use of the IVIR-AC framework, and it does not include adequate consideration of methods for testing the approach for use of the IVIR-AC framework.
- With regard to aims of the proposed research to inform and improve the HPV vaccination programme in South Africa, the IVIR-AC review identified several points that require further attention.
- Approaches should be explored to explicitly test the framework, considering what the counterfactual may be.
- The acceptability of the 1st dose of HPV vaccine in the South African study was good (80% or more), which raises the question why the coverage for the 2nd dose is lower. This may be due to low acceptance, but it is also possible that this is due to a health system problem in making the 2nd dose accessible (e.g. lack of follow-up) or the way the vaccine is offered (opt-in versus opt-out, school-based vs. practitioner-based). To explore this cause, the researchers are recommended to enquire about general vaccine acceptance and general health system issues, and whether HPV vaccine-specific issues (e.g., adverse events associated with dose 1) may have caused decreased uptake of the 2nd dose.
- The Committee considered the qualitative aspects of the protocol to overcome hesitancy to be well developed, but noted potential biases in the design of the study, particularly related to entry into the study (e.g. parents who decline vaccination may also be more likely to decline participation in the study).
- The researchers could inform in advance and only include participants who agree to take part in both rounds of interviews.

Country level dashboard

- The Committee suggested that the development of the dashboard should explicitly indicate target audiences of country-level users (e.g., researchers or policy makers).

- Methods for collecting and analyzing meta-data should be transparent; sources, quality and limitations of meta-data should be explicitly stated (e.g. show when data is derived from neighbouring countries).
- The Committee recommended exploring ways to ensure that country-level data are comparable and can be used to make comparisons, so as to avoid problems of measurement (e.g. influence of local culture).
- Continuous dialogue with decision-makers and local immunization program staff about their information needs should be established.
- Balance between iterative process and cost need to be considered in optimizing the use of the dashboard.

Session 2: Cervical cancer elimination model comparison

Introduction

In response to the global call for action to eliminate cervical cancer that was made by the Director-General of WHO in May 2018, a model comparison was undertaken to inform the cervical cancer elimination thresholds and the strategies towards global cervical cancer elimination. The individual mathematical models used in the cervical cancer elimination comparison study were presented as well as the collaborative model comparison work. Evidence generated by these epidemiological and economic modelling studies will inform the decisions made by the WHO Strategic Advisory Group of Experts (SAGE) on Immunization in October 2018.

IVIR-AC was requested to review the individual mathematical models and the collaborative modelling comparison exercise, in particular to address the following questions:

- Whether the Committee has any specific concerns on the modelling methods of the individual models used in the cervical cancer elimination comparison study;
- Whether the Committee's impression of the process, methods used and interpretation of the collaborative model comparison work for defining the cervical cancer elimination thresholds and the strategies towards global cervical cancer elimination are valid.

RECOMMENDATIONS

Overall recommendations

IVIR-AC finds that the individual models (i.e. Policy-1, Harvard, HPV-ADVISE and Spectrum model) used are well-established, well-suited for the purpose of this work and that the model comparison exercise was well conducted. In terms of framing the model results for policy making, IVIR-AC would like to see more emphasis on the public health impact of interventions over time, financial resources required, health systems implications, and the incremental cost-effectiveness of each intervention, which ideally should inform the development of evidence-based thresholds for defining elimination.

Assessment of individual mathematical models

- Although the individual models were not originally designed to explore very low cancer incidence targets in the distant future, the models included in this model comparison are all well-established and well-known for their vaccine and screening applications in multiple HICs and LMICs.
- The criteria and selection of models are transparent and appropriate, with only individual-based or hybrid models being included, and each modelling group willing and able to contribute time towards conducting these analyses. The Committee is impressed by the amount and the quality of the work already produced in a relatively short period of time.

- For the purpose of this comparison, the models were individually calibrated and validated to a sufficient variety of end points and in a sufficient variety of countries.
- The vaccination and screening strategies are varied, specific and mostly pragmatic enough to be potentially implemented in any country.
- The models are sufficiently distinct and compatible to explore the model uncertainty in estimating whether short and long-term intervention impacts can be attained, and if so, when these impacts could be expected through feasible combined screening and vaccination strategies.
- It would be instructive to estimate and display not only the total impact of the intervention packages, but to also estimate and display the effects of each component (e.g. of direct vaccine protection, of indirect vaccine protection, and of screening and treatment, and how these impacts vary over time). This could be done by HPV type.
- It is reassuring to see that the models, despite their substantially different structure and set-up, produce broadly similar results in terms of estimating the evolving impact of the various strategies over time.
- Recognizing that the purpose of model comparison is to understand better the unknowns in key drivers of results (i.e. achieving transparency on disease dynamics and processes), the Committee felt that harmonization, differences in parameterization, structural similarities and differences between the models should be transparently communicated.
- As a longer-term research agenda, if possible, more work should be done under assumptions of heterogeneities in geographical location or sexual network contact structures or both. It is likely that the long-term equilibrium level that is achievable may be directly related to the degree of such heterogeneities. Ideally there should be conversations between HPV modelers with modelers of HIV and other sexually transmitted diseases to develop data and methods to address such heterogeneities.

Collaborative model comparison

- The Committee acknowledges that the modelers responded to the questions of whether cervical cancer elimination is feasible, and if so what the strategies towards global cervical cancer elimination targets are. However, the Committee felt that it is more important to determine what the gains are at different milestones (e.g. 2030, 2045 or 2060) recognizing that vaccinated cohorts need time to grow and become adults eventually being protected (or not) against cervical cancer.
- IVIR-AC believes that the thresholds for elimination should not be defined in advance of the modelling work, but should be defined in light of evidence from

modelling regarding feasibility, cost-effectiveness, financial resources required, health systems implications, and public health impact of different options.

- The Committee indicated that focusing on longterm arbitrary elimination targets underemphasizes the most important public health impacts—which are the massive reduction in cervical cancer cases and mortality—whether or not such targets are formally reached in the distant future.
- The Committee has concerns about the use of the terminology of elimination and suggests an alternative term such as ‘massive reductions in disease’ or ‘advanced control of disease’.
- The time frame of up to 100 years to reach thresholds may give rise to concerns about the public health significance of the conclusions. Demonstration of the percentage decrease in cases accumulated at different points in time may be preferable, as it provides highly useful information about the impact of the different strategies over time. This could be presented as a complement to the results showing whether or not a specific strategy is able to push cancer incidence below the defined low threshold rates in the distant future.
- Aside from cancer incidence, intermediate outcomes should be considered such as the incidence of pre-cancerous lesions and detection of infection prevalence.
- The Committee suggests that it might be wise to revise the concept of these threshold targets in light of the model results (e.g. based on proportionate reduction instead of absolute incidence). There is a paradox in that the very same countries that will be unable to meet the arbitrary thresholds will benefit most in terms of reduced numbers of cases.
- As part of the planned next steps, the economic analysis should focus on the marginal costs and marginal benefits over time, both with and without discounting.
 - In terms of marginal benefits, these should include percentage of cases and deaths averted, life years gained and DALYs averted related to cervical cancer and other cancers.
 - In terms of marginal costs, care should be given to document the most influential time dependent and scale-specific costs of setting up and maintaining screening practices, as well as the marginal costs of ramping up and maintaining vaccination coverage at high levels. At the same time, consideration should be given to changing costs of vaccines, screening technology and cancer treatment over time; as well as the opportunity costs to the local health systems of embarking on cervical cancer control campaigns (e.g. diversion of human and physical resources toward campaigns rather than focusing on routine tasks).

THEME 2: Research to conduct impact evaluation of vaccines currently in use

Session 3: Total System Effectiveness (TSE)

Introduction

In response to IVIR-AC recommendations made in March 2018, the TSE project was revised. IVIR-AC's assessment regarding the methods and tools used to support country-level uptake of vaccines and/or R&D decisions were requested.

RECOMMENDATIONS

- IVIR-AC appreciated the work around TSE, and in particular found it commendable that the team had radically redesigned the platform after receiving feedback from country pilots and partners.
- The flexibility of the new TSE interface to allow countries to use self-defined criteria is excellent. However, TSE needs to be aligned with, and ideally embedded in, other priority-setting initiatives in countries, such as efforts to strengthen HTA and NITAG mechanisms. Doing so will help to avoid duplicating existing efforts in countries, such as priority-setting initiatives led by WHO, World Bank and iDSI.
- There is a need to ensure that TSE actually provides useful market signals to vaccine developers, including developers of vaccines targeted to LMICs, considering the long lead time (>10 years) needed to develop a new vaccine. It would be useful to get input from vaccine developers of characteristics of TSE that would be most helpful to them in making decisions about whether to try to develop and market potential vaccines.
- The name TSE suggests inclusion of more than vaccines and immunization, and so it may need to be reconsidered. The Committee suggests a name such as *Immunization related Health Technology Assessment (i-HTA)* or *Evidence based decision making for Priority setting of Vaccines and Immunization programmes (EPVI)*.

Session 4: Measles Rubella investment case and intervals between SIAs

Introduction

In March 2018 IVIR-AC set up a measles-rubella working group to assess measles-rubella modelling efforts related to the measles eradication investment case and the timing of SIAs. They reviewed the KidRisk model which was used to assess elimination goals which had already been reviewed by IVIR-AC's predecessor QUIVER in October 2011, September 2012 and November 2013.

Following the 2011-13 reviews, it was suggested that the model be revised and resubmitted to IVIR-AC. However, the model has not been reviewed by IVIR-AC since 2013. Over the last few months, it has been reviewed by the IVIR-AC measles-rubella working group, which concluded that further details would need to be clarified before it could recommend that the work be used to inform global policy.

As follow-up after the IVIR-AC meeting in March 2018, an update was provided on the modelling work to determine the optimal intervals between SIAs to achieve optimal immunity in populations, avoid measles outbreaks and make progress toward regional elimination of measles.

RECOMMENDATIONS

Investment case

- IVIR-AC agrees with the conclusions of the IVIR-AC measles-rubella working group.
- It is important to measure the impact of measles and rubella elimination activities on the overall immunization system, including for example, strengthening the 2nd year of life platform and implementing school entry checks for not only measles and rubella, but all recommended antigens and providing those vaccines to children in need.
- IVIR-AC supports having an alternative group modelling the impact of the elimination program to address some of the concerns raised with the current model, to potentially use innovative modelling approaches, and to obtain greater confidence in the results.

Intervals between SIAs

- IVIR-AC was impressed with the quality of the work presented on estimating intervals for new SIAs, the potential impact of various methodologies, and the analysis of the strengths and weaknesses of the various models used.
- IVIR-AC emphasizes that the models should be capable of indicating when to conduct national as well sub-national SIAs.

- For future modelling work, IVIR-AC suggests that interruption of transmission, defined as at least 1 year of no sustained indigenous transmission, is a critical outcome to be considered regarding SIA interval and frequency.
- IVIR-AC furthermore made several recommendations regarding the need and performance of SIAs within routine immunization programs:
 - The need for SIAs indicates a failure in the routine immunization program to achieve immunity levels needed to interrupt transmission. Considering potential concerns that SIAs may be disruptive to routine immunization systems as well as overall health systems, it is critical to document how SIAs impact these. Therefore, protocols should be developed to assist program managers in assessing the positive and negative impacts or opportunity costs of SIAs on the overall systems, as previously recommended by IVIR-AC.
 - When outbreaks occur after SIAs, it is important to investigate whether the cases are primarily due to accumulation of susceptible persons born since the last SIA (i.e. an SIA is needed earlier than predicted) or a problem with implementation and coverage of previous SIAs. The latter may require follow-up SIAs including older age groups. Outbreak investigations and better surveillance are required to identify and measure causes of immunization gaps.
 - While SIAs are needed now, the ultimate goal is a routine immunization system that is capable of inducing adequate population immunity to interrupt transmission, making SIAs unnecessary.

Introduction

Availability of new Vi-Tetanus Toxoid conjugate vaccines (TCV) is likely to increase the demand for evaluation of cost-effectiveness and affordability to inform national vaccination strategies. Currently there are few economic evaluation studies of typhoid vaccination and the studies that are available use a wide range of methodologies. IVIR-AC was asked to comment on draft guidelines for economic evaluation of typhoid vaccination.

RECOMMENDATIONS

- The Committee proposed that the similarities and differences between typhoid vaccine-specific and general guidelines for economic evaluation should be clearly articulated.
- A number of elements critical to conduct economic evaluations of typhoid vaccines should be emphasized further including:
 - the use of dynamic modelling to evaluate impact of chronic carriage;
 - the specification of essential unknowns/uncertainties (e.g. duration of vaccine protection);
 - the consideration of broader impacts such as reduction of antimicrobial resistance (AMR) and equity;
 - the description of “current practice” and health system constraints such as the delivery platforms utilized (routine vs. campaign delivery) and utilization of routine health services.
- The document would gain in clarity by:
 - using equations and diagrams to highlight the different modelling approaches;
 - advocating for rigorous model parametrization and quantification of uncertainty;
 - advocating for modelling of discrete entities when possible;
 - stressing out-of-sample validity and mentioning cross-validation as desirable;
 - highlighting consistencies with WHO's general guidelines on economic evaluations of vaccination programmes, and where the document adds further detail to these guidelines.

Session 6: Multi-Model Comparison guidelines

Introduction

In May 2016, evaluation of a systematic review of vaccine-related model comparisons, which was presented to IVIR-AC, indicated the need for standardizing the process and technical procedures to compare mathematical models. A meeting was held in June 2018 in London hosted by the London School of Hygiene and Tropical Medicine to learn from other infectious disease model comparison studies and to develop guidelines for multi-model comparison studies. A first draft of these guidelines was presented to IVIR-AC for feedback.

RECOMMENDATIONS

- The Committee endorsed the processes established for the development of the guidelines for multi-model comparisons.
- The document should emphasize that the purpose for model comparisons is to provide the best possible inputs into policy decision-making. Indeed, model comparisons are just one aspect of this process, which includes data sharing, conveying a sense of model ownership to decision makers, and conveying and communicating results. This whole process might better be referred to as the “meta-modelling” process.
- Early in any multi-modelling process, there should be discussion and explicit agreements about the mechanisms that are being represented in the models, such as what is known about the dynamics of disease transmission from person to person, the natural history of disease and disease expression, the efficacy of available treatments, and other fundamentals.
- Each modelling group should be free to represent and parameterize these processes as they see fit, but agreement of what is shared could allow a sharper analysis of differences of outcomes.
- To facilitate comparisons, each model should be described in several ways. Ideally each model should be fully described in words, in diagrams, in equations, and in computer code.
- A valuable “by-product” of model comparisons for decision support is the identification of critical gaps in scientific knowledge and in data availability that prevent robust and valid conclusions (e.g. value of information analyses). These gaps should be identified and presented to decision makers in the hope that they will invest in new research and data collection to advance future decision-making.
- IVIR-AC recommends that the guidelines for model comparisons:
 - Include recommendations on how to describe models, including how structures differ.

- Recommend the inclusion of a mixture of different types of models (different structures).
- Highlight what to do if model outputs differ.
- Recommend the use of intermediate outputs (e.g. infection) in addition to final outputs (e.g. disease).

THEME 3: Research to improve methods for monitoring of immunization programmes

Session 7: Data for risk analysis

Introduction

An unexpected worldwide surge in diphtheria outbreaks over the last few years, coupled with a global shortage of diphtheria antitoxin (DAT), highlights the urgency of understanding where possible outbreaks may occur in the future. An MS Excel-based tool developed by US-CDC and WHO was presented to IVIR-AC for review. The purpose of the tool is to predict the level of diphtheria outbreak risk by country in order to inform vaccination policy to prevent future epidemics, as well as to advise demand for DAT, assisting manufacturers with an appropriate timeline and quantity for production.

Researchers from the University of Pittsburgh introduced Project Tycho – Data for Health which aims to make existing data usable for country-level decision support.

RECOMMENDATIONS

Pragmatic tool to identify immunization gaps

- IVIR-AC recognizes the value of the Diphtheria risk survey form, designed for guiding EPI managers in high-burden countries.
- Further experience on how to keep data current and accounts of the experience of programme managers, who make use of these graded criteria-based assessments of risk to guide vaccination-related priorities, will help to further improve the survey methods and their effective use.
- Continued assessment of the correlation between predictions and outcomes and continued improvement of the tool.
- As the work proceeds, more sophisticated data analytic methods for deriving weights should also be considered to improve the usefulness of the survey data. These could be used to inform the value of weights given to different criteria, without needing to make the actual tool used by programme managers any more complicated.
- Consider using the risk model for diphtheria outbreaks as a template for other diseases.

Vaccine Decision Information Systems

- Notwithstanding needs for improved vaccine and population data, the efforts towards compiling various existing data at various levels of granularity is a welcome contribution to available resources.

- The current efforts to create a database based on FAIR data principles (viz., findable, accessible, interoperable and re-usable) are encouraged. Further consideration of how this data may be used for research and programme guidance at various levels of global, national and local health systems will benefit from further consideration and refinement as this work proceeds.