

Report on Immunization and vaccine related implementation research

Advisory committee meeting

Chamonix, France

6-8 March 2018



Contents

Abbreviations	3
Executive summary	4
Introduction	13
Session 1: Rotavirus	14
Session 2: HPV	17
Session 3: WHO guide on standardisation of economic evaluations of immunization programmes.....	20
Session 4: Malaria decision-making and impact modelling.....	22
Session 5: Measles: optimal intervals between SIAs.....	25
Session 6: Vaccine hesitancy	28
Session 7: Development of full public health value propositions for the new vaccines framework	30
Session 8: Total System Effectiveness	33
Session 9: Standardization of delivery costing.....	36

Abbreviations

BMGF	Bill & Melinda Gates Foundation
C4P	Cervical Cancer Prevention and Costing Control Tool
CHAI	Clinton Health Access Initiative
EPI	Expanded Programme on Immunization
FVC	Fully Vaccinated Child
GAVI	The Vaccine Alliance (Global Alliance on Vaccines and Immunizations)
GBS	Group B Streptococcus
GVAP	Global Vaccine Action Plan
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
ICVA	International Collaboration for Vaccine Acceptance Initiative
IMR	Implementation Research and Economic Analysis
IVIR-AC	Immunization and Vaccine-related Implementation Research Advisory Committee
IVR	Initiative for Vaccine Research
LMICs	Low and middle income countries
LSHTM	London School of Hygiene and Tropical Medicine
MCDA	Multiple-Criteria Decision Analysis
MCV-1	Measles-containing-vaccine first-dose
MCV-2	Measles-containing-vaccine second-dose
NITAGs	National Immunization Technical Advisory Groups
PATH	Program for Appropriate Technology in Health
PCV	Pneumococcal Conjugate Vaccine
PDVAC	Product Development Vaccine Advisory Committee
PHVP	Public Health Value Proposition
RCT	Randomized Controlled Trial
R&D	Research and Development
ROBIN-I	Risk of Bias in Non-randomized studies of Intervention
SAGE	Strategic Advisory Group of Experts
SIA	Supplementary Immunization Activities
SIR	Susceptible-Infectious-Recovered (model)
TSE	Total System Effectiveness
UHC	Universal Health Coverage
UNICEF	United Nations Children's Fund
USA	United States of America
WHO	World Health Organization

Executive summary

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

Session 1: Rotavirus vaccine global research update

Introduction

The IVIR-AC received a summary of recent activities to update the evidence on rotavirus vaccines in collaboration with various partners: the London School of Hygiene & Tropical Medicine (LSHTM), Emory University, the US Centers for Disease Control and Prevention, the Program for Appropriate Technology in Health (PATH), the Rotavirus Accelerated Vaccine Introduction Network and the Bill & Melinda Gates Foundation. An ad-hoc consultation was held in October 2017 to review the evidence on the efficacy, effectiveness and safety of rotavirus vaccines, the burden of disease and epidemiology, the vaccine characteristics and operational challenges, economic considerations and a risk–benefit analysis. The committee concluded that the current policy on rotavirus vaccine did not require updating.

Researchers reported on the follow-up to recommendations made by the Committee during their meeting in September 2017 on methods for determining the age distribution of rotavirus disease, the efficacy of rotavirus vaccine and its waning efficacy and the benefit–risk of use of the vaccines. The Committee expressed its satisfaction with the follow-up and made additional remarks. The WHO Secretariat proposed research on introducing rotavirus vaccines and increasing their coverage.

Recommendations

Age distribution of rotavirus disease among children < 5 years

Explore determination of the age distribution by using mortality rates from diarrhoea or from rotavirus gastroenteritis, instead of mortality rates from all causes, for stratifying countries. Another approach would be to use a regression model on the full set of age distributions to predict the scale and shape of the log logistic distribution with different potential predictors.

- Investigate the heterogeneity seen in low and very low strata of under-5 mortality, as the median age at hospital admission for rotavirus disease ranges from 27 weeks in France to 101 weeks in Ukraine. Explain the limitations of existing surveillance systems and other study designs for reliable detection of the age distribution for clinic visits, emergency visits and hospitalizations.
- Consider other indicators, besides median age, for summarizing the weekly age distribution of hospitalization of children < 5 years for rotavirus disease. The report of the study should present the cumulative percentage of hospitalizations for rotavirus gastroenteritis by week of age, including key ages such as 6, 10, 14, 15, 26 and 52 weeks.
- Investigate shifts in the age distribution of rotavirus disease post-vaccination, and determine whether administration of rotavirus vaccine to infants is resulting in a shift towards a higher incidence of rotavirus disease in older children, and, if so, whether the shift is resulting in more severe or milder outcomes. The post-vaccination datasets should be extracted with the same methods used for the pre-vaccine analysis. Emory University will lead the analysis.

Rotavirus vaccine efficacy and waning efficacy

Randomized control trials (RCTs) on the efficacy of rotavirus vaccine have been stratified according to low (e.g. Europe, USA), medium (e.g. Latin America, Viet Nam) and high (e.g. Africa, Asia) mortality rates among children < 5 years. As for the age distribution of rotavirus disease, other stratifications could be tested, such as by diarrhoea-specific or rotavirus-specific mortality rates.

- The Vesikari scoring system could be used for “breakthrough” cases that occur after vaccination to measure whether they are more or less severe than earlier cases, perhaps in RCTs.
- Manuscripts reporting the results of RCTs should clearly state that they are individually randomized and not cluster-randomized, and the conclusion should not be drawn that rotavirus vaccines provide strong protection *only* in the first year of life. RCTs on vaccine efficacy (especially with non-cluster randomization) do not represent the real world with, e.g. herd effects. The authors of the manuscript should be careful in stating that the analysis of the 3-dose infant schedule in Indonesia suggests a protective effect of the vaccine in the first year of follow-up but a negative effect thereafter, as the issue of negative effectiveness may be controversial.

Benefit–risk of rotavirus vaccines

- In the benefit–risk analysis, the case fatality rates for intussusception among children < 5 years were derived from hospital studies, and an adjustment was made to account for children who would have died before reaching hospital. To make this adjustment, coverage with 1 dose of diphtheria-tetanus-pertussis vaccine was used as a proxy for access to hospital care for children with intussusception. The Committee considered that this is not an appropriate proxy, and other options should be considered.

Session 2: Human papillomavirus vaccine global research update

Introduction

The WHO Secretariat presented a comprehensive approach for increasing the introduction and uptake of human papillomavirus (HPV) vaccination.

To assess some of the identified barriers, the WHO Secretariat is: (i) ensuring that the most recent evidence is available to inform policy; (ii) coordinating a social and behavioural study in a low- or middle-income country to identify the barriers to introduction and uptake and translate it into messages suitable for different stakeholders; (iii) performing a costing study in a non-Gavi-eligible country to estimate the costs of various delivery strategies, using the WHO Cervical Cancer Prevention and Control Costing Tool (C4P), and to estimate cost–effectiveness using PRIME in one low- or middle-income country and in one upper–middle-income country; and (iv) modelling the impact of different vaccination strategies to assess whether vaccination schedules can be simplified.

Two activities were presented in detail:

- a template for improving vaccine acceptance and the effectiveness of HPV vaccination programmes, including the respective roles of policy-makers, clinicians, vaccinators and communities in raising awareness and the priority of HPV vaccination; and
- evidence from the consortium on evaluating use of a single dose of HPV vaccine that suggests that a single dose may be sufficiently immunogenic over time to prevent HPV infection and, ultimately, prevent cervical cancer.

Recommendations

Acceptance of vaccine

To improve vaccine acceptance, the Committee proposed that further attention be paid to the criteria for selecting countries for pilot implementation and consideration of several issues in planning and community acceptance:

- identifying barriers to receipt of the first dose and subsequent completion of series;
- acknowledging the limitations of school-based programmes in reaching adolescents who have left school; and
- opposition to or support of vaccination programmes by religious leaders, who may either question or endorse myths and rumours.

Single-dose HPV vaccine evaluation consortium

The IVIR-AC welcomed continued presentations by the consortium of independent reviews to ensure the quality of trials, non-trial data and evidence-based modelling of the impact of one dose. The consortium concluded that:

- Current data from trials and other studies have biases (from minor to important) that should be investigated and clearly presented to allow clear interpretation for decision-making on use of single-dose HPV vaccination.
- As the Risk of Bias in Non-randomized studies of Intervention (ROBIN-I) tool is used for systematic reviews of non-trial studies, it was proposed that the same tool be used to assess bias in the results of the clinical trials in Costa Rica and India, in which participants received only one dose as part of an interrupted series.
- Consideration should be given to whether the findings from the clinical trials in Costa Rica and India could be extrapolated to other settings, such as countries in Africa.
- Prospective studies of 1-dose and 2-dose schedules should be conducted in HIV-infected populations and among girls who are HIV-negative when vaccinated but become HIV-positive later. The results will be essential for anticipating the effects of these schedules on HPV disease burden in sub-Saharan Africa.
- The results of further implementation research are required to inform policy, especially comparisons of routine and campaign strategies. If a 1-dose schedule is supported by adequate evidence, it would help to overcome programmatic and administrative constraints.

Session 3: WHO Guide on standardization of economic evaluations of immunization programmes

Introduction

An update of the 2008 WHO Guide on standardization of economic evaluations of immunization programmes¹ was presented to the IVIR-AC for comment.

Recommendations

- The Committee noted that the 2008 guide had been updated throughout and substantially modified in relevant parts. The guide would be useful for national immunization technical advisory committees, other national decision-making bodies and agencies with an interest in vaccine evaluation. However, more guidance is needed for users and analysts in low- and middle-income countries (LMICs), where technical capacity is often limited and data are scarce.

¹ Walker DG, Hutubessy R, Beutels P. Vaccine. 2010;28(11):2356–9.

- The IVIR-AC generally agreed with the content of chapters that have been most radically changed, but noted that the following issues require further attention:
 - Expand to cover additional analytical approaches (e.g. macroeconomic models).
 - Ensure that the terminology used is consistent throughout the document.
 - Extend the description of how vaccine efficacy is estimated from parameters such as the “take” and “degree” of the intended impact, similarly to estimation of the duration of protection already described in the document.
 - Further clarify what determines the choice between static and dynamic models (using simplified figures and tables).
 - Add estimates of the cost to communities of vaccine delivery.
 - Provide recommendations on addressing uncertainty by describing the types of uncertainty and including guidance on when modelling could enhance value for information analysis.

Session 4: Malaria RTS,S policy decision-making framework and impact modelling

Introduction

Modelling is being used to evaluate the level of vaccine coverage that may benefit public health. Some protection is offered by 3 doses of the malaria RTS,S vaccine, and the 4th dose has been shown to be necessary to extend the duration of protection and to maintain protection against severe malaria, optimizing the potential public health impact of vaccination. Thus, the WHO Strategic Advisory Group of Experts (SAGE) has recommended a 4-dose regimen.

IVIR-AC was asked to provide feedback on the appropriate metric (or metrics) for estimating a threshold for RTS,S vaccine coverage that would predict impact and cost-effectiveness.

Recommendations

- There was consensus that the current presentation of “fully vaccinated children” could be confusing, as the population effects of high 3-dose coverage and lower 4th dose coverage could be misleading when presented “per fully vaccinated children”.
- The Committee strongly suggested incremental analysis of the effects of a 4th dose, without changing the denominator. The Committee proposed multiple metrics – per 100 000 children vaccinated, per at least 1 dose or per total population of children aged < 5 years – and suggested that results be given for both percentage effectiveness and cumulative effectiveness.
- The following scenarios were proposed:
 - Show a comparison of the impact of 3 doses versus no vaccination.
 - Show the impact of 4 doses (assuming the same coverage as with the 3rd) versus no vaccination.
 - Show the incremental impact of the 4th dose: impact of 4 doses (versus no vaccination) and impact of 3 doses (versus no vaccination).
 - Conduct sensitivity analyses for:
 - coverage of 3 doses, showing the additional benefit of the 4th dose, assuming the *same* coverage for 3 and 4 doses, and
 - coverage of 3 doses, showing the additional benefit of the 4th dose, assuming a *different* coverage of the 4th dose.
- The results should be easily interpretable by public health decision-makers.
- Include all-cause hospitalizations, on which data will be collected during the pilot study, as an outcome measure, in addition to those already planned.
- Detailed follow-up will be planned for the IVIR-AC meeting in March 2019. A conference call before the meeting may also be needed.

THEME: Research to conduct impact evaluation of vaccines in use

Session 5: Measles: optimal intervals between supplementary immunization activities (SIAs) and mortality model

Introduction

The current “rule of thumb” for determining the time between SIAs might have to be updated to achieve optimal coverage in populations, avoid measles outbreaks and make progress toward regional elimination of measles. The rule of thumb is to approximate the number of susceptible pre-school children and conduct an SIA when the number approaches the size of 1 birth cohort (approximately 2–5 years, depending on the level of routine immunization achieved). The Measles and Rubella SAGE working group is reviewing guidance on SIA intervals for the October 2018 SAGE meeting, and IVIR-AC will support work in this area before that meeting.

In response to the IVIR-AC recommendations in February 2017, Pennsylvania State University, USA, presented an updated measles mortality model.

Recommendations

Modelling of SIAs

- Set up a working group to provide detailed input before SAGE. The group will meet and provide feedback to the WHO Secretariat and the IVIR-AC Chair by mid-May on the simplest approach, which is not overly onerous to the health system. For example, annual SIAs are not feasible; however, a need for annual SIAs indicates that a country should strengthen routine coverage in order to achieve elimination.
- Conduct further work to understand the divergence between the models of Knapp and of Verguet & Jit from the restrictive rule of thumb method. It was noted that the methods do not include susceptibility in older age groups or the shortening of maternal protection.
- Analysis by the McKee method should be completed and presented to the Committee.
- A model used in Europe in the 1990s that was presented to SAGE in October 2017, which includes susceptibility in age groups ≥ 5 years, should be considered for use in subsequent work.
- WHO should design a protocol(s) to evaluate the positive and negative impacts of SIAs on the health system and on routine programmes in countries.
- Susceptibility is heterogeneous among countries (e.g. WHO subnational tool for measles susceptibility assessment). In the longer term, the IVIR-AC working group should investigate geographical variation in SIA intervals within countries. Targeted SIAs could be less disruptive to routine programmes but have the same benefits if there are “pockets” of susceptibility among people who are hard to reach.
- The Committee suggested that models be evaluated by comparing observed SIA intervals and achieved SIA quality and coverage with the timing and size of outbreaks and serological data.

Measles mortality model

- The IVIR-AC expressed appreciation to the analyst of the study for addressing the considerations from the previous meeting and following up issues.
- The Committee proposed a direct comparison of the new mortality model with simulations of standardized incidence ratios.

Session 6: Global vaccine demand and acceptance: research update

Introduction

The International Collaboration for Vaccine Acceptance Initiative (ICVA) is an open, international, multidisciplinary network of social and behavioural researchers linked to immunization programmes to address the demand for and acceptance of vaccines and vaccination. The ICVA presented its objectives and plans to the IVIR-AC for feedback.

Recommendations

- The Committee recognized the urgency of better integration of social and behavioural insights into programme planning. Strategies should be developed and implemented to generate and sustain demand and acceptance.
- The Committee expressed its appreciation for the opportunity to provide input at an early stage to the ICVA, which responds to the 2014 SAGE recommendations on vaccine hesitancy. The proposed plans of the network are aligned with the interests and previous activities of IVIR-AC in this area.
- The Committee proposed establishment of an IVIR-AC working group on demand and acceptance to serve as a link between IVIR-AC and ICVA, with the following objectives:
 - represent the broad interests of IVIR-AC in relation to research on vaccine demand and acceptance, especially by:
 - identifying research projects,
 - supporting research activities,
 - reviewing proposed strategies and methodology,
 - identifying current and potential vaccine- and vaccination-related issues that might benefit from social and behavioural insight and
 - linking with social and behavioural scientists in LMICs.
 - advise ICVA on:
 - scaling up implementation and evaluation of local interventions with innovative methods and strategies for community engagement;
 - facilitating partnerships and capacity-building to strengthen systems and build programme resilience;
 - expanding the evidence base;
 - developing and validating new metrics specific to acceptance that clearly distinguish acceptance from access; and
 - increasing the representation of LMICs on ICVA, especially programme managers.
 - Report regularly to IVIR-AC on progress in the ICVA's proposed plans of vaccine demand and acceptance

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

Session 7. Development of full public health value propositions for the new vaccines framework

Introduction

In September 2017, the Committee concluded that the “full public health value proposition” is a meaningful contribution to the field but that the approaches and terms should be standardized. A scoping review of investment cases of vaccines was presented, followed by a presentation of work in progress on the economic accounting framework applied to vaccines and immunization programmes in collaboration with the WHO Health Governance Financing

department. The work includes a prototype decision support model and interface, presented during the session, to help decision-makers to assess and evaluate data, parameters and outcomes for exploring different immunization policy options and scenarios. National immunization technical advisory committees and other decision-making bodies increasingly require appropriate, readily accessible information for policies on monitoring and assessing the impact of vaccines. A prototype decision support interface for country decision-makers to evaluate vaccine schedules, developed by LSHTM, was presented for feedback from IVIR-AC

Recommendations

Scoping review:

- The Committee suggested that more data be extracted from the scoping review on funders, evidence developers and target audiences (if available).
- Subgroup analyses should be conducted to determine the “political economy” and “trend” of evidence required by different groups for making a vaccine “investment case”.
- The Committee expressed its appreciation for attempts to centralize “all available methodological approaches” on vaccine investment cases in order to identify their similarities and differences, which would be helpful for all stakeholders in the field.
- Potential users will require guidance, especially in countries. The “pros” and “cons” of each methodological approach should be listed to direct country users to the appropriate method.

Economic accounting framework:

- The “two by two” table in part 4 of the scoping review simplifies the concept, but the document should make it clearer that this part is based on the assumption that a “societal perspective” is adopted for the analysis.
- It was suggested that the term “global economic investment case” be used for the economic component of the full public health value proposition.
- The vaccine investment strategy of Gavi should be incorporated into the framework.

Access to evidence to inform policy

- The Committee considered that the decision support model would be useful for countries. People would have to be trained in using the model for actual decision-making.
- It was recommended that software other than MS Excel® be used, although MS Excel® is already well known and widely used.
- The tool should be readily accessible, and the programme interface should be user-friendly.

Session 8: Total system effectiveness (TSE)

Introduction

The Bill & Melinda Gates Foundation-funded pilot project on TSE, which is led by the WHO Immunization Vaccines and Biologicals programme in collaboration with partners (e.g. PATH, CHAI, UNICEF, Gavi), was presented to IVIR-AC for feedback. The aim of the pilot project is to test “multi-criteria decision analysis” as a support for countries in choosing vaccine products and/or prioritizing pathogens.

Recommendations

- The Committee welcomed the ambitious TSE project but asked for a clearer definition of TSE and the specific goals of the project.
- It noted that it will be difficult to differentiate among vaccine products with regard to the many population outcomes (health benefits, equity, financial risk protection), especially in view of the uncertainties in input, structure and model.
- A simple MS Excel®-based static model may not be sufficient to capture such differences and uncertainties, particularly for vaccine products that differ negligibly in efficacy. TSE could, however, be useful for differentiating among vaccine products with regard to cold chain requirements, schedules and procurement prices.
- Implementation and modelling require further consideration and should be more systematic. It might be useful to involve anthropologists in finding out why vaccines are not taken up.
- The Committee therefore suggested that key informant interviews be conducted in countries to determine: where and by whom decisions are made; the important factors (rather than pre-designed components) and data gaps; and how and whether TSE will be used. These criteria should be revised before a pilot study is conducted, which should have clearly stated objectives. Formulating the objectives may require changing the timing of the pilot study.
- Mali was suggested as a potential country for a pilot study, in addition to Indonesia and Thailand.
- The Committee requested an update of the status of the TSE pilot project at the next IVIR-AC meeting, in September 2018.

Session 9: Standardization of vaccine delivery and operational costs

Introduction

In the past, IVIR-AC reviewed the micro-costing and planning tools supported by WHO to assist countries in estimating the cost of introducing and delivering new vaccines that often target populations who are not among the standard age groups of the Expanded Programme on Immunization, such as adolescents, adults, health workers and people with chronic diseases. The tools for costing vaccine delivery and introduction supported by WHO include C4P, the RTS,S malaria vaccines introduction costing tool and introduction costing tools for influenza vaccine, oral cholera vaccines and, recently, typhoid vaccines. As these delivery costing tools are based on different methods and sometimes different terminology, a plan to standardize delivery costs has been prepared.

Recommendations

- IVIR-AC concluded that standardization of the costing tools would be useful and necessary for comparing the costs of delivery within and across countries and by product or delivery strategy.
- Economic costs should be included for economic evaluations. Modelling may be required if economic costs are projected over long periods.
- IVIR-AC suggested that the standardization methods also include uncertainty analysis; most of the tools provide no means for including uncertainty or sensitivity analyses.
- The Committee suggested that guidance would be useful on where to obtain data, at what level (national, subnational or district level) and how to conduct sampling. In addition, the data collection tools and forms should be validated.

- Finally, the Committee suggested that the costing guide for standardization of delivery costs be linked with the Global Health Costing Consortium. Reference costs should be used as a checklist to ensure quality, and definitions and terminology should be aligned.

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 behavioral 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: Rotavirus

Introduction

The WHO rotavirus position paper was last updated in January 2013. There was a need to determine if updates of this position were needed. A scoping meeting was held by WHO in October 2017 and scientific results are presented following this meeting. The conclusion was that there is no need to update policy recommendations.

Review

Analyses were undertaken to determine if the median age distribution of rotavirus disease in unvaccinated populations is the same in all countries, and therefore if the peak of protection from vaccines coincides with the peak of risk of rotavirus disease.

Individual-level data from over 100 studies of unvaccinated cohorts was collated, and countries were stratified into quintiles of under-5 mortality for analysis. The lowest median age of infection was in the very high strata (38 weeks) which marks a trend that the median age of rotavirus disease decreases as under-5 mortality increases.

Determining if peak protection coincides with peak of risk also depends on the duration of protection offered by the vaccine. Analyses were undertaken, stratified by the same under-5 mortality quintiles, which show initial high protection followed by slow decline in countries with low/very low and medium under-5 mortality. In high/very high under-5 mortality countries, the initial efficacy is lower (around 70%) and rapidly wanes. In addition, there is high heterogeneity between countries.

A need was identified for updated estimates on the relationship between the number of deaths from rotavirus averted by vaccine, and number of deaths from intussusception due to the vaccine. As of 2012 the ratio was 600 rotavirus deaths averted per 1 associated intussusception death. If there were no age restrictions, this ratio would be 160:1 in the older age group that would be eligible. This work resulted in SAGE guidelines to remove age restrictions in 2013. There is now a need to update these ratios, in line with current, lower rotavirus mortality. As of 2015, in the age-restricted cohort, this is 570:1, and in the older age group, 280:1, which is a more favourable ratio than in 2012. These conclusions, made with conservative assumptions, support the current guidelines.

Discussion

Discussion centred on key points:

- Are these under-5 mortality quintiles the correct stratification for heterogeneity? Is there another grouping that is more immunologically relevant, which could also explain the differences in waning? These differences may be so pronounced that different functional forms are needed. Quintiles of rotavirus mortality specifically (not all cause), or diarrhoea mortality could be used.
- Median age of rotavirus may not be the ideal measure, given the distribution in risk by age, and heterogeneity within under-5 mortality groupings. Other measures are given in [to be] published manuscripts that more fully describe these distributions.
- The epidemiology of rotavirus is changing, and some of this is in response to both direct and indirect effects of vaccination, for example shifts in age distribution of cases. There may be implications for recommendations, and for country-specific decisions on schedules and introduction.
- Diarrhoea is a leading cause of mortality. Is the contribution of rotavirus to this mortality burden being overestimated?

- There may be a need for enhanced surveillance of rotavirus, especially in older age groups. Other infections require lab confirmation (e.g. measles), but this is not currently feasible in rotavirus, although the field is advancing, and genotyping is becoming more common.

Questions to be answered

Is this approach comprehensive, robust, and can it support decision-making?

- Does the committee support the current recommendations?
- If not, what else is needed?

Summary and Recommendations

The IVIR-AC received a summary of recent activities to update the evidence on rotavirus vaccines in collaboration with various partners: the London School of Hygiene & Tropical Medicine (LSHTM), Emory University, the US *Centers for Disease Control* and Prevention, the Program for Appropriate Technology in Health (PATH), the Rotavirus Accelerated Vaccine Introduction Network and the Bill & Melinda Gates Foundation. An ad-hoc consultation was held in October 2017 to review the evidence on the efficacy, effectiveness and safety of rotavirus vaccines, the burden of disease and epidemiology, the vaccine characteristics and operational challenges, economic considerations and a risk–benefit analysis. The committee concluded that the current policy on rotavirus vaccine did not require updating.

Researchers reported on the follow-up to recommendations made by the Committee during their meeting in September 2017 on methods for determining the age distribution of rotavirus disease, the efficacy of rotavirus vaccine and its waning efficacy and the benefit–risk of use of the vaccines. The Committee expressed its satisfaction with the follow-up and made additional remarks. The WHO Secretariat proposed research on introducing rotavirus vaccines and increasing their coverage.

Age distribution of rotavirus disease among children < 5 years

- Explore determination of the age distribution by using mortality rates from diarrhoea or from rotavirus gastroenteritis, instead of mortality rates from all causes, for stratifying countries. Another approach would be to use a regression model on the full set of age distributions to predict the scale and shape of the log logistic distribution with different potential predictors.
- Investigate the heterogeneity seen in low and very low strata of under-5 mortality, as the median age at hospital admission for rotavirus disease ranges from 27 weeks in France to 101 weeks in Ukraine. Explain the limitations of existing surveillance systems and other study designs for reliable detection of the age distribution for clinic visits, emergency visits and hospitalizations.
- Consider other indicators, besides median age, for summarizing the weekly age distribution of hospitalization of children < 5 years for rotavirus disease. The report of the study should present the cumulative percentage of hospitalizations for rotavirus gastroenteritis by week of age, including key ages such as 6, 10, 14, 15, 26 and 52 weeks.
- Investigate shifts in the age distribution of rotavirus disease post-vaccination, and determine whether administration of rotavirus vaccine to infants is resulting in a shift towards a higher incidence of rotavirus disease in older children, and, if so, whether the shift is resulting in more severe or milder outcomes. The post-vaccination datasets should be extracted with the same methods used for the pre-vaccine analysis. Emory University will lead the analysis.

Rotavirus vaccine efficacy and waning efficacy

- Randomized control trials (RCTs) on the efficacy of rotavirus vaccine have been stratified according to low (e.g. Europe, USA), medium (e.g. Latin America, Viet Nam) and high (e.g. Africa, Asia) mortality rates among children < 5 years. As for the age distribution of rotavirus disease, other stratifications could be tested, such as by diarrhoea-specific or rotavirus-specific mortality rates.
- The Vesikari scoring system could be used for “breakthrough” cases that occur after vaccination to measure whether they are more or less severe than earlier cases, perhaps in RCTs.
- Manuscripts reporting the results of RCTs should clearly state that they are individually randomized and not cluster-randomized, and the conclusion should not be drawn that rotavirus vaccines provide strong protection only in the first year of life. RCTs on vaccine efficacy (especially with non-cluster randomization) do not represent the real world with, e.g. herd effects. The authors of the manuscript should be careful in stating that the analysis of the 3-dose infant schedule in Indonesia suggests a protective effect of the vaccine in the first year of follow-up but a negative effect thereafter, as the issue of negative effectiveness may be controversial.

Benefit–risk of rotavirus vaccines

- In the benefit–risk analysis, the case fatality rates for intussusception among children < 5 years were derived from hospital studies, and an adjustment was made to account for children who would have died before reaching hospital. To make this adjustment, coverage with 1 dose of diphtheria-tetanus-pertussis vaccine was used as a proxy for access to hospital care for children with intussusception. The Committee considered that this is not an appropriate proxy, and other options should be considered.

Session 2: HPV

Introduction

WHO has produced a dashboard to aid HPV vaccine decision-making. Acceptance of the vaccine is critical to successful introduction.

The original HPV vaccine regimen was 3 doses, and has been introduced in some high-income countries, before changing to 2-dose regimens. There is some evidence that single dose vaccination may provide substantial benefit.

Review

Vaccine acceptance is complex, and although some issues are faced in all countries (e.g. sexuality/morality, the temporally-distant effects of HPV on cancer), there are issues particular to each context, and must be investigated as such. There may be variation in acceptance and/or approach needed for acceptance on a sub-national level.

Most evidence for the efficacy of single-dose HPV vaccination comes from RCTs where there has been interruption of 3-dose regimens.

In a trial in Costa Rica (iRCT, 7500 women, active control, 10 years follow up) some women did not complete three doses. In posthoc analyses, 1-dose participants appear to have protective effect from virological infection at 10 years post vaccination (although numbers are small). It is of note that the 1-dose regimen gives lower antibody titres (although these are higher than found following natural infection) although the threshold of protection (or whether this is a correlate of protection) is unknown.

A trial in India (2 vs 3-dose 4-valent non-inferiority trial, approx. 20,000 participants) was stopped, leading to over 5,000 women with single dose vaccination. Unlike in Costa Rica, there is unlikely to be bias in characteristics of women with 1 vs 2 vs 3 doses (although Costa Rica data have been investigated for biases). At 7 years, the 1 dose appears to offer equal virological protection compared to 2 or 3 doses.

There is currently a 1 vs 2-doses non-inferiority trial ongoing (20,000 participants, 4 arms) to firm up evidence. As well as the trials, there are systematic reviews and meta analyses in progress on single dose vaccination through the HPV vaccine consortium.

A major focus of previous recommendations was to investigate potential biases in use of non-randomised data, and formally assess risk of bias. This is being undertaken in meta analysis, although there are some complications of combining data that has different “buffer” time periods (time windows excluded to avoid including prevalent infections). The timeline for these results is approximately a year, although may be longer.

Modelling work with a 3 different models will be undertaken, but there will not be formal model comparison. In high-income countries, current models have found 2-dose are likely cost effective, even if protection lasts only 10 years, and early findings show similar for 1 dose. The cost effectiveness of the second dose depends on the duration of protection of the first dose, and therefore waning is critical. Next steps will be modelling of a LMIC.

Discussion

- Issue was raised about whether single-dose regimens would be off-label use, and what would happen to new vaccine manufacturers who do not currently have a

vaccine but may soon. There will be encouragement for manufacturers to complete paperwork for new suggested regimens, and for new manufacturers to consider this issue.

- Although participants of RCTs who received single-doses are considered “observational data”, the quality of these data depends on the reason for partial vaccination, and may not be subject to some of the same biases that would exist for single-dose recipients in the community. BMGF are keen to bring manufacturers on board and accelerate timelines for vaccination. Some new manufacturers will be prequalified.
- Acceptability of vaccination could investigate the acceptability of single doses, because completion of longer courses is a problem, and if 1 dose is more efficacious, that could help achieve coverage levels.
- There was discussion of implementation of delivery of HPV vaccination programmes, through campaigns or through health systems strengthening and improvement of routine programs. This may require increasing contact with health systems during life.

Questions to be answered

1. Are the methods appropriate?
2. Are there implementation research considerations which should be added?
3. Is there any further evidence required?

Summary and Recommendations

The WHO Secretariat presented a comprehensive approach for increasing the introduction and uptake of human papillomavirus (HPV) vaccination.

To assess some of the identified barriers, the WHO Secretariat is: (i) ensuring that the most recent evidence is available to inform policy; (ii) coordinating a social and behavioural study in a low- or middle-income country to identify the barriers to introduction and uptake and translate it into messages suitable for different stakeholders; (iii) performing a costing study in a non-Gavi-eligible country to estimate the costs of various delivery strategies, using the WHO Cervical Cancer Prevention and Control Costing Tool (C4P), and to estimate cost-effectiveness using PRIME in one low- or middle-income country and in one upper-middle-income country; and (iv) modelling the impact of different vaccination strategies to assess whether vaccination schedules can be simplified.

Two activities were presented in detail:

- a template for improving vaccine acceptance and the effectiveness of HPV vaccination programmes, including the respective roles of policy-makers, clinicians, vaccinators and communities in raising awareness and the priority of HPV vaccination; and
- evidence from the consortium on evaluating use of a single dose of HPV vaccine that suggests that a single dose may be sufficiently immunogenic over time to prevent HPV infection and, ultimately, prevent cervical cancer.

Acceptance of vaccine

To improve vaccine acceptance, the Committee proposed that further attention be paid to the criteria for selecting countries for pilot implementation and consideration of several issues in planning and community acceptance:

- identifying barriers to receipt of the first dose and subsequent completion of series;

- acknowledging the limitations of school-based programmes in reaching adolescents who have left school; and
- opposition to or support of vaccination programmes by religious leaders, who may either question or endorse myths and rumours.

Single-dose HPV vaccine evaluation consortium

The IVIR-AC welcomed continued presentations by the consortium of independent reviews to ensure the quality of trials, non-trial data and evidence-based modelling of the impact of one dose. The consortium concluded that:

- Current data from trials and other studies have biases (from minor to important) that should be investigated and clearly presented to allow clear interpretation for decision-making on use of single-dose HPV vaccination.
- As the Risk of Bias in Non-randomized studies of Intervention (ROBIN-I) tool is used for systematic reviews of non-trial studies, it was proposed that the same tool be used to assess bias in the results of the clinical trials in Costa Rica and India, in which participants received only one dose as part of an interrupted series.
- Consideration should be given to whether the findings from the clinical trials in Costa Rica and India could be extrapolated to other settings, such as countries in Africa.
- Prospective studies of 1-dose and 2-dose schedules should be conducted in HIV-infected populations and among girls who are HIV-negative when vaccinated but become HIV-positive later. The results will be essential for anticipating the effects of these schedules on HPV disease burden in sub-Saharan Africa.
- The results of further implementation research are required to inform policy, especially comparisons of routine and campaign strategies. If a 1-dose schedule is supported by adequate evidence, it would help to overcome programmatic and administrative constraints.

Session 3: WHO guide on standardisation of economic evaluations of immunization programmes

Introduction

The WHO Guide for standardisation of economic evaluations of immunization programmes was first published in 2009 to allow easier comparison of results between different vaccines (and other interventions). Contents draw from existing guidelines but are vaccine-specific and represent the start-of-the-art, including WHO-CHOICE guidance.

The guide reflects a compromise between acceptable practice (i.e. feasible evaluations under time pressure and limited biomedical/vaccine-specific understanding) and best practice (i.e. preferred scientific approach when time, knowledge and analytical capacity are less of an issue) and reflects the requirement to be relevant for local decision makers.

The main changes have been made in the sections on analytical framework, model choice and uncertainty. Regarding analytical framework, the section on evaluation types has been updated. A flow diagram helps users to select the appropriate type of economic analysis to use for a vaccine evaluation. For costing the changes have been predominantly on future unrelated costs recommending that these are not included, both because of the practical difficulties of estimation and because their inclusion involves conceptual and ethical issues concerning differences in incomes. However, if including future unrelated costs is a requirement of the reference case for the local policy maker, it is recommended to present the results with and without these costs. In chapter 5 on effects, there have been some changes regarding the duration of protection over time, and there is increased emphasis on use of QALYs. Chapter 6 on model choice emphasizes that an as simple model as possible should be chosen but not simpler (i.e. when to use a static vs. a dynamic model). The section on discounting has been updated to be in line with WHO-CHOICE guidance. Finally, there is updated information about the handling of uncertainty.

Review & Discussion

The target audience for the guideline should be users in LMIC. These countries are less likely to have their own guidelines and are therefore more reliant on the WHO's guideline for conducting cost-effectiveness analysis.

Can, everything that is recommended in the guideline, be done by researchers with limited resources and capacity, e.g. macroeconomic evaluation, cost benefit analysis, societal study perspective, dynamic modelling, and the use of QALY as an outcome measure. The section on the choice between static and dynamic models can be expanded to be more comprehensive and it can be presented in a better way.

Instead of recommending a societal perspective it might be better to require analysts to be explicit about the perspective and to point out any consequences of this choice. The choice of perspective is always and everywhere a matter for the study sponsors to determine together with any stakeholders they select.

Does the guideline help LMICs to overcome existing challenges in the following domains: lack of high quality local clinical data, poor reporting, insufficient data to conduct study from chosen perspective, lack of commonly accepted standard for economic evaluation, absence of locally relevant health state preference data suitable for QALYs or DALYS, inappropriate choice of comparator.

To improve the usability of the guideline, it could be a more succinct document. It is also important that language is used consistently throughout the document. There could be more information about the use of appropriate types of economic evaluation.

Questions to be answered

1. Does IVIR-AC have any feedback on the updated version of the WHO guide on cost-effectiveness, in particular on chapters with major changes compared to the 2008 version?

Summary and Recommendations

An update of the 2008 WHO Guide on standardization of economic evaluations of immunization programmes² was presented to the IVIR-AC for comment.

- The Committee noted that the 2008 guide had been updated throughout and substantially modified in relevant parts. The guide would be useful for national immunization technical advisory committees, other national decision-making bodies and agencies with an interest in vaccine evaluation. However, more guidance is needed for users and analysts in low- and middle-income countries (LMICs), where technical capacity is often limited and data are scarce.
- The IVIR-AC generally agreed with the content of chapters that have been most radically changed, but noted that the following issues require further attention:
 - Expand to cover additional analytical approaches (e.g. macroeconomic models).
 - Ensure that the terminology used is consistent throughout the document.
 - Extend the description of how vaccine efficacy is estimated from parameters such as the “take” and “degree” of the intended impact, similarly to estimation of the duration of protection already described in the document.
 - Further clarify what determines the choice between static and dynamic models (using simplified figures and tables).
 - Add estimates of the cost to communities of vaccine delivery.
 - Provide recommendations on addressing uncertainty by describing the types of uncertainty and including guidance on when modelling could enhance value for information analysis.

² Walker DG, Hutubessy R, Beutels P. Vaccine 2010;28(11):2356-9

Session 4: Malaria decision-making and impact modelling

Introduction

RTS,S is a vaccine developed for African children, which aims to prevent blood-stage infection. A phase III trial (11 sites in 7 countries, in 15,000 children, 4 dose regimen) found efficacy estimates of 30-60% depending on endpoint. There was no impact on all-cause mortality, although it was noted that all-cause mortality was low in participants of the trial. There were some adverse sequelae following vaccination that were rare and clustered at particular sites.

A January 2016 WHO position paper recommended pilot implementation of the vaccine to resolve some uncertainties, and to determine feasibility of introducing a 4-dose regimen, noting that this schedule requires new immunisation contacts.

Review

There will be a 3-country pilot implementation, with vaccine and control clusters of approximately 4,000 children, planned to start in late 2018. Each country will have slightly different schedules but the first dose will be around 5-6 months of age. This pilot is not aiming to form a binding decision for policymaking on use of this vaccine.

Modelling is being used to evaluate levels of vaccine coverage that may give rise to public health benefit. There has been robust model comparison of 4 models by different institutions (published work), and there are plans to continue with this.

Discussion

- The main focus of the pilot was discussed, whether it is on i) feasibility of the 4-dose schedule; ii) public health impact of a partially efficacious vaccine; iii) safety of vaccine. The pilot will likely answer all of these questions. There was discussion on whether the pilot could determine overall effectiveness of the vaccine, although many do not expect this vaccine to provide indirect protection.
- There was discussion of the safety signal from the original trial, and how this will be investigated in the pilot implementation. There is continued follow up on safety in the original trial, and there will be focus on safety signals in the pilot. There was discussion on the increased rate of cerebral malaria in the vaccine group. This could be the result of an efficacious vaccine causing an increase in the age of infection, and infections at older ages are more likely to result in cerebral malaria, as compared with infections in younger children, which are more likely to result in anaemia.
- It was highlighted that although there are implementation and control areas in the pilot, this is not a trial. However, there is still a need to maintain comparability between arms, for example by ensuring that health care provision (e.g. quality of hospitals) is equal in both areas. To that end, hospitals in study areas will be improved but with limited provision of extra staff, and will be aiming for 6 months of steady-state performance before start of the pilot.
- The 4th dose was discussed at length. Some protection is offered after three doses, but the 4th dose has been shown to extend the effect of the vaccine, and a 4-dose regimen has been recommended by SAGE. SAGE has requested from IVIR-AC some guidance on the definition of a “fully vaccinated child” as either having received 3 or 4 doses. This definition is important for showing effects of the pilot, because results using different regimens are often standardised as “per FVC”. It was highlighted that alternative dosing strategies are being tested already, including fractional dosing, e.g. as funded by BMGF.

- There was conclusion that the current presentation of FVC could be confusing, where population effects conferred by high 3-dose followed by lower 4th dose coverage can give misleading results when presented as “per FVC”. The committee strongly suggests not changing the number of vaccinated children when comparing 3 and 4 dose regimens, and to make clarify the incremental benefit of the 4th dose. It was suggested to compare the same coverage levels in each regimen to a baseline of no vaccination, giving results for both percent effectiveness as well as cumulative effectiveness. There was a call for making sure the results are easily interpretable by public health decision makers.
- There was discussion of the immune protection offered by the vaccine and whether other immunological measures can be presented, especially in relation to the 4th dose.
- Some evidence suggests there is a lower risk of meningitis in children who have had rabies vaccine, suggesting complex immunological interactions, but this interaction currently remains hypothetical.
- The vaccine is made with a hepatitis B antigen, and it is noted that the vaccine could potentially be evaluated as a replacement for hepatitis B vaccine.
- The pilot could also measure all-cause admissions in test areas, because there may be an effect on this due to reducing the impact of malaria as a co-infecter, e.g. synergism of malaria and pneumonia. It was noted that healthcare seeking behaviour may vary in the population, and may be correlated with propensity to be complete the vaccination schedule.
- The role of this vaccine in health inequities should be investigated. There is work underway to determine who benefits from the vaccine, and data will be collected on socioeconomic status of participants. It was suggested that social scientists investigate whether this is likely to a popular vaccine, both to gauge demand, and so vaccine-seeking for a malaria vaccine could be utilised to bring up coverage in other vaccines.
- The cost of the vaccine as well as the implementation was raised. Current analyses have assumed \$5 per dose, but there is no data on this. Usually delivery and distribution costs are borne by countries, so the pilot will be critical for determining these costs, especially because the regimen requires extra contacts beyond current EPI programs.
- Finally the geographic selection of areas for implementation, due to variation in malaria prevalence was discussed. This could be politically sensitive, and there may need to be coordination with country-level malaria programs, to support those where there may already be geographically targeted interventions in place.

Questions to be answered

1. Are the model inputs and outputs appropriate?
2. Which definition of a fully vaccinated child should be used (3 or 4 dose)?
3. Should the group only model outcomes that will be shown in the pilot? (??)
4. What criteria of impact are most useful and appropriate for making an interim recommendation?
5. Are there further modelling questions and analyses needed for policy recommendations?

Summary and Recommendations

Modelling is being used to evaluate the level of vaccine coverage that may benefit public health. Some protection is offered by 3 doses of the malaria RTS,S vaccine, and the 4th dose has been shown to be necessary to extend the duration of protection and to maintain

protection against severe malaria, optimizing the potential public health impact of vaccination. Thus, the WHO Strategic Advisory Group of Experts (SAGE) has recommended a 4-dose regimen.

IVIR-AC was asked to provide feedback on the appropriate metric (or metrics) for estimating a threshold for RTS,S vaccine coverage that would predict impact and cost-effectiveness.

- There was consensus that the current presentation of “fully vaccinated children” could be confusing, as the population effects of high 3-dose coverage and lower 4th dose coverage could be misleading when presented “per fully vaccinated children”.
- The Committee strongly suggested incremental analysis of the effects of a 4th dose, without changing the denominator. The Committee proposed multiple metrics – per 100 000 children vaccinated, per at least 1 dose or per total population of children aged < 5 years – and suggested that results be given for both percentage effectiveness and cumulative effectiveness.
- The following scenarios were proposed:
 - Show a comparison of the impact of 3 doses versus no vaccination.
 - Show the impact of 4 doses (assuming the same coverage as with the 3rd) versus no vaccination.
 - Show the incremental impact of the 4th dose: impact of 4 doses (versus no vaccination) and impact of 3 doses (versus no vaccination).
 - Conduct sensitivity analyses for:
 - coverage of 3 doses, showing the additional benefit of the 4th dose, assuming the same coverage for 3 and 4 doses, and
 - coverage of 3 doses, showing the additional benefit of the 4th dose, assuming a different coverage of the 4th dose.
- The results should be easily interpretable by public health decision-makers.
- Include all-cause hospitalizations, on which data will be collected during the pilot study, as an outcome measure, in addition to those already planned.
- Detailed follow-up will be planned for the IVIR-AC meeting in March 2019. A conference call before the meeting may also be needed.

Session 5: Measles: optimal intervals between SIAs

Introduction

High coverage of measles vaccine coverage has historically been achieved through routine immunisation programs, and supplemental immunisation activities (SIAs) to target particular age groups. Measles milestones on coverage, incidence, and mortality reduction were set by the World Health Assembly in 2010, and GVAP goals on elimination of measles (and rubella) were endorsed in 2012. The current “rules of thumb” for determining the time between SIAs may need updating, in order to achieve optimal coverage in populations, and avoid measles outbreaks. The rule of thumb requires monitoring accumulation of susceptible pre-school children and conducting an SIA when the number approaches the size of 1 birth cohort (approx. 2-5 years). The Measles and Rubella SAGE working group is reviewing guidance on SIA intervals for the October 2018 SAGE meeting, and IVIR-AC aims to support work in this area ahead of the meeting.

Review

Since the last meeting, there has been effort to improve the methodology behind the “rule of thumb” for determining the SIA interval. 6 methods for determining the optimal SIA interval were presented, all using birth rates in countries: i) permissive rule of thumb (the interval is as the population crosses the threshold); ii) restrictive rule of thumb (the interval is before the population crosses the threshold); iii) Knapp method (birth cohort model corrects susceptible population for vaccine coverage and efficacy); iv) Verguet method (mathematical method assuming that an SIR model is at equilibrium); v) McKee method (work is currently incomplete. Includes MCV1 and MCV2 coverage by age); vi) Funk method (includes contact patterns of children as well as age-specific susceptibility). The complexity (and potentially the realism) increases for each method, although Funk can only be used in countries with a validated contact matrix defining mixing within the population. Comparison of permissive and restrictive rule of thumb with Knapp and Verguet show that the permissive usually gives the longest SIA interval, and although there is some agreement with the restrictive rule of thumb, there needs further investigation into the disagreements and the reasons behind those disagreements. For the few countries that Funk can be used, it always finds the same or shorter SIA interval suggesting that the inclusion of contact patterns highlights the risk of clustering of susceptibility in these groups. Further investigation of the McKee method is needed, because it is the most complex method that can be used globally.

In a separate study from the SIA analysis, there was a report back to IVIR-AC on measles mortality. At the last meeting the committee requested that these analyses were completed with a dynamic model. There has been validation of the model using SIR model simulations, including mechanistic age, geographic, and seasonal components. There was a call for direct comparison of the new findings with the SIR results.

Discussion

SIA intervals:

- There was discussion of validation of these models, although it was noted that the implementation quality of the SIA is important for this, and also that absence of an outbreak may not be evidence that the SIA interval was correct (chance could prevent an outbreak even if the fraction susceptible would permit an outbreak). The Funk method has been most thoroughly validated (but is not yet published) but mostly in Europe and to serological data not outbreaks. The Verguet method has

been compared to simulated data (provided in the publication). The Knapp method has compared SIAs with outbreak timing.

- The elimination of measles in the Americas is held as an example of “what works” but it was emphasised that this example is more complex than it seems: the countries all had coverage of 80-90%, then repeated SIAs in both young and older age groups were used. The vaccine is not perfect, so even with very high coverage, not all individuals are protected. In response to this, extra SIAs in under 14s were used. It was emphasised that the success of in the Americas was the result of a concerted effort on many fronts, and particular aspects cannot be “cherry picked” - the effort has to be viewed as a whole, and context specific.
- An older model used in the 1990s in Europe was suggested as a potential addition to this work. This was based on a 5-age group model from 1996 by Gay et al (used in Appendix 2 of http://www.euro.who.int/_data/assets/pdf_file/0003/119802/E68405.pdf) although is not valid in countries with rapidly growing populations. The Funk method is an extension of this model (referenced as Orenstein & Gay 2004, although the original model is older, e.g. Gay et al 1995, *Epidemiology & Infection* in England and Wales). The Funk et al model could be revisited in this simpler 5-age group structure to determine: i) if this is an appropriate model; ii) if population-growth occurring in key countries violates the assumptions of the model.
- The age distribution of observed cases was discussed, because cases are frequently older teenagers and early 20s in current outbreaks. This could be the result of decreasing quality of SIAs over the past decades, where if those campaigns are not incomplete, susceptible individuals are left and as they age, can appear as cases at older ages.
- The impact of SIAs on routine immunisation programs was raised. SIAs are quite disruptive in countries, because staff are moved around to undertake them. These programs are not necessarily popular with funders for these reasons. It was suggested both to evaluate the impact of SIAs on health systems, as well as to consider interventions that increase vaccine coverage through the routine program. Improvements to health systems could also help to avoid “missed vaccination opportunities” during any life-course contact with health services.

Questions to be answered

1. Is there feedback/suggestions for this work?

Summary and Recommendations

Modelling of SIAs

The current “rule of thumb” for determining the time between SIAs might have to be updated to achieve optimal coverage in populations, avoid measles outbreaks and make progress toward regional elimination of measles. The rule of thumb is to approximate the number of susceptible pre-school children and conduct an SIA when the number approaches the size of 1 birth cohort (approximately 2–5 years, depending on the level of routine immunization achieved). The Measles and Rubella SAGE working group is reviewing guidance on SIA intervals for the October 2018 SAGE meeting, and IVIR-AC will support work in this area before that meeting.

- Set up a working group to provide detailed input before SAGE. The group will meet and provide feedback to the WHO Secretariat and the IVIR-AC Chair by mid-May on the simplest approach, which is not overly onerous to the health system. For

example, annual SIAs are not feasible; however, a need for annual SIAs indicates that a country should strengthen routine coverage in order to achieve elimination.

- Conduct further work to understand the divergence between the models of Knapp and of Verguet & Jit from the restrictive rule of thumb method. It was noted that the methods do not include susceptibility in older age groups or the shortening of maternal protection.
- Analysis by the McKee method should be completed and presented to the Committee.
- A model used in Europe in the 1990s³ that was presented to SAGE in October 2017, which includes susceptibility in age groups ≥ 5 years, should be considered for use in subsequent work.
- WHO should design a protocol(s) to evaluate the positive and negative impacts of SIAs on the health system and on routine programmes in countries.
- Susceptibility is heterogeneous among countries (e.g. WHO subnational tool for measles susceptibility assessment). In the longer term, the IVIR-AC working group should investigate geographical variation in SIA intervals within countries. Targeted SIAs could be less disruptive to routine programmes but have the same benefits if there are “pockets” of susceptibility among people who are hard to reach.
- The Committee suggested that models be evaluated by comparing observed SIA intervals and achieved SIA quality and coverage with the timing and size of outbreaks and serological data.

Measles mortality model

In response to the IVIR-AC recommendations in February 2017, Pennsylvania State University, USA, presented an updated measles mortality model.

- The IVIR-AC expressed appreciation to the analyst of the study for addressing the considerations from the previous meeting and following up issues.
- The Committee proposed a direct comparison of the new mortality model with simulations of standardized incidence ratios.

³ Interpretation of serological surveillance data for measles using mathematical models: implications for vaccine strategy. Gay NJ, Hesketh LM, Morgan-Capner P, Miller E. *Epidemiol Infect.* 1995; 115(1):139-156.

Session 6: Vaccine hesitancy

Introduction

The International Collaboration for Vaccine Acceptance Initiative (ICVA) is an open, international, multidisciplinary network of social and behavioural researchers linked to immunization programmes to address the demand for and acceptance of vaccines and vaccination. The ICVA presented its objectives and plans to the IVIR-AC for feedback.

The ICVA proposes four main areas of focus: 1) Expand the evidence-base and validate new strategies, 2) Develop and validate new metrics for monitoring and evaluation, 3) Scale-up implementation e.g. via tailoring immunization programmes, and 4) Facilitate partnerships and build capacity. Activities for all of these four areas were proposed.

Review and discussion

- “Barriers to coverage” is a bigger topic than “hesitancy.” The latter term fails to acknowledge other key issues regarding the commitment of policymakers and vaccinators (i.e., clinicians, health workers or school health staff), including missed opportunities for vaccination. Furthermore, the issues currently associated with hesitancy are so diverse that they may lack capacity for guiding a coherent unified strategy for action. For example, community questions about safety and efficacy are different from issues related to distrust of the clinic, prior off-putting experience in a clinic, suspicion of danger of vaccination programmes related to religious and political conflicts, and so forth.
- The stated aims for developing metrics for hesitancy and demand should also relate methods to objectives for assessment. The metrics and methods for high-level comparative studies are different from research designed to identify local issues to guide programme strategies. Both the formulation of questions and the relative mix of quantitative and qualitative methods are different, as are needs and strategies for monitoring vaccination practices of communities and clinicians.
- The role of research to monitor and guide identification and response in local problems may benefit from surveillance based on a framework of cultural epidemiology rooted in research methods capable of integrating an appropriate mix of quantitative and qualitative methods. Medical anthropological concepts should guide strategies based on a cultural formulation of issues that consider ideas about illness and vaccines, the role of cultural identities that may affect acceptance and demand, the influence of social networks and community leaders, and structural features of health system vaccination practices and of relevant societal stressors and supports.

Questions to be answered

1. Does IVIR-AC have any comments / feedback / suggestions on the methods?
2. Does IVIR-AC have any comments / feedback / suggestions on the research plan?

Summary and Recommendations

The International Collaboration for Vaccine Acceptance Initiative (ICVA) is an open, international, multidisciplinary network of social and behavioural researchers linked to immunization programmes to address the demand for and acceptance of vaccines and vaccination. The ICVA presented its objectives and plans to the IVIR-AC for feedback.

- The Committee recognized the urgency of better integration of social and behavioural insights into programme planning. Strategies should be developed and implemented to generate and sustain demand and acceptance.

- The Committee expressed its appreciation for the opportunity to provide input at an early stage to the ICVA, which responds to the 2014 SAGE recommendations on vaccine hesitancy. The proposed plans of the network are aligned with the interests and previous activities of IVIR-AC in this area.
- The Committee proposed establishment of an IVIR-AC working group on demand and acceptance to serve as a link between IVIR-AC and ICVA, with the following objectives:
 - represent the broad interests of IVIR-AC in relation to research on vaccine demand and acceptance, especially by:
 - identifying research projects,
 - supporting research activities,
 - reviewing proposed strategies and methodology,
 - identifying current and potential vaccine- and vaccination-related issues that might benefit from social and behavioural insight and
 - linking with social and behavioural scientists in LMICs.
 - advise ICVA on:
 - scaling up implementation and evaluation of local interventions with innovative methods and strategies for community engagement;
 - facilitating partnerships and capacity-building to strengthen systems and build programme resilience;
 - expanding the evidence base;
 - developing and validating new metrics specific to acceptance that clearly distinguish acceptance from access; and
 - increasing the representation of LMICs on ICVA, especially programme managers.
 - Report regularly to IVIR-AC on progress in the ICVA's proposed plans of vaccine demand and acceptance

Session 7: Development of full public health value propositions for the new vaccines framework

Introduction

In the past year, the WHO Product Development Vaccine Advisory Committee (PDVAC) initiated discussions around Product Preferred Characteristics and business and investment cases for new pipeline vaccines. At the same time, Implementation Research and Economic Analysis (IMER) at Initiative for Vaccine Research (IVR) identified the need for developing a framework for value proposition of new vaccines. In September 2017, a draft framework referring to two case studies on Group B Streptococcus (GBS) and Herpes Simplex Virus (HSV) was presented to IVIR-AC for review. Acknowledging the importance of value propositions in understanding and representing the complex and dynamic system of vaccine development, the committee recommended standardization of approaches and terminologies around value proposition and further development of the work.

The session 7 of the open session meeting on March 7, 2018 included several streams of work developed as a response to such recommendations, including the introduction of Public Health Value Proposition (PHVP). The development of new vaccines for infectious diseases and improved access to existing vaccines are fundamental pillars to achieving Universal Health Coverage (UHC). With UHC as imperative, WHO IVR has developed a public health value proposition (PHVP) framework that evaluates the public health need, use case and potential impact of a vaccine, from the perspective of early product development through to late stage decision making and policy recommendation.

A scoping review of existing investment cases identifies common characteristics that define investment cases for vaccines and immunization programs based on 21 results from published studies and grey literature. Existing investment cases communicate information that facilitate the understanding of relevant costs, benefits, risks and other factors associated with the investment in five broad categories (disease and economic burden, vaccine price and quantity, cost of investment, impact of investment and other considerations). The investment cases present heterogeneity in terms of their objectives, structures and components, demonstrating the need for standardization.

The draft WHO/HGF framework for economic evaluations, which is being developed by the HGF/EAE and is under informal review, has been adapted to the field of vaccines and immunization programs to provide guiding principles for defining the value of vaccines and immunization, choosing an appropriate methodology for a policy question and conducting accounting exercises that are fundamental to economic evaluations. The draft framework will be included in the PHVP to guide the standardization of approaches to economic evaluations for new vaccines in early development.

The second part of the session voiced the need for more appropriate and accessible information for policy. As immunization programs become more ambitious and complex, with higher targets for the vaccination coverage, a new review of evidence base is required to inform policies regarding immunization schedules. The evidence base should be packaged for different users on different levels comprising a) global/regional summaries b) country data and estimates c) full systematic reviews and source reports and articles.

To support decision making at the country level, a prototype decision support model interface was presented to the committee. The prototype decision support model intends to help decision makers in seven areas: 1) recognize the factors relevant to the modelled

aspect of the decision making, 2) access and evaluate the available data, 3) appreciate that data alone are usually not enough 4) appreciate sensitivity of outcomes to parameter changes 5) explore alternative parameter values in scenario analyses 6) appreciate the uncertainty around modelled outcomes and 7) appreciate what the model does and does not do. The result section of the dashboard for the decision support model, with a user-friendly interface, aims to include results such as baseline deaths, total and % deaths prevented across different schedules.

Review and discussion

In general, the scoping review was considered to be interesting and meaningful work. Additional data extracted from the reviewed literature could be used to generate subgroup analyses, which facilitate the understanding of political economy and trend of evidence needed by different groups of actors for vaccine investment cases. This additional information could help share the recommendations on the Public Health Value Proposition (PHVP). It is recommended that future investment cases include specific concerns regarding reverse vaccinology or transmission blocking vaccines.

The reviewers found it encouraging to see the adaptation of the draft WHO/HGF framework which will be helpful for all stakeholders by clarifying the similarities and differences of all available methodological approaches on vaccine investment case. To enable more effective utilization of the suggested framework, it would be important to present 'pros' and cons' for each methodological approach that will serve as guidance for potential users especially at the country level. The reviewers mentioned that the scoping review could provide invaluable input into the guidance and direction regarding different approaches. The conclusion section should narrow down approaches to be used by country NITAGs/relevant authorities or provide justification on approaches selected by WHO SAGE. While it was suggested that the two-by-two table outlining market-traded and non-market traded inputs and outcomes incorporate a societal perspective, adopting a societal perspective not a context-free requirement, a point that was repeatedly emphasized.

Questions to be addressed:

- Does IVIR-AC have any comments/feedback on the generalized guiding principles of the economic accounting framework proposed as part of the Value Proposition framework?
- Is the framework useful and helpful for different stakeholders?

Summary and Recommendations

The full public health value proposition

In September 2017, the Committee concluded that the "full public health value proposition" is a meaningful contribution to the field but that the approaches and terms should be standardized. A scoping review of investment cases of vaccines was presented, followed by a presentation of work in progress on the economic accounting framework applied to vaccines and immunization programmes in collaboration with the WHO Health Governance Financing department. The work includes a prototype decision support model and interface, presented during the session, to help decision-makers to assess and evaluate data, parameters and outcomes for exploring different immunization policy options and scenarios.

Scoping review:

- The Committee suggested that more data be extracted from the scoping review on funders, evidence developers and target audiences (if available).

- Subgroup analyses should be conducted to determine the “political economy” and “trend” of evidence required by different groups for making a vaccine “investment case”.
- The Committee expressed its appreciation for attempts to centralize “all available methodological approaches” on vaccine investment cases in order to identify their similarities and differences, which would be helpful for all stakeholders in the field.
- Potential users will require guidance, especially in countries. The “pros” and “cons” of each methodological approach should be listed to direct country users to the appropriate method.

Economic accounting framework:

- The “two by two” table in part 4 of the scoping review simplifies the concept, but the document should make it clearer that this part is based on the assumption that a “societal perspective” is adopted for the analysis.
- It was suggested that the term “global economic investment case” be used for the economic component of the full public health value proposition.
- The vaccine investment strategy of Gavi should be incorporated into the framework.

Access to evidence to inform policy

National immunization technical advisory committees and other decision-making bodies increasingly require appropriate, readily accessible information for policies on monitoring and assessing the impact of vaccines. A prototype decision support interface for country decision-makers to evaluate vaccine schedules, developed by LSHTM, was presented for feedback from IVIR-AC

- The Committee considered that the decision support model would be useful for countries. People would have to be trained in using the model for actual decision-making.
- It was recommended that software other than MS Excel® be used, although MS Excel® is already well known and widely used.
- The tool should be readily accessible, and the programme interface should be user-friendly.

Session 8: Total System Effectiveness

Introduction

The vision of Total Systems Effectiveness (TSE) is to improve cohesion between upstream product development and downstream country uptake of innovative vaccine products, and to promote decision-making from a holistic systems perspective with consideration of coverage and equity. It aims to promote a multi-criteria decision-making approach to product selection and prioritization decisions at the country, global, and R&D level.

A consortium of partners, including BMGF, CHAI, Gavi, PATH, UNICEF, WDI and WHO, has convened to form the TSE initiative. WHO has received a planning grant from BMGF to lead the TSE initiative and to conduct a six-month pilot focussed on the country use case for applying TSE to vaccine product selection decisions.

Review

A standardised vaccine product framework for TSE is under development, to support prioritisation decisions between vaccine products (e.g. between rotavirus vaccines products). The framework is organised around five critical components - health and financial impact, coverage, safety, delivery cost, commodity cost - with an equity lens applied throughout the framework.

The TSE framework considers product selection from a societal perspective, considering the impact and cost for the entire health system and society, in line with UHC goals. However, it is envisioned that there will be multiple users of TSE, and it is expected that the framework scope will be modified to suit the requirements of the end-user.

To illustrate, TSE can support countries to make evidence-based decisions to introduce innovative vaccine products (country use case), for global policy setting and donor decisions (global use case), or to prioritise product attributes and investment decisions during development of pipeline products (R&D use case). Ultimately, all use cases should be informed and shaped by country preferences and priorities.

The TSE pilot began in December 2017. The rationale of the pilot is to assist WHO and its partners with concept development and design of the TSE country use case, and to understand its potential applicability using rotavirus vaccines as an example; it is not intended to inform policy or implementation decisions at this stage.

If successful, the pilot will have achieved the following objectives:

- Communicate and develop the TSE concept with in country stakeholders;
- Demonstrate the potential value of TSE approach for the country use case; and
- Develop a set of recommendations to (i) optimize and operationalize country use case (including building out to other disease areas); (ii) adapt TSE approach for other use cases.

At the time of the IVIR-AC session, WHO and its partners had conducted a landscaping exercise of existing models and tools relevant to TSE and developed overarching methodology for a simple TSE model. Planned activities outlined for the remainder of the pilot include to develop an Excel-based model for comparing between different rotavirus vaccine products, based on the overarching methodology presented; to conduct TSE sensitisation workshops with EPI managers and NITAGs, in order to discuss the applicability of TSE to product selection decisions; and to test the TSE Excel-based model in up to 5 pilot countries.

Discussion:

- There is benefit to having a tool such as TSE to show trade-offs. However, MCDA is a complex process and the TSE methods presented require further work to adhere to good MCDA methodology. It was highlighted multiple times that the choice of components is very important and will determine the results from the analysis, thus the components of the TSE framework should be validated by countries.
- There was concern that TSE could place an additional burden on countries. To mitigate against this, every effort should be made to link TSE with existing tools/systems, and to align with the social context and local decision-making process.
- The specific purpose and objectives of the pilot were unclear to the committee, making it difficult to give specific advice relating to the pilot. In general, it was encouraged to select a range of pilot countries, including Francophone/Lusophone Africa, and that the pilot needs to be re-oriented to a bottom-up approach that solicits country input into the design of TSE. The committee cautioned against oversimplification during the pilot, especially in relation to removing health systems changes from the scope of the pilot.
- The greatest benefit of TSE may not be in applying TSE to product selection decisions within a specific disease area, especially as there is large uncertainty in differences between products. Instead, TSE might have greatest value in prioritising between vaccines (e.g. rotavirus and PCV) or in considering combinations of innovative technologies for a specific platform (e.g. all vaccines for 1st year of life delivered using a microarray patch).

Questions to be addressed:

- Does the TSE framework incorporate the necessary elements to holistically consider total systems effectiveness?
- Are the methods proposed for the rotavirus test case robust to support decision-making?
- How can the outputs be most optimally presented to facilitate decision-making?

Summary and Recommendations

The Bill & Melinda Gates Foundation-funded pilot project on TSE, which is led by the WHO Immunization Vaccines and Biologicals programme in collaboration with partners (e.g. PATH, CHAI, UNICEF, Gavi), was presented to IVIR-AC for feedback. The aim of the pilot project is to test “multi-criteria decision analysis” as a support for countries in choosing vaccine products and/or prioritizing pathogens.

- The Committee welcomed the ambitious TSE project but asked for a clearer definition of TSE and the specific goals of the project.
- It noted that it will be difficult to differentiate among vaccine products with regard to the many population outcomes (health benefits, equity, financial risk protection), especially in view of the uncertainties in input, structure and model.
- A simple MS Excel®-based static model may not be sufficient to capture such differences and uncertainties, particularly for vaccine products that differ negligibly in efficacy. TSE could, however, be useful for differentiating among vaccine products with regard to cold chain requirements, schedules and procurement prices.
- Implementation and modelling require further consideration and should be more systematic. It might be useful to involve anthropologists in finding out why vaccines are not taken up.

- The Committee therefore suggested that key informant interviews be conducted in countries to determine: where and by whom decisions are made; the important factors (rather than pre-designed components) and data gaps; and how and whether TSE will be used. These criteria should be revised before a pilot study is conducted, which should have clearly stated objectives. Formulating the objectives may require changing the timing of the pilot study.
- Mali was suggested as a potential country for a pilot study, in addition to Indonesia and Thailand.
- The Committee requested an update of the status of the TSE pilot project at the next IVIR-AC meeting, in September 2018.

Session 9: Standardization of delivery costing

Introduction

In the past, IVIR-AC reviewed the micro-costing and planning tools supported by WHO to assist countries in estimating the cost of introducing and delivering new vaccines that often target populations who are not among the standard age groups of the Expanded Programme on Immunization, such as adolescents, adults, health workers and people with chronic diseases. The tools for costing vaccine delivery and introduction supported by WHO include C4P, the RTS,S malaria vaccines introduction costing tool and introduction costing tools for influenza vaccine, oral cholera vaccines and, recently, typhoid vaccines. As these delivery costing tools are based on different methods and sometimes different terminology, a plan to standardize delivery costs has been prepared.

Review and discussion

Costing tools can help in standardization of costs and to include economic costs that are often left out of analysis (e.g. in-kind costs, personnel time costs, etc). Furthermore tools ensure that users list their assumptions and sources of information and tools can be used to calculate costs of different scenarios so that these can be compared.

Challenges with using different tools include lack of standardization of cost categorization (e.g. omissions, misclassifications), availability of economic costs, inclusion of capital costs, differentiation between fixed and variable costs, and variable cost perspective.

Questions to be addressed

1. Is the suggested framework for cholera vaccine delivery costs appropriate and useful?
2. What is the guidance from IVIR-AC around addressing different perspectives and capital costs in delivery costing tools and methods?
3. Is it always necessary to include both economic and financial costs?
4. To what extent should vaccine delivery costing methodologies be standardised across vaccines?

Summary and Recommendations

In the past, IVIR-AC reviewed the micro-costing and planning tools supported by WHO to assist countries in estimating the cost of introducing and delivering new vaccines that often target populations who are not among the standard age groups of the Expanded Programme on Immunization, such as adolescents, adults, health workers and people with chronic diseases. The tools for costing vaccine delivery and introduction supported by WHO include C4P, the RTS,S malaria vaccines introduction costing tool and introduction costing tools for influenza vaccine, oral cholera vaccines and, recently, typhoid vaccines. As these delivery costing tools are based on different methods and sometimes different terminology, a plan to standardize delivery costs has been prepared.

- IVIR-AC concluded that standardization of the costing tools would be useful and necessary for comparing the costs of delivery within and across countries and by product or delivery strategy.
- Economic costs should be included for economic evaluations. Modelling may be required if economic costs are projected over long periods.
- IVIR-AC suggested that the standardization methods also include uncertainty analysis; most of the tools provide no means for including uncertainty or sensitivity analyses.

- The Committee suggested that guidance would be useful on where to obtain data, at what level (national, subnational or district level) and how to conduct sampling. In addition, the data collection tools and forms should be validated.
- Finally, the Committee suggested that the costing guide for standardization of delivery costs be linked with the Global Health Costing Consortium. Reference costs should be used as a checklist to ensure quality, and definitions and terminology should be aligned.