

**Report on the Immunization and Vaccine related
Implementation Research (IVIR)
Advisory Committee Meeting**

**Menthod St-Bernard, France,
24-26 September 2018**



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Abbreviations

AMR	Antimicrobial resistance
CDC	Centers for Diseases Control and Prevention
CEA	Cost-effectiveness analysis
CFR	Case fatality rate
CMMID	Centre for the Mathematical Modelling of Infectious Diseases
COI	Cost of illness
CHEERS	Consolidated Health Economic Evaluation Reporting
DALY	Disability Adjusted Life Year
DAT	Diphtheria antitoxin
DoV	Decade of Vaccines
EPI	Expanded Programme on Immunization
FPHVP	Full Public Health Value Proposition
Gavi	The Vaccine Alliance (Global Alliance on Vaccines and Immunizations)
GPS	Global positioning system
GVAP	Global Vaccine Action Plan
HIC	High Income Countries
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
HTA	Health Technology Assessment
iDSI	International Decision Support Initiative
IVB	WHO Department of Immunization, Vaccines and Biologicals
IVIR-AC	Immunization and Vaccine-related Implementation Research Advisory Committee
LMICs	Low and middle income countries
LSHTM	London School of Hygiene and Tropical Medicine
MCV1	Measles-containing-vaccines first-dose
MCV2	Measles-containing-vaccine second-dose
MCDa	Multi-criteria decision analysis
NITAG	National Immunization Technical Advisory Group
PPCs	Preferred Product Characteristics
R&D	Research and Development
SAGE	Strategic Advisory Group of Experts
SIA	Supplementary Immunization Activities
TCV	Typhoid conjugate vaccine
ToR	Terms of reference
TSE	Total System Effectiveness
Vi-PS	Vi-polysaccharide
WHO	World Health Organization
QALYs	Quality-adjusted life year
QUIVER	Quantitative Immunization and Vaccines related Research

Executive summary

THEME: 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 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 had a comment regarding 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 participants in advance about the two rounds of interviews and only include those who agree to this in advance.

Country level dashboard

- The Committee suggested that 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.

THEME: Research to conduct impact evaluation of vaccines in use

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 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 modeling comparison exercise, in particular to address the following questions:

- Whether the Committee has any specific concerns on the modeling 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 have each been 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 spend time to make 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 different and compatible to explore the model uncertainty in estimating whether short- and long-term intervention impacts can be attained, and if so, when they could be expected to be attainable 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 i.e. 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 are towards global cervical cancer elimination targets. However, the Committee felt that it is more important to determine what the gains are at different milestones (e.g. 2030, 2050 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 about feasibility, cost-effectiveness, financial resources required, health systems implications, and public health impact of different options.
- The Committee indicated that focusing on long term 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 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 over time of vaccines, screening technology and cancer treatment; 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).

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 a critical outcome to be considered regarding SIA interval and frequency is interruption of transmission, defined as at least 1 year of no sustained indigenous transmission.
- 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.

Session 5: WHO Guide on typhoid vaccine cost-effectiveness

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 used 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 vaccine should be emphasized further including:
 - the use of dynamic modeling 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 like 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 modeling approaches;
 - advocating for rigorous model parametrization and quantification of uncertainty;
 - advocating for modeling 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 endorses 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: Research to improve methods for monitoring of immunization programs

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 to predict the level of diphtheria outbreak risk by country to inform vaccination policy to prevent future epidemics, as well as 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.
- Continue to assess the correlation between predictions and outcomes and continue to improve 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 these 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.

Introduction

Dr. R. Breiman opened the 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: Global vaccine acceptance and demand

Introduction

Terms of reference of the IVIR-AC working group

The IVIR-AC working group on Vaccine Acceptance and Demand, which was established in March 2018, presented their draft terms of reference (ToR) for review and requested IVIR-AC for comments.

IVIR-AC Framework on vaccine acceptance and demand

The working group presented a draft generic IVIR-AC stakeholder framework for vaccine acceptance and demand. The framework identifies three relevant stakeholders based on functional role: 1) policy makers, 2) vaccinators, 3) community, and three core operational (essential) features of acceptance and demand: 1) awareness, 2) priority, 3) practice. Combined in a three by three table, these form the framework of essential features of acceptance and demand, and their particular relevance for stakeholder groups.

HPV vaccine acceptance and demand study protocol South Africa

The Reproductive Health & HIV Institute from the University of the Witwatersrand presented the results of an evidence review of HPV vaccination experience in South Africa as well as the findings of a stakeholder consultation, followed by an HPV vaccine demand and acceptance study proposal, in which the IVIR-AC framework was used. The study methodology consists of observation of vaccination sessions, in-depth interviews with vaccinators and educators, surveys of caregivers, and interactive workshops with adolescent girls. Planned testing in South Africa is intended to inform the generic approach of IVIR-AC for Human papilloma virus (HPV) and other vaccination programmes in other country settings.

Country level dashboard

Finally, an introduction to Project Tycho was given which aims to make health data available and accessible. As part of this, and 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.

Review

Terms of reference of the IVIR-AC working group

It was proposed to map knowledge gaps to help identify priority research questions. Specific research studies or projects addressing these questions can then be supported by the working group.

IVIR-AC Framework on vaccine acceptance and demand

Equity consideration should be added. This was illustrated with an example of school based HPV vaccination where the poorest and most marginalized population might not attend school or drop out leading to coverage problems in the most difficult to reach populations.

Research protocol

It was noted that the protocol does not include sufficient methods for assessing the use of the IVIR-AC framework, and it was proposed to add explicit methods for testing the framework. This includes consideration of a counterfactual.

A number of comments were made towards the quantitative methods of the proposal. There might be a risk of selection bias if parents who decline vaccination are also be more likely to decline participation in the study. Other methodological suggestions included considering to use one respondent and not multiple responders (i.e. both parents) per child, recruiting only participants willing to participate in both rounds, and include efforts to include vaccine decliners in interactive workshops.

Discussion

Terms of reference of the IVIR-AC working group

A suggestion was made for the working group to explore the use of behavioural modelling, to reflect the underlying processes of decision making. This may be done by a diagram or computational representation, with quantification of the input variables.

IVIR-AC Framework on vaccine acceptance and demand

The Committee discussed how the relevant vaccine related science could be considered, e.g. regarding surveillance data, safety and vaccine effectiveness. In some cases people might be deliberately hesitant and accept one vaccine but not another for specific reasons.

Country level dashboard

It is important to consider who the target audience of the dashboard is. IVIR-AC discussed the possibility of asking decision-makers about what information they need. It was proposed to provide data regarding methods in order to provide insight in the quality of the data. This should include being explicit if data is derived from neighbouring countries. Another point was about data comparability, for example in order to compare different countries (because if data is obtained from different sources they may represent different things).

Questions to be addressed

- What are IVIR-AC's comments/suggestions to the proposed ToR of IVIR-AC working group?
- What is IVIR-AC's assessment on the generic vaccine acceptance and demand framework proposed?
- Is the study protocol from South Africa aligned with the IVIR-AC generic framework on vaccine acceptance and demand? Are there any differences to be addressed?
- What are the impressions of IVIR-AC on the usefulness of the country level dashboard? Are there any suggestions for improvement?

Summary and recommendations

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-

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- Ensure linkage with other ongoing projects and partnerships with stakeholders active in this area.

IVIR-AC Framework on vaccine acceptance and demand

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- 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.

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- 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.
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Country level dashboard

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- 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 elimination thresholds and the strategies towards global cervical cancer elimination.

The following models are included in the model comparison: Policy-1, Harvard, HPV-ADVISE and Spectrum model. The details of the structure, including modelling of sexual activity, and calibration and validation examples/results of the Policy-1 model (developed by Cancer Council NSW, Australia), the Harvard Model (developed by the Harvard School of Public Health), and the HPV-ADVISE model (developed by Université Laval and Imperial College London) were presented to the Committee.

This was followed by a presentation of the collaborative model comparison work which showed whether elimination can be achieved, using which screening and vaccination strategies, and by which year. Future work is planned to show the cost-effectiveness of different elimination strategies for different countries and elimination targets.

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.

Review

The Committee showed appreciation for the work carried out by the individual modelling groups as well as for the joint model comparison exercise. The model comparison was thought to include appropriate models and was considered to be done well. The differences between the models that remain after the comparison should still be described in more detail.

Questions were raised regarding the public health benefit of having the threshold at 4 or 10 or even 15 per 100,000. These thresholds seem arbitrary, and reaching the threshold does not mean that screening and vaccination can be stopped. Having these thresholds as starting point of the model comparison exercise requires a time frame of 100 years. It was suggested that in addition it might be helpful to show percentage decrease in cases accumulated at different points in time. Furthermore, it was proposed to show proportionate reduction instead of absolute incidence, to also reflect the different starting points for different countries.

In relation to the concern about the 100 year time window, it was proposed to explore what might be done to reach the elimination target faster, e.g. what target product profiles would be needed. The Committee would also be interested to see confidence bounds of long-term projections.

In the next step cost-effectiveness will be modelled. Challenges were anticipated with the 100 years time frame of the analysis, for example related to the prize evolution of vaccines and the availability of other vaccines and cancer treatments. Furthermore, it was pointed out that there will be huge cost investments at the beginning of the program, while the benefits will take a lot of time to show.

It was mentioned that at low disease incidence, the underlying sexual behaviors in a country might determine whether or not the threshold is reached. It was proposed to explore how to represent these sexual network structures and to receive input from other modellers of sexual transmitted diseases.

Discussion

Concerns were raised about using the word elimination because this raises expectations among the public. Reaching an elimination target might also impact availability of resources, although activities (i.e. vaccination) do need to continue. Questions were also asked about the choice of the targets. It was thought to be important that there is a rationale for the values, linked to defining what elimination as a public health concern actually means.

It was thought to be important to show also other / intermediate benefits (e.g. infections, cases prevented) at intermediate timepoints, particularly if it is not possible to show reductions in mortality yet. Similarly, it was considered to be important to present relative reductions, considering that some countries might achieve massive reduction but do not achieve elimination targets.

Questions to be addressed

- Does IVIR-AC have any specific concerns/comments on the modelling methods of the individual models used in the cervical cancer elimination comparison study?
- What is IVIR-AC'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?

Summary and recommendations

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 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.

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 have each been well-established and well-known for their vaccine and screening applications in multiple high income countries (HICs) and low and middle income countries (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 spend time to make 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 different and compatible to explore the model uncertainty in estimating whether short- and long-term intervention impacts can be attained, and if so, when they could be expected to be attainable 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 i.e. 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 human immunodeficiency virus (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 are towards global cervical cancer elimination targets. However, the Committee felt that it is more important to determine what the gains are at different milestones (e.g. 2030, 2050 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 about feasibility, cost-effectiveness, financial resources required, health systems implications, and public health impact of different options.
- The Committee indicated that focusing on long term 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 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 Disability Adjusted Life Years (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 over time of vaccines, screening technology and cancer treatment; 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).

Session 3: Total System Effectiveness (TSE)

Introduction

In response to IVIR-AC recommendations made in March 2018, the TSE project was revised. Country pilots in Mali, Indonesia and Thailand were carried out. Lessons learned from the pilots were shared and plans and proposed activities for 2019-2022 were shared. IVIR-AC was requested to provide an assessment regarding the methods and tools used to support country-level uptake of vaccines and/or R&D decisions.

Review

The Committee highlighted the two aims for TSE: 1) to support evidence-based country decision making regarding vaccine choices, and 2) to provide market signals for R&D. With regard to the first aim, the Committee noticed that the process and instruments have really evolved after receiving pilot country feedback. It was also applauded that there was a move towards country ownership. However, it was suggested to give further thought about how to align TSE with existing HTA and NITAG processes and the broader health system strengthening agenda. It was noted that although TSE uses multi-criteria decision analysis (MCDA) methodology, there is still a need to match local criteria for funding such as for example cost-effectiveness thresholds.

Regarding the second aim, it was commented that it is important to balance the country needs with generating the data warehouse. Considering that the product development pathway takes at least a decade, it was also highlighted that there needs to be a continuous process to update signals as country needs might evolve. Another comment related to the need to address the changing vaccine landscape: it was suggested to target not just big pharmaceuticals but also domestic vaccine production and emerging manufacturers. IVIR-AC provided caution around using an undifferentiated instrument such as Preferred Product Characteristics (PPCs) – some markets have more weight for manufacturers – and it is important to ensure that individual country needs are still met. Finally, it was proposed to connect with manufacturers who would be receptive to a structured and consolidated signal from countries.

The Committee noted that the insights from the pilots were useful, showing that TSE was more useful for some countries than for others. Some practical issues were raised such as how TSE would work in real-life settings, the need to provide sufficient time for capacity building, to identify the niche for TSE considering existing initiatives in countries, and to ensure that the right stakeholders are involved at country level, e.g. surveillance.

Discussion

The idea for a data repository was well received; it was suggested this should be publicly available.

It was mentioned that the involvement of Regional Office is important, in particular in getting more support from countries, to coordinate related initiatives at country level, to collate information from countries, and in discussions with manufacturers.

It was found that the name TSE suggests inclusion of more than vaccines and immunization and it was suggested to consider changing the term TSE to something else.

Questions to be addressed

- Are all TSE recommendations from the IVIR-AC March 2018 meeting addressed?
- Does IVIR-AC have any feedback on the methods and tools used to support country level up take of vaccines and/or R&D decisions?
- Does IVIRAC have any suggestions on the proposed future scope and activities for TSE?

Summary and recommendations

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

Investment case

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.

Timing of SIAs

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. After feedback from IVIR-AC, the plan is to present findings to SAGE in 2019 and to revise the policy on SIAs.

Review

The need to repeat SIAs every 0-1 years indicates gaps in the routine implementation of measles vaccination. With increased coverage of measles-containing-vaccines first-dose (MCV1) (and second-dose (MCV2)), there would be less need for SIAs.

The committee highlighted that tools and models should be able to address sub-regional heterogeneity and not be able to identify when a SIA is needed, but also where.

When outbreaks occur after SIAs, it is important to investigate whether the cases are occurring in people targeted for a SIA and not reached, or in those born since the last SIA. These identify different problems and have different implications for action (i.e. problem with implementation and coverage of previous SIAs, versus a SIA is needed earlier than predicted). In-depth epidemiological analysis, such as outbreak investigations and better surveillance to measure this problem, are needed.

It is critical to document how SIAs can improve both the overall immunization system and more globally the health system. Therefore, protocols should be developed to assist program managers in assessing the positive and negative impacts of SIAs on the overall systems, as previously recommended by IVIR-AC. Having a protocol for assessment available may help planners of SIAs to more seriously consider how they can be used for a positive impact.

Discussion

There is a correlation between measles immunization coverage and measles outbreaks. Subnational aspects are important, particularly in large countries. It would be helpful to have a measure of heterogeneity of coverage and information on sub-national coverage to identify distinct areas with low coverage.

Regarding the Funk (F1) approach, which considered immunity profiles under 10 year olds and age-dependent mixing, it was questioned whether over-10 year olds should also be included in the model and how that might impact the results. The disadvantage may be that no serological data is available for many countries.

There was debate regarding the definition of outbreaks used in the models. An outbreak is not necessarily a major public health problem if it is contained and disappears on its own. Furthermore, these models are meant to inform guidance for hyperendemic countries with sustained transmission. It was thus questioned what the models are meant to explore and what the SIAs are meant to target: endemicity of outbreaks?

IVIR-AC discussed that the message coming out of this work should be carefully considered - promoting 0-1 year SIAs is not the right message. The need to ultimately eradicate transmission should focus the discussion, as opposed to how can we get some level of control.

It was emphasized that models can be used to answer three different questions: 1) how to control outbreaks and bring them to a minimum, including estimates of the timing of SIAs; 2) how to bring down sustained transmission; 3) how to achieve elimination. These questions should not be mixed up.

Questions to be addressed

- Does IVIR-AC have any comments/suggestions on the investment case and proposed ways forward?
- Are all SIA recommendations from the IVIR-AC March 2018 meeting addressed?

Summary and recommendations

IVIR-AC was informed about the comments of the IVIR-AC measles-rubella working group which reviewed the KidRisk model over the last few months and which concluded that further details would need to be clarified before it could recommend that the work be used to inform global policy. An update was also 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 a critical outcome to be considered regarding SIA interval and frequency is interruption of transmission, defined as at least 1 year of no sustained indigenous transmission.
- 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.

Session 5: WHO Guide on typhoid vaccine cost-effectiveness

Introduction

The two typhoid vaccines which have been previously licensed, live-oral Ty21a vaccines and parenteral/intra-muscular Vi-polysaccharide (Vi-PS) vaccines, have severe limitations, including limited (50-70%) effectiveness, a relatively short duration of protection, and they cannot be used in children under 2 years of age. A newer version of typhoid vaccine, Typhoid conjugate vaccines (TCVs) is likely to overcome those challenges and has recently become available. The first TCV, Typbar-TCV was prequalified by WHO in December 2017.

In October 2017, WHO's Strategic Advisory Group of Experts on Immunization (SAGE) re-emphasized the importance of the use of typhoid vaccines in tackling the increase in anti-microbial resistance in low- and middle-income countries, as well as for the control of endemic typhoid. The SAGE recommendations led to a WHO position paper, published in March 2018, recommending the use of TCV with a single IM dose for infants and children from 6 months of age and adults up to 45 years in typhoid endemic regions – routine programmatic use at 9 months of age, or in the 2nd year of life, with catch up to 15 years of age when feasible and supported by epidemiology.

In order for policy-makers to decide whether the vaccine should be used and how it should be delivered, several crucial sources of information are needed, including economic evaluation of vaccine strategies. The few existing economic evaluations of typhoid vaccination vary largely in methodology. A guideline was therefore developed to provide an overview of key theoretical concepts, best-practice methodologies, and guidance and recommendation on the economic evaluation of typhoid vaccination. The guidelines cover the following items: 1) framing the typhoid vaccination economic evaluation analysis, 2) the estimation of costs, 3) estimation and modelling the effect of vaccination, 4) presentation of results, and 5) assessing the impact of vaccination on a country's budget.

Review

It was suggested that the guideline should contain a description of how to account for variability in incidence and possibly case fatality rate (CFR) by age group. Clarity could be provided on how to capture indirect effects of different vaccination strategies for example, vaccination targeting food handler vs. school-based approach.

The possible impact of vaccine on equity aspects was discussed with regard to different geographical areas or socio-economic status. This is particularly important for cost estimates since the typhoid fever complications leading to severe and long-term health issues which are important cost drivers for typhoid fever. This becomes especially important for Africa as literature suggests proportion and severity of complications is higher in Africa than in other regions. Importance of costs related to long-term complications could be mentioned in guidelines.

Because of the high CFR, cost-effectiveness analysis (CEA) might want to emphasize the outcome deaths averted. The analytical horizon should be long enough to capture the

impact of the vaccine, for example, the impact of intestinal proliferation which lasts a life time.

The guideline currently accepts the use of both dynamic and static models. The question was raised whether the guideline should indicate a preference for dynamic models for a disease like typhoid which is complex because of several factors including chronic carriers and herd effects. The decision of what model to choose should be based on the WHO guidance on model selection.

The guideline mentions that it is important to compare with current practice. As vaccines are licensed in many countries (e.g. India), the usage of the vaccine in the private sector may be an important consideration which is not mentioned. Also, several countries have used other vaccines sporadically. Also important to consider is the current care seeking status.

Discussion

The policy/research question has significantly changed in last year due to WHO prequalification, the WHO position paper and Gavi support. The comparison of TCV with ViPS or Ty21a has therefore become less relevant. Directions for future research and example questions can be made more specific to the current context of typhoid fever. Relevant questions at country level are related to target / at risk populations, specific geographical locations, campaigns versus routine immunizations etc.

In estimating DALYs there is a large variability of disability weight used by previous studies ranging from 0.13 to 0.27. This difference can make big differences in DALYs estimates and thus the results of cost-effectiveness analysis. Furthermore, typhoid has variable severity (minor illness to complications) depending upon access to health care and many other factors. It was suggested that thought should be given to accommodate this complexity. It was also commented that new WHO guidelines (2018) seem to move towards quality-adjusted life years (QALYs) instead of DALYs. However, there is no data on QALYs for Typhoid. It is proposed that the Typhoid CEA guidelines provide some consideration on this.

The Typhoid CEA guidelines need to be consistent with WHO vaccine delivery costing guidance and tool to estimate vaccine delivery costs for TCV. Thought should be given on how we account for broader benefits of typhoid vaccinations such as done in the WHO Full Public Health Value Proposition (FPHVP) for Vaccines approach.

The guidance should capture the impact on the access to typhoid treatment in terms of the costs associated with it. This is linked to the perspective undertaken in the study. It was also commented that the guide should address how to account for costs related to deaths and loss of future income.

The terminology on efficacy, effectiveness and impact should be separated and clarified.

The guidelines briefly mention CEAs performed alongside clinical trials but does not address introductions/demonstration projects. It was proposed that the guidelines might provide further guidance on how to use actual data from field sites compared to data from

elsewhere, especially focusing on how long-term benefits (which may not be measured) be accounted for.

It was suggested that the Typhoid CEA guideline could should explicitly address how it relates to the WHO updated immunization CEA guidelines (upcoming 2018) and how it is of value in addition to that. The differences between the Typhoid CEA guidance and the generic guidance should be explained.

The guidelines describe treatment costs (cost of illness-COI) briefly at conceptual levels. There are several COI studies going on, funded by various donors. Their approach and duration of follow-up differs, making it difficult to compare results. As COI is an input parameter, will affect final CEA results. Should this guideline address COI issue in details? Perhaps economic burden estimation could be a separate guidance.

Is it important to consider friction costs, particularly when disability and care giving lasts for several months in long-term complications.

It was commented that the productivity costs shouldn't be included in BIA especially when payer perspective is selected.

Questions to be addressed

- Does IVIR-AC have any feedback on the CEA guide for Typhoid vaccines, specifically on the modelling chapter?

Summary and recommendations

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 used 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 vaccine should be emphasized further including:
 - the use of dynamic modeling 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 like 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 modeling approaches;
 - advocating for rigorous model parametrization and quantification of uncertainty;
 - advocating for modeling 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, IVIR-AC requested that WHO develops guidelines for multi-model comparisons to standardize the process and technical procedures to compare mathematical models. In May 2018 a systematic review of comparisons of vaccine models was published. Following a scientific conference and workshop in June 2018, organized in London by WHO in collaboration with the Centre for the Mathematical Modelling of Infectious Diseases (CMMID) at the London School of Hygiene and Tropical Medicine (LSHTM), a draft guideline was developed.

The guideline focuses on infectious diseases and interventions (not just vaccines), on comparison with new simulations (compared to published results) and has a focus on model comparison to support policy decision. The draft guideline for multi-model comparison of infectious diseases and interventions was presented to IVIR-AC, including principle and practice statements in five domains: 1) policy and research question, 2) model identification and selection, 3) harmonization, 4) exploring variability, and 5) presenting and pooling results.

In the next step input will be requested from the Multi-model Comparison Guideline Group. The target is to publish the guideline as a peer reviewed publication in a scientific journal.

Review

The use of the acronym of MMC for multi-model comparison was considered premature. Referring to the process as “meta-modelling” was considered more appropriate since the process of providing inputs into policy decision-making is a process which requires decisions to be made with input from multiple groups.

The model comparison guide should have a stronger focus on how to compare mechanistic components of models, such as for example dynamics of disease transmission from person to person, the natural history of disease and disease expression, the efficacy of available treatments, etc. Furthermore, it was proposed to enhance the focus on the process of data sharing and standardization (interoperability) and to emphasize the importance of explicit agreements on this early in the process. The role of model comparisons in the decision-making process was reiterated and it was commented that the policy makers should state the questions, not the modellers themselves.

It was proposed to make it a requirement to explain model structures and differences explicitly. This should ideally be done by describing and explaining models in different ways: in words, arrow diagrams, equations, and in code, in order to reduce ambiguity. Such description would also facilitate information exchange across models.

It was commented that best practice in modelling should be observed, and that individual models should adhere to guidelines for models, such as CHEERS guidelines. A quality assessment might allow exclusion of models based on quality. Furthermore, considerations of equity and distributional outcomes should be addressed.

It was commented that there are two applications of models for policy. First, in answering the policy question, and secondly in identifying what additional information is needed to answer the policy question better. It might be necessary to go back to the decision maker and explain that better data is necessary to provide a better answer to the question. This also requires the involvement of LMIC.

There was an emphasis on the fact that model comparisons require resources and that funders should not expect it to be done for “free”. It was proposed that the Gates Foundation might provide funding for model comparison consortia and that WHO might set aside funds for these efforts.

With regard to pooling and weighting of results, it was suggested that it may be better for this to be done by an external party rather than one of the modellers involved in the model comparison exercise because these might be biased.

Discussion

Questions were raised regarding the optimum level of harmonization and how to identify over-harmonization. It was also questioned whether the purpose of harmonization is to better understand the models, or to answer a policy question. It was proposed that presenting the sequential steps within a model comparison might be helpful, for example the first step would be to identify how the models vary at the beginning, then to explore model variation that account for differences in results, followed by harmonization. A comment was made that advice should also be given about the steps and processes to follow when outputs differ. Considering this, it was suggested that intermediate outputs should also be explored (e.g. so not just cervical cancer, but also infection stage). It was also proposed to recommend a use of a mixture of types of models (e.g. stochastic / deterministic, different parameter structure) in model comparisons.

This project could benefit from some more formalism about what models are, for example we can use models to make a prediction (forward problem), but this project is also implicitly talking about the inverse problem, which involves taking data to estimate the parameters of a system. Incorporating and formalizing inverse problem theory in the guidelines might help to add additional clarity on model choices, parameter choices, etc. It was thought to be useful to differentiate between model comparisons for policy (i.e. modelling to answer a clearly defined policy question (prediction)), and model comparisons to understand the drivers of models to understand differences between models.

Questions to be addressed

- Does IVIR-AC have any feedback on the model comparison guideline as follow-up from the IVIR-AC recommendations from May 2016?

Summary and recommendations

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 endorses 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)

Session 7: Data for risk analysis

Introduction

Pragmatic tool to identify immunization gaps

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 to predict the level of diphtheria outbreak risk by country to inform vaccination policy to prevent future epidemics, as well as advise demand for DAT, assisting manufacturers with an appropriate timeline and quantity for production. The tool uses data on vaccination coverage and vaccination strategy, disease burden, adequacy of surveillance reporting and current country instability and weighs these in an Excel-based tool.

Vaccine Decision Information Systems

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

Review

Explore possibilities for integrating different tools and datasets to enhance practical utility. If good data is available, then it can also be used to answer other questions.

The Committee emphasized the importance that data is available and accessible at local and national level, e.g. by National EPI managers. To encourage use it is also important that data is current and up-to date.

Data from different sources can be used but an algorithm is needed to merge data from multiple sources. This is also the case for GPS data. Different data sources can also be used to validate data or risk assessment tools.

Discussion

Quality of surveillance data should be improved and these data should be used. But, even if there are some concerns with regard to the quality of data, it is important to start using the data that is there. Once data is used, it creates an incentive to improve the quality of the data. For many analysis it is important to have an accurate estimate of the denominator, for example by getting data on every birth. This requires political will as well as resources.

Questions to be addressed

- Are current methods of the tool sufficient for a risk assessment?
- Are the inputs of adequate quality to predict risk?
- Are there any additional inputs needed to improve the accuracy/utility of the tool?
- Is the tool actionable, and useful for immunization programs?

Summary and recommendations

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 to predict the level of diphtheria outbreak risk by country to inform vaccination policy to prevent future epidemics, as well as 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.
- Continue to assess the correlation between predictions and outcomes and continue to improve 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 these 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.

Annex 1:Agenda

Annotated IVIR-AC Agenda 2018

Monday, 24 September 2018

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
12.30-12.45	Welcome	Charge of the Committee		R. Breiman
<i>THEME 1: Research to minimize barriers and improve coverage of vaccines currently in use</i>				
12.45-14.15	Session 1: Acceptance and demand	<ul style="list-style-type: none"> - Introduction and context by L. Menning (10 min) - Update IVIR-AC WG on Vaccine Demand and Acceptance including generic framework on vaccine acceptance and demand by M. Weiss (10 min) - HPV vaccine demand and acceptance study protocol South-Africa by F. Scorgie (10 min) - Country level dashboard to inform policy and monitoring progress by W. Panhuis (10 min) - IVIR-AC reviewers' comments (each 3 min) Discussion (40 min) 	<ul style="list-style-type: none"> - What are IVIR-AC's comments/suggestions to the proposed ToR of IVIR-AC working group? - What is IVIR-AC's assessment on the generic vaccine acceptance and demand framework proposed? - Is the study protocol from South Africa aligned with the IVIR-AC generic framework on vaccine acceptance and demand? Are there any differences to be addressed? - What are the impressions of IVIR-AC on the usefulness of the country level dashboard? Are there any suggestions for improvement? 	<p>IVIR-AC members: V. Nankabirwa J-D. Lelièvre</p> <p>WHO focal point: L. Menning</p>

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
<i>THEME 2: Research to conduct impact evaluation of vaccines in use</i>				
14.15-15.30	Session 2: Cervical cancer elimination model comparison	<ul style="list-style-type: none"> - Introduction by R. Hutubessy (5 min) - WHO's cervical cancer elimination roadmap by N. Broutet (10 min) - Introduction of Policy-1 model by K. Canfell (10 min) (<i>by WebEx</i>) - Introduction of Harvard model by J. Kim (10 minutes) - Introduction of HPV-ADVISE model by M. Brisson (10 minutes) - High level discussions/questions for clarifications on individual models (15 min) - Cervical cancer elimination model comparison exercise to inform the elimination targets and scenarios by J. Kim and M. Brisson (30 min) 	<ul style="list-style-type: none"> - Does IVIR-AC have any specific concerns/comments on the modeling methods of the individual models used in the cervical cancer elimination comparison study? - What is IVIR-AC's impression of the process, methods used and interpretation of the collaborative model comparison work for defining the cervical elimination thresholds and the strategies towards global cervical cancer elimination? 	<p>IVIR-AC members: P. Beutels D. Burke</p> <p>WHO focal point: R. Hutubessy</p>
15.30-16.00	<i>Coffee/tea break</i>			
16.00- 17.30	Session 2 continued:	<ul style="list-style-type: none"> - IVIR-AC reviewers' comments (each 5 min) Discussion (80 min) 		
17.30	Cocktail			

Tuesday, 25 September 2018

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
08.30-10.00	Session 3: Total System Effectiveness (TSE)	<ul style="list-style-type: none"> - Introduction and context by A-L Kahn (10 min) <i>(by WebEx)</i> - An update on TSE following the recommendations from IVIR-AC March 2018 and future scope by S. Botwright (15 min) - IVIR-AC reviewers' comments (each 3 min) - Discussion (45 min) 	<ul style="list-style-type: none"> - Are all TSE recommendations from the IVIR-AC March 2018 meeting addressed? - What is IVIR-AC's assessment regarding the methods and tools used to support country level up take of vaccines and/or R&D decisions? - What is IVIR-AC impression on the TSE implementation activities in Indonesia, Thailand, Mali and Rwanda? - Does IVIRAC have any suggestions on the proposed future scope and activities for TSE? 	<p>IVIR-AC members : M. Jit A. Lopez</p> <p>WHO focal point: A-L. Kahn</p>
10.00-10.30	<i>Coffee/tea break</i>			

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
10.30 – 11.45	<p>Session 4:</p> <p>Measles Rubella vaccines investment case and timing of SIAs</p>	<ul style="list-style-type: none"> - Introduction and context by A. Dabbagh (10 min) - Measles Rubella Investment Case by M. Jit (10 min) - An update of the timing of SIAs project following the recommendations from March 2018 by Mark Jit (10 min) - IVIR-AC reviewers' comments (each 3 min) Discussion (35 min) 	<ul style="list-style-type: none"> - Does IVIR-AC have any comments/suggestions on the update on the investment case and proposed ways forward? - Are all SIA recommendations from the IVIR-AC March 2018 meeting addressed? 	<p>IVIR-AC members: Q. Bassat W. Orenstein</p> <p>WHO focal points: A. Dabbagh</p>
11.45-12.45	Lunch			

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
12.45-14.00	Session 5: WHO Guide on typhoid vaccine cost-effectiveness	<ul style="list-style-type: none"> - Introduction and context by A. Bentsi-Enchill (10 min) - Presentation of WHO Guide by N. Chaiyakunapruk and G. Pitzer (20 min) - IVIR-AC reviewers' comments (each 3 min) - Discussion (30 min) 	<ul style="list-style-type: none"> - Does IVIR-AC have any feedback on the CEA guide for Typhoid vaccines, specifically on the modelling chapter? 	<p>IVIR-AC members: S. Verguet W. Ndifon</p> <p>WHO focal point: A. Bentsi-Enchill</p>
14.00-15.15	Session 6: Guidelines for multi-model comparisons	<ul style="list-style-type: none"> - Introduction and context by R. Hutubessy (5 min) - Multi-model comparison guidelines by S. den Boon (15 min) IVIR-AC reviewers' comments (each 3 min) Discussion (30 min) 	<ul style="list-style-type: none"> - What is IVIR-AC's assessment on the model comparison guide as a follow up from the IVIR-AC recommendations from May 2016? Are there any gaps concerning the guidelines? 	<p>IVIR-AC members: D. Burke S. Verguet</p> <p>WHO focal point: R. Hutubessy</p>
15.15-15.45 <i>Coffee/tea break</i>				
THEME 3: Research to improve methods for monitoring of immunization programs				
15.45-17.00	Session 7: Using available data to identify areas of risk	<ul style="list-style-type: none"> - Introduction and context by A. Henao-Restrepo (5 minutes) - Pragmatic tool to identify immunization gaps by S. Hadler (15 minutes) (<i>by WebEx</i>) - Options for risk analysis: Vaccine Decision Information Systems by W. Panhuis (15 minutes) 	<ul style="list-style-type: none"> -Are current methods of the tool sufficient for a risk assessment? -Are the inputs of adequate quality to predict risk? -Are there any additional inputs needed to improve the accuracy/utility of the tool? 	<p>IVIR-AC members: S. Sow M. Weiss</p> <p>WHO focal point: A. Henao-Restrepo</p>

IVIR-AC reviewers' comments (each 3 min)
 Discussion (30 min) -Is the tool actionable, and useful for immunization programs?

17.00-17.15	Summary Day 2	Summary of key conclusions and next steps	R. Breiman
17.15	<i>Adjourn</i>		

Wednesday, 26 September 2018

CLOSED SESSION FOR IVIR-AC MEMBERS ONLY

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
9.00-10.30	Formulation of IVIR-AC recommendations			
10.30-11.00	<i>Coffee/tea break</i>			
11.00 -12.30	Formulation of IVIR-AC recommendations			
12.30	<i>Adjourn</i>			

Annex 2: List of Participants

Advisory Committee Members

Quique Bassat, Pediatrician and ICREA Research Professor, ISGlobal Barcelona Institute for Global Health, Hospital Clínic - Universitat de Barcelona, Barcelona, **Spain**

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Victoria Nankabirwa, Professor, Department of Epidemiology and Biostatistics, School of Public Health, College of Health Sciences, Makerere University, Kampala, **Uganda**

Wilfred Ndifon, Chair, Career Development Research, African Institute for Mathematical Sciences, Kigali, **Rwanda**

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

*Samba Ousmane Sow, Director General, Center for Vaccine Development-Mali (CVD-Mali), CNAM, Ministère de la Santé, CNAM-ex-Institut Marchoux, Bamako, **Mali (regretted)***

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