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

Montreux, 30 May – 1 June 2016

Immunization, Vaccines and Biologicals (IVB)

World Health Organization

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Abbreviations

aP	acellular pertussis vaccine
BCG	Bacille Calmette–Guérin
BMGF	The Bill and Melinda Gates Foundation
CFR	Case-fatality rate
CDC	Centres for Disease Control
COI	Cost-of-Illness
CEA	Cost-Effectiveness Analysis
DALY	Disability Adjusted Life Year
DoVE	Decade of Vaccine Economics
DTP	Diphtheria–tetanus–pertussis
EPI	Expanded Programme of Immunization
Gavi	The Vaccine Alliance (Global Alliance on Vaccines and Immunizations)
GVAP	Global Vaccine Action Plan
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B vaccine
HCC	Hepatocellular carcinoma
HIC	High Income Country
HPV	Human papilloma virus
Hep B	Hepatitis B
Hib	*Haemophilus influenzae* type b
IPV	Inactivated polio vaccine
IVAC	International Vaccine Access
IVB	WHO Department of Immunization, Vaccines and Biologicals
IVIR-AC	Immunization and Vaccine-related Implementation Research Advisory Committee
IVR	Initiative for Vaccine Research
LMICs	Low and middle income countries
MOV	Missed opportunities for vaccination
NIP	National Immunization Programs
NSE	Non-specific effects
OPV	Oral polio vaccine
PCV	Pneumococcal Conjugate Vaccine
PRIME	Papillomavirus Rapid Interface for Modelling and Economics
QUIVER	Quantitative Immunization and Vaccines related Research
ROI	Return on Investment
SAGE	Strategic Advisory Group of Experts
Swiss TPH	Swiss Tropical and Public Health Institute
UNICEF	United Nations Children's Fund
VPD	Vaccine-preventable disease
WASH	Water, Sanitation and Hygiene
WHO	World Health Organization
WPR	WHO Western Pacific Region
wP	whole cell pertussis vaccine

Executive Summary

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

Session 1: Missed opportunities for vaccination (MOV)

Introduction
As a follow-up to the IVIR-AC recommendations in 20141 the Committee considered a new methodology to assess missed opportunities for vaccination (MOV) as part of scaling-up the WHO MOV strategy. In order to assess the magnitude and causes of missed opportunities, the new methodology captures additional quantitative information, including explanatory demographic variables in combination with qualitative information based on anthropological variables. This is expected to yield more appropriate, better tailored interventions to reduce MOV within each local context.

Recommendations

- IVIR-AC supported the approach and commended the effort to incorporate qualitative assessment into the MOV strategy. Opportunities to assess MOV as a complement to assessing coverage in other facility-based surveys should be considered, such as in-depth assessments of data quality undertaken every 5 years. IVIR-AC also proposed exploring possibilities to analyse MOV in recent demographic and health surveys and the datasets of middle-income countries, and to conduct MOV surveys in some countries.
- The MOV survey is a recognized means of initiating a process to improve the issues of many health systems. The priority of locally-generated data should help to distinguish what is local and can be generalized, thereby facilitating effective communication and empowerment at all levels.
- IVIR-AC proposed standardizing and simplifying the language of the knowledge, attitude and practice (KAP) questionnaire and assisting with guidance on methodological issues such as the number of focus group discussions and key informant interviews to be conducted, and sampling strategies for both public and private sectors.
- The approach should include assessing the impact of MOV interventions. Longitudinal and follow-up surveys, and analysis of existing data, would be applicable – for example the use of district monthly coverage reports submitted to the WHO African Region.
- As implementation of the MOV assessment strategy and follow-up activities proceed, IVIR-AC recommends compiling a database of evidence for interventions and their impact on reducing MOV, thereby determining which are most effective.

Session 2: Non-specific effects (NSEs) of vaccines

Introduction
The IVIR-AC meeting in 2015 emphasized the importance of randomized trials within nested immunological studies. The Committee considered priority questions for NSE clinical trials, including trial designs for each priority question, as proposed by the participants of an ad-hoc consultation in February 2016.

Recommendations

- IVIR-AC considered the conclusion of the IVIR-AC meetings in 2014 and 20152 that further observational studies are unlikely to inform public health decision-making, thus reaffirming the importance of randomized clinical trials. The Committee acknowledged the progress made towards the refinement of priority research questions and trial designs resulting from

the ad-hoc expert consultation, and also recommended that any trial design proposed should have its own rationale.

- IVIR-AC endorsed the designing of one or more protocols to assess the prospective non-specific effects of immunization on mortality. The work of the WHO Secretariat needs to be completed in preparing the protocols for the questions identified and trials outlined during the ad-hoc expert consultation of February 2016. These generic protocols would enable harmonized implementation of the trials across multiple settings. While further development of all the proposed trial designs is important, IVIR-AC recognizes that full evaluation necessitates a complete protocol. IVIR-AC will help inform decisions on feasibility and the selection of designs, and formulate questions.
- IVIR-AC members will continue to guide future WHO consultations, and review and comment on the protocols while being developed.

THEME: Research to conduct impact evaluation of vaccines in use

Session 3: WHO vaccine-preventable disease (VPD) evidence synthesis tool

Introduction
In 2014, IVIR-AC recommended that WHO facilitate a "hub" of work to assess the burden of disease and its economic impact, to include an associated network of experts. The WHO Secretariat commissioned the work through a competitive bidding process and presented the Committee with a preliminary draft which included the underlying tools used to synthesize the evidence.

Recommendations

- The VPD evidence synthesis tool should contain evidence vetted by WHO for decision-making criteria or parameters and should create and support discussion during country-level decision-making processes.
- The tool should be linked to the National Immunization Technical Advisory Committee (NITAG) Resource Center and other sites including the National Institute for Health Research SYSVAC,3 a database of systematic research on vaccines and immunization.4
- WHO should establish standard operating procedures to define how the emerging content will be vetted and updated to the portal (including timelines).
- Special attention should continue to be given so that common challenges of sustainability and comprehensiveness of the tool are anticipated and addressed.
- Main targets of the portal should be policy-makers and supporting staff, particularly those of NITAG including its secretariats and decision-makers.
- Follow-up meetings should be arranged to discuss and plan data visualization and communication efforts.

Session 4: Rotavirus mortality

Introduction
Rotavirus is a recognized cause of mortality from diarrhoea in children; however there is considerable disagreement on the number of deaths that occur each year. IVIR-AC was presented with a comparison of 3 sources of estimates (global, regional and national) of deaths from rotavirus in children aged <5 years5 for the year 2013 that aimed to identify the drivers of such difference.

Recommendations

- State directly that most deaths from diarrhoea reflect a lack of access to health care to provide rehydration which results from dysfunctional health-care systems. Assessment of basic health-care services should be incorporated into the presentation and analysis of mortality.
- Understand that estimates of mortality from rotavirus derive from the attribution of aetiology to total deaths from diarrhoea. Therefore, the same comparable sources for aetiology and mortality data should be used.
- Clarify that the purpose of this process is not to create one rotavirus mortality estimate, but to benefit from lessons learned from each estimate and to guide health decision-makers in their consideration of the sources and nuances of the data.
- Continue to improve data sources; consider how to address uncertainty of estimates; consider finer-age strata (important for impact assessment of on-time or delayed vaccination); evaluate the impact of different covariates in the model; and compare the implications of national and subnational data.
- Reliance on proprietary data limits the capacity of interested parties to understand rotavirus mortality estimates, and to conduct independent analyses. IVIR-AC should therefore

examine and address strategies for optimally sharing databases and issue a recommendation regarding this at a future meeting.

Session 5: Guide for disease and economic impact model comparisons

Introduction

As a follow-up to the IVIR-AC recommendation of 2015, the Committee emphasized the need for guidelines on the best practice for conducting disease and economic impact model comparison exercises. A preliminary framework of the model comparison was presented to the Committee for review.

Recommendations

- IVIR-AC considered that the framework proposed for model comparison was appropriate and that an IVIR-AC working group should be established to develop this.
- One of the goals of model comparison is to report and understand variability and uncertainty between models while taking into account parameter, structural and methodological uncertainty. In order to do this, model comparison exercises need to standardize reporting rather than modelling methods. To correspond with existing checklists, such as the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement, and to allow for results to be reproduced, modelling methods should be transparent.
- Reporting of a model quality assessment is encouraged.
- Pooling models through a weighting score should be considered in future model comparison studies.
- IVIR-AC noted that the informatics capacities now available for modellers and a wide array of scientists make the issue of how to approach transparent, open databases particularly germane and important to facilitate model comparison exercises, and for advancing implementation research in general. Other groups such as Chatham House, and leading journals have been exploring this topic; IVIR-AC should obtain consensus opinions from other forums, and consider inviting appropriate participants who could provide relevant perspectives and input for discussions during a future meeting.

Session 6: Human papillomavirus (HPV) modelling in low- and middle-income countries

Introduction

As a follow-up to a WHO ad-hoc expert consultation in 2015 on priorities for HPV vaccine research in general disease and the economic impact, IVIR-AC proposed modelling activities specifically to compare 9-valent versus 2/4-valent vaccines; gender-neutral versus girls-only vaccination strategies; and 3-dose versus 2-dose schedules in low- and middle-income countries (LMICs). The modelling framework and plans to address the questions were presented to IVIR-AC for review.

Recommendations

- IVIR-AC endorsed the proposed framework to evaluate different HPV immunization strategies, particularly the intention to review systematically the burden of HPV-related cancers and anogenital warts, immunogenicity and efficacy of HPV vaccines in clinical trials, and effectiveness in post-introduction impact evaluations. Through modelling, the framework would also encourage the estimation of incremental effectiveness and cost–effectiveness of gender-neutral HPV immunization and catch-up vaccination compared with the currently recommended “girls-only” strategy.

- In the short term (within the second quarter of 2016), modelling with the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) tool should be conducted to contrast the cost– effectiveness of bivalent, quadrivalent and nanovalent vaccines in 179 countries of the strategy targeting girls only. The inclusion of population-level herd effects in PRIME is advised. With regards to the adaptation of transmission-dynamic models – which have been helpful to support policy-making in high-income countries – key issues relating to HPV immunization effectiveness in LMICS (such as variability of sexual behaviour, cervical cancer-screening patterns, and background HPV infection rates) should be characterized. Finally, the worldwide burden of anogenital warts, including by serotype, should be systematically reviewed to provide input data to further modelling.
- In the medium and long terms, transmission-dynamic models adapted to LMICs should examine the effectiveness and cost–effectiveness of different HPV immunization strategies comparing "no vaccination" and in combination with cervical cancer screening strategies, schedules and vaccine types. This work may start by re-calibrating the existing individual-based HPV model to the specific situation of 3–6 LMICs. Given the complexity of trans-mission-dynamic models, IVIR-AC suggests the use of one or more emulators that serve as user interfaces to simplify the evaluation of a variety of permutations, thereby facilitating in-country assessments and local ownership of effectiveness and cost–effectiveness analyses.

Session 7: Influenza-specific economic guidelines

Introduction

IVIR-AC reviewed the WHO influenza disease and economic value chain – a set of guidance documents and tools that supports country-level decision-makers in assessing the economic and social benefits of introducing influenza vaccination or expanding existing vaccination to specific target groups, such as pregnant women, health workers and older people.

Recommendations

- IVIR-AC suggested that the WHO influenza disease and economic value chain should include epidemiological surveillance standards; that the underlying data should include local information from a variety of sources; and that the value chain should address how to communicate the evidence and results from economic studies with decision-makers.
- WHO should support the sharing of existing country experience regarding consideration of disease and economic burden in policy- and decision-making in order to generate policy demand for such studies in other settings.
- The original question to IVIR-AC on the use of a fixed cost–effectiveness threshold is beyond the scope of this Committee due to it being related to general cost–effectiveness in health rather than specifically to vaccines. However, if countries have not gone through the process of defining their cost–effectiveness thresholds, IVIR-AC recommends they use alternatives such as 1) benchmarking against the least cost–effective health interventions already funded by relevant jurisdictions; 2) using cost–effectiveness league table approaches; and/or 3) transferring outcomes (in either DALY6 or QALY7 format) into monetary units for benefit to cost ratios or return on investments.
- Economic burden outcomes should clarify who bears the costs of the disease in question.
- IVIR-AC recommends that the influenza vaccine-specific economic evaluation guidelines should recognize differences in the effectiveness and cost– effectiveness of various influenza vaccines based on presentation, formulation, and circulating types and subtypes that vary over time and place.

Session 8: Cholera disease burden

Introduction

IVIR-AC reviewed an effort to map estimates of reported subdistrict cholera incidence with the prospect of inferring the global burden of cholera including extrapolation to areas with little or no data available.

Recommendations

- The investigators should acknowledge more clearly that their model is descriptive rather than predictive. A predictive model for cholera is unlikely to be accurate in view of limited data and the diversity of transmission patterns and risk factors, which change over time and in various geographical settings. In addition, arbitrarily small geographical units, and the paucity of high-quality data on detection and incidence, limit the accuracy of predictive models for cholera.
- The model structure should start with questions posed (for example on the purpose of developing the model and graphs); confirmation of the target audience and how the model would be of benefit; confirmation of its potential use for advocacy, for immunization recommendations by NITAG secretariats, by the GAVI Alliance, for public health messaging or for impact assessment.
- The modelling effort at global level should focus on issues identified by the Global Taskforce for Cholera Control and the GAVI Alliance being key decision-makers on the use of vaccines.
- Data sources should be clearly identified, including the number of cases, the time period of acquisition, geography, source, and whether cases are suspected or confirmed.
- Outbreaks of cholera (e.g. variation from baseline) should be distinguished from endemic disease. Maps should include both since public health implications and interventions differ based on whether cholera is changing from baseline or is static.
- The model should distinguish confirmed cases from suspected cases, to determine whether, and to what extent, epidemiological patterns change, if at all.
- Uncertainty needs to be better acknowledged with regard to knowledge of the disease, the unpredictable spread of cholera due to the diversity of transmission patterns, and risk factors.

THEME: Research to improve methods for monitoring of immunization programmes

Session 9: Immunization E-Registries (IERs)

Introduction

Electronic immunization registries (IERs) facilitate coverage monitoring in terms of particularity, timeliness and accuracy. The Committee reviewed a conceptual framework to identify research barriers to implement IERs for monitoring immunization programmes.

Recommendations

- IVIR-AC appreciated the value of work presented and acknowledged its potential use within countries for supply chain evaluations, pharmacovigilance, vaccine coverage and effectiveness studies.
- IERs can be regarded as a tool for implementation research, for example by indicating the immunization status of hard-to-access populations and by linking IER with civil and birth registrations.
- The work on IERs should be linked to a similar study at PATH,8 funded by the Bill & Melinda Gates Foundation to identify barriers for implementing IERs in the United Republic of Tanzania and Zambia.
- The work on IERs should focus on country-level programme managers since some might be opposed to moving from paper to e-registries, particularly if both are used in a transition period.
- Paper registries have a long history of use in measuring immunization coverage and individual immunization status; countries choosing to implement IERs should ensure, demonstrate and disseminate that, in comparison with existing methods and relative to cost, IERs improve efficiency in terms of data accuracy, effectiveness and timeliness.
- IVIR-AC suggests WHO support the development of IERs in various ways such as by identifying circumstances in which they can be successfully introduced; identifying the “killer risks” to avoid failures; and identifying resources needed to ensure their long-term sustainability.
- IVIR-AC recommends that research and implementation of IERs should be prioritized and that WHO should find ways of making financial and human resources available.

Introduction

Dr. R. Breiman opened the fifth meeting of the WHO Immunization and Vaccines-related Implementation Research Advisory Committee (IVIR-AC). IVIR-AC has no executive, regulatory or decision-making function. Its role is to provide advice and recommendations to the Strategic Advisory Group of Experts (SAGE) and Director of the Immunizations, Vaccines and Biologicals (IVB) Department of the World Health Organization (WHO).

The key objectives of IVIR-AC are:

- To appraise methods to estimate disease burden and resolve differences in disease burden estimates.
- To appraise guidance documents including methods to estimate disease and economic impact of vaccines.
- To advance techniques to assess cost-effectiveness of vaccines.
- To develop behavioural research to facilitate optimal and timely acceptance of vaccines.
- To define how disease and post-marketing surveillance should be conducted.

IVIR-AC aims to make critical recommendations for the Decade of Vaccines (DoV) – Global Vaccine Action Plan (GVAP), and the advancement of priorities for vaccine-preventable disease in the 21st century.

Session 1: Missed opportunities for vaccination

Introduction

As a follow-up to the IVIR-AC recommendations in 2014, the Committee considered a new methodology to assess missed opportunities for vaccination (MOV) as part of scaling-up the WHO MOV strategy. A missed opportunity for vaccination is any visit to a health facility by a child (or adult) who is eligible for vaccination (unvaccinated, partially vaccinated, or not up-to-date, and free of contraindications to vaccination), which does not result in the person receiving all the vaccine doses for which he or she is eligible. In order to assess the magnitude and causes of missed opportunities, the new methodology captures additional quantitative information, including explanatory demographic variables in combination with qualitative information based on anthropological variables. This is expected to yield more appropriate, better tailored interventions to reduce MOV within each local context.

An overview was given of the current burden of MOV and the WHO strategy for addressing the issue. Many opportunities for vaccination are being missed. The WHO had commissioned the Association pour la Médecine Préventive (AMP) to undertake a systematic review of the magnitude of missed opportunities for vaccination. This was to determine whether or not MOV are still an important issue, and the review showed the extent of the problem of missed opportunities. The review found that the estimated pooled proportion of missed opportunities for vaccination among people under age 18 in developing countries is about 32%. This indicates that one out of three people coming to a health facility are missing or not receiving vaccines. This is consistent with the previous MOV global review carried out in 1993, indicating that the number of children missing vaccinations has not changed and confirming that MOV remains an important discussion.

In 2015, the WHO completed the “proof-of-concept” phase of the MOV strategy. We have now developed and field-tested the MOV tools and completed assessments in the Dominican Republic, Panama, Peru, Colombia, Chad, and Malawi. This pilot testing phase allowed for the recognition that tools needed to be revised and updated; the program was then expanded into other countries in the AFRO and AMRO regions. In 2016 and 2017, our focus is on building a strong MOV partner coordination framework to complete the interventions, evaluate the interventions and prioritize the next wave of countries for scale-up of the strategy. Currently, assessments are planned in Burkina Faso, DRC, Timor Leste, Kenya, Indonesia, Mauritania, British Virgin Islands, Costa Rica, and Ecuador. The expansion plan is ongoing and additional countries have expressed interest in implementing the MOV strategy, including Madagascar, Mozambique, Myanmar, Nigeria, and South Sudan. Globally, there are about 20 million of the global birth cohort of 140 million that remain unvaccinated with DTP3. The children are within reach and the population has been captured in terms of health services, but they are still not receiving full immunization care.

A ten-step process has been developed for addressing missed opportunities. This process is organized into three phases: planning and preparation (how to plan for the strategy), assessment field work (how to document the results), and interventions (how to help countries develop a plan for action).

Plan and prepare for the MOV strategy:

1) Plan for the assessment
2) Prepare for fieldwork and secure funding

Conduct the fieldwork:

3) Collect field data (including qualitative data)
4) Analyse data
5) Debrief to partners

6) Brainstorm on potential interventions (draft a work-plan)

Implement and monitor interventions:

7) Implement agreed-on interventions
8) Provide ongoing supportive supervision
9) Rapid outcome assessments
10) Incorporate into long-term health (immunization) system improvement plans

The new MOV strategy determines how many opportunities are being missed at existing vaccination sites, why those opportunities are being missed, and what can policies, procedures, or behaviours can be adjusted to reduce missed opportunities. Exit interviews of mothers, health worker surveys, focus group discussions, and key informant interviews were completed in order to ascertain MOV and assess whether children were eligible for more doses.

Review

It was discussed how teams used the documents provided in order to give input into the MOV work that was happening. Teams were guided by wanting to move the process forward and address MOV at the community level. Based on the received protocol and tools for data collection, it was noted that it would be useful to know the approximate costs of the strategy in the various countries. This was missing from the protocols but would provide information on whether countries can find the strategy sustainable or whether it needs to be facilitated by partners. It was also noted that it is important to consider MOV within the context of ongoing vaccination campaigns, such as polio, as well as issues with extension services. Comments were made on the study protocol, particularly the exit interviews and the health worker surveys. Although the MOV factors are cross-cutting between countries, implementation of the strategy should be adapted to each local context in order to ensure utility and sustainability. The integration of qualitative components is beneficial because they provide meaning to quantitative results within the local context. In terms of the exit interviews, the protocol should clarify who is excluded, such as if mothers were very ill and were unable to participate. For the health worker surveys, the language was very detailed, particularly when examining the workers in terms of their training, and the questions need to be simplified. It was also noted that while the protocol employed the use of districts, the language should be changed in AFRO region countries to reflect the use of administrative units. It was questioned whether requiring ten health worker interviews might exclude the smaller facilities, and that either the minimum should be lowered or small health facilities should be merged together.

Other similar questions were raised about the sampling instructions in the guidelines and how there were ambiguous situations for the interviewers that might alter the outcomes. One suggestion was that if a mother had two children, the older child rather than the younger one should be selected because they would be more overdue for vaccinations and might have had more missed opportunities. It was noted that sampling protocols were unclear in terms of how many mothers needed to be interviewed, and whether this would impact the urban or rural setting. Opportunities are being missed at facilities that also offer curative services and well-baby check-ups. Age disparities among healthcare workers might not be consistent with their training, as younger workers are likely more up-to-date and might prove to be more efficient supervisors. The approach is not necessarily addressing underlying system issues. Supply chain situations with multi-dose vials being used on only one child are systemic issues that are still severely restricting coverage, and this approach is not designed to look at those issues. The importance of Gavi support in the focus on implementation research and health systems strengthening was also discussed.

Discussion

The presented work is part of a wide effort to reduce missed opportunities for vaccination. With support from WHO, UNICEF, and other immunization partners, the Ministry of Health in each country will be focused on ensuring sustainability. This can be carried out firstly by focusing on "winnable battles", or solutions that are implementable and have the highest short-term potential for success. The intervention strategies should seek synergies with existing health system improvement plans, and be part of the annual EPI work plan. The qualitative and quantitative data collections are beneficial practices, but the language of the surveys should be simplified and standardized. The benefits of this strategy include increasing vaccination coverage, improving the timeliness of vaccination, and promoting integration between programs via preventive and curative services. The regional disparities were stressed, indicating that health systems strengthening and adaptations to local contexts are critical for ensuring the strategy's success. The approach needs to be communicated to national authorities to improve vaccination and extend outreach activities within the existing health systems infrastructure.

Questions to be addressed

- Do IVIR-AC members have any suggestions on the study protocol?
- How generalizable is the study protocol to other settings?

Summary and recommendations

Overall, IVIR-AC was very supportive of the approach and commended the emphasis on qualitative assessment that is part of the MOV materials. It was well understood that the MOV survey was a means to initiate a process of improvement that touched upon many health system issues. It was also noted that MOV (and having locally generated data) is really about communication at all levels.

Recommendations

- IVIR-AC supported the approach and commended the effort to incorporate qualitative assessment into the MOV strategy. Opportunities to assess MOV as a complement to assessing coverage in other facility-based surveys should be considered, such as in-depth assessments of data quality undertaken every 5 years. IVIR-AC also proposed exploring possibilities to analyse MOV in recent demographic and health surveys and the datasets of middle-income countries, and to conduct MOV surveys in some countries.
- The MOV survey is a recognized means of initiating a process to improve the issues of many health systems. The priority of locally-generated data should help to distinguish what is local and can be generalized, thereby facilitating effective communication and empowerment at all levels.
- IVIR-AC proposed standardizing and simplifying the language of the knowledge, attitude and practice (KAP) questionnaire and assisting with guidance on methodological issues such as the number of focus group discussions and key informant interviews to be conducted, and sampling strategies for both public and private sectors.
- The approach should include assessing the impact of MOV interventions. Longitudinal and follow-up surveys, and analysis of existing data, would be applicable – for example the use of district monthly coverage reports submitted to the WHO African Region.
- As implementation of the MOV assessment strategy and follow-up activities proceed, IVIR-AC recommends compiling a database of evidence for interventions and their impact on reducing MOV, thereby determining which are most effective.

Session 2: Non-specific effects (NSEs) of vaccination

Introduction

Researchers have ascertained that vaccines can have non-specific effects (NSEs): beneficial or detrimental effects on child mortality and morbidity other than those affecting the target disease. In April 2014, WHO Strategic Advisory Group of Experts on Immunization (SAGE) concluded that NSEs on all-cause mortality warranted further research. SAGE thus recommended that IVIR-AC be tasked with providing advice and adequate studies as evidence for priority research questions.

IVIR-AC considered NSEs in September 2014 and in June 2015. The Committee agreed with SAGE that additional observational studies are unlikely to provide conclusive evidence on NSEs. IVIR-AC thus committed to guiding the development of standard protocols and the implementation of high quality prospective studies, including randomized controlled trials where feasible.

Following up on SAGE and IVIR-AC recommendations, the WHO Secretariat organized an ad-hoc expert consultation on NSE clinical trials in February 2016. The specific objectives of the consultation were to reach a consensus on priority questions for NSEs clinical trials and to propose trial designs for each of the priority questions. Organized around three sessions (background and previous recommendations, priority questions, and outline of potential trial designs), the consultation allowed ample time for the experts to debate. These discussions led to the recognition of three main groups of possible research questions: questions related to early and late BCG vaccination, questions on the order of vaccines, and questions linked to the general hypothesis that killed vaccines are harmful while live vaccines are beneficial. These question groups became the basis for experts to outline possible NSEs trials. Generally speaking, the experts agreed on the need to equally evaluate questions of both deleterious and beneficial effects, although deleterious effects may have a greater role in terms of policy-making.

The first potential trial proposed was an individually randomised controlled trial to assess various schedules of traditional vaccines to reduce overall childhood morbidity. The vaccines considered were DTP (either alone or as combined pentavalent vaccine with Haemophilus influenzae type b and hepatitis B components), oral and inactivated polio vaccines, and measles-containing vaccines. Designed as a multi-arm comparative or as a factorial experiment, the trial would essentially compare schedules with an additional dose of measles-containing vaccine at 18 weeks of age and a sequence of vaccines between ages 14 weeks and 9 months different from the traditional EPI schedule. The distinct feature of this trial is that it would simultaneously test both the general principle of detrimental effects of DTP- and measles-containing vaccines and the influence of the order of vaccines traditionally included in national immunization schedules. Nevertheless, it is in principle a complex trial, particularly because of the potentially large sample size.

The second potential trial proposed was a randomised placebo-controlled trial to assess the effect of BCG given within 24 hours of birth or later (e.g. at first immunization contact) against severe clinical infections and death. Randomization could either be individually or by cluster. Testing vaccine NSEs by deferring the BCG administration usually indicated at birth is not a novel proposition, as several similar trials have been completed or are being carried out. The proposed trial essentially aims to generalize some of the ongoing trials by replicating them in diverse settings that also feature low HIV-infection background rates. BCG is an ideal vaccine for assessing NSEs because it is given early in life, there is only one dose, and it is a live vaccine.

The third proposed set of trials aimed to leverage the opportunity of new vaccine introductions to test the potential effects of the order of live versus killed vaccines on all-cause mortality and

morbidity. The general principle tested is whether NSEs depend on the time spent in which a killed or live vaccine was last in the administration sequence.

Review

Many possibilities exist because new vaccines have been continuously introduced. Depending on whether the vaccine being introduced is live-attenuated or killed, a cluster-randomized trial would test the effects of the order with an already planned or additional dose of a killed or live-attenuated vaccine, respectively, with an interval of 1 month between vaccines doses. Passive or active surveillance (depending on setting) could be used to monitor morbidity and mortality, and samples from some participants could be stored for embedded immunological testing.

With perhaps the exception of the proposed trials linked to BCG vaccination (for which several experiences exist), a caveat is that experts had limited time to debate on the feasibility of the proposed trials. In fact, it may not be until full proposals are developed that challenges may become apparent and may require additional discussion.

It was noted that the second proposed trial seemed to be the most feasible and cost-effective approach. This is especially true given that countries are currently introducing HPV, PCV, dengue, and other newly available vaccines, precluding the use of the third proposed trial. It was argued that the first proposed trial sounded complicated, and that the questions can likely be answered from previous studies. Comments on the drafted protocols for the three proposed trials included the need to include ninth month IPV doses in one of the study arms, the practicality of implementing individual randomized controlled trials, and the need to include settings with different levels of morbidity and mortality. Cluster-randomized trials were suggested instead of individual randomization in order to simplify the trial design and make the results easier to interpret. In order to reduce confounding within the trial, the use of placebos and blinding in the protocol for the third proposed trial was discussed.

Discussion

The feedback of the IVIR-AC members will be used to develop the trial outline into generic protocols that can be widely applied. The more prospective approach was employed in order to determine what NSEs issues needed the most attention. The next mandate is to develop the protocols for the various questions and address morbidity and mortality. The committee discussed whether one of the proposed approaches or another approach entirely might have the greatest policy impact and the most credible outcome. The focus was shifted to prioritizing the three approaches and the six incorporated questions, and to proposing whether or not the questions seemed reasonable. It was stressed that both beneficial and deleterious NSEs need to be examined, particularly with regards to IPV doses, in combination with measles, or in a specific sequence. There is a great need to address the general hypothesis that killed vaccines are harmful while live vaccines are beneficial, but perhaps the four proposed study arms are not the most efficient study design. The third arm of the first proposed trial could potentially include just IPV and measles, as it was stressed that the existing study arms are trying to address too many questions without remaining comparable.

Questions to be addressed

- Should additional questions be considered? If so, why?
- Does IVIR-AC have any comments on the proposed synopses and protocol drafts?

Summary and recommendations

The IVIR-AC meeting in 2015 emphasized the importance of randomized trials within nested immunological studies. The Committee considered priority questions for NSE clinical trials, including trial designs for each priority question, as proposed by the participants of an ad-hoc consultation in February 2016.

Recommendations

- IVIR-AC considered the conclusion of the IVIR-AC meetings in 2014 and 20152 that further observational studies are unlikely to inform public health decision-making, thus reaffirming the importance of randomized clinical trials. The Committee acknowledged the progress made towards the refinement of priority research questions and trial designs resulting from the ad-hoc expert consultation, and also recommended that any trial design proposed should have its own rationale.
- IVIR-AC endorsed the designing of one or more protocols to assess the prospective non-specific effects of immunization on mortality. The work of the WHO Secretariat needs to be completed in preparing the protocols for the questions identified and trials outlined during the ad-hoc expert consultation of February 2016. These generic protocols would enable harmonized implementation of the trials across multiple settings. While further development of all the proposed trial designs is important, IVIR-AC recognizes that full evaluation necessitates a complete protocol. IVIR-AC will help inform decisions on feasibility and the selection of designs, and formulate questions.
- IVIR-AC members will continue to guide future WHO consultations, and review and comment on the protocols while being developed.

Session 3 WHO vaccine-preventable disease (VPD) evidence synthesis tool

Introduction

In 2014, IVIR-AC recommended that WHO facilitate a "hub" of data evidence and visualizations to assess the burden of disease and its economic impact. An overview was given of the WHO-commissioned project, including the creation of a web-based information portal detailing the international burden of vaccine-preventable diseases (VPD) and vaccine impact. Specific objectives included providing transparent information on VPD burden and impact assessment work to principal users (such as NITAG and decision-makers), identifying gaps and priorities for researchers, policy-makers, and donors, and bringing issues to the attention of other advisory committees and independent review groups. The user interface of the VPD portal was developed with front-end users in mind: NITAG members, EPI project managers, researchers and academics, donors, and journalists. In terms of data management, the data is stored in a Drupal relational database on the back-end. The data management structure allows interaction with data both in the user interface and through an application programming interface.

It was outlined how a literature review was carried out in order to obtain 60 to 80 papers per VPD, organize those papers into sub-categories, enter the key data from each paper into a spreadsheet, and determine major themes by VPD. This enabled the team to evaluate the strength of evidence so that the data could be used for visualization. The general approach to data visualization included assessing the goals and target users, creating basic design mock-ups for critique, verifying data availability and access, creating functional prototypes, and deploying the visualizations. It was noted that one form of data visualization cannot serve all needs; rather, the approach depends on the intended audience and purpose of communication. There is a trade-off between user motivation and interface complexity, but identifying the users and their levels of expertise can help inform the complexity of the visualizations. The design process included evaluating existing resources, establishing clear goals based on the target audience, and following an iterative approach critique and development.

The major categories for data visualizations include burden, incidence, and prevalence, health and economic impact, and efficacy/effectiveness. The data is output in three ways: graphs/visualizations, tables, and narrative summaries of evidence. The challenge was the need to make visualizations unique but intuitive. The types of information conveyed included age, location, magnitude, strength of evidence, and epidemiological details. The different tools available for visualization and gave a number of examples of the way the data was represented were discussed, such as for the disease burden of rotavirus in different regions in order to better understand the economic impact of vaccination and inform a national recommendation.

Review

This was an ambitious undertaking, and the website needs to be tailored to the users, especially because many different groups may be using the website. In terms of tailoring the website for different users, it was noted that more technically competent users want full functionality while a journalist would need less technical communication. There were multiple issues with the quality of the website, but noted that it was at least easy to use. It was questioned whether translations were planned in different languages. A credible website needs to have very careful editing, and multiple errors were found in the draft versions. Some of the visualizations, particularly the bubble graphs, were confusing to understand and interpret, particularly when comparing different settings that had

significantly different levels of disease prevalence. There was a lack of consistency in terms of using proportions or rates, and said that one data field needed to be selected and applied throughout.

It was also argued that the website needed a better sense of the objectives behind the hub so that policy-makers, donors, and other users can draw out research gaps more easily in order to inform recommendations. The presentation was heavily based on the development of the visualizations, as opposed to the meaning behind them, and that this issue was also present with the website itself. While uploading new resources is important over time, it needs to be confirmed that only authenticated, high-quality submissions are being included. There was a heavy focus on managers and NITAG members, but the importance of policy-makers being able to use the website and interpret the data more easily. The website was arguably excessively technical in some areas and difficult to interpret from a policy perspective. The timeframe for populating the website with other diseases was questioned to ensure that the data is updated in a timely manner. There were questions about issues with methodological differences between papers and how to ensure that the methodology in each paper is sound and that they are consistently represented on the website.

Discussion

The utility of the website was brought up as a means to convey the collected information, and the importance of using not just any data, but only evidence that has already been vetted by WHO committees. The WHO has internationally accepted mechanisms to evaluate the standard of evidence, ensuring that the papers included from the systematic reviews are only of high quality and evidence grade. It was stressed that approach, rather than the technical details of the visualizations, was most important: the creation of a global repository of data that can actually be used and interpreted to answer specific questions. This aligns with the issues of the interpretability of the visualizations brought up by the reviewers, as the website's utility depends on its users being able to make use of the data.

The issue of fully authenticated information was continually discussed, because of the importance of ensuring that all data included in the system is valid and reliable. It was clarified that the overall data hierarchy included data authenticated by WHO, WHO position papers, SAGE recommendations and articles, other systematic reviews, and then other papers. The idea of unauthenticated users came from the use of a system where users can alert the system of new information, but new data first checked by administrators rather than posted immediately. The importance of balancing data quality with timeliness was stressed, so that new data can be entered but without making the process dependent on unauthenticated users.

Researchers and policy-makers in low-resource settings need to be able to identify research gaps and understand the data from both generic and technical perspectives. This indicates that the website needs to be simplified, both in ease of use and in data presentation. From a regional perspective, it is critical that users in LMICs are able to access and interpret the information. Capacity-building and training can help with access, but this kind of website with all of this information readily available will prove extremely useful for those in low-resource settings who are otherwise unable to perform literature reviews. The website will also be useful for EPI managers to educate and train healthcare providers on disease burden, intervention impact, and vaccine safety. This will reduce hesitancy and ensure that the medical community supports the introduction of new vaccines. Journalist access and interpretability was questioned, particularly in terms of portals on vaccine safety and efficacy, because the terminology is not necessarily readily interpreted. Spread of misinformation based on incorrect interpretation of the data could cause further issues with vaccine hesitancy and reluctance in LMICs. The website needs to be able to handle a wide variety of requests, from data visualizations to high-level summaries to brief overviews of evidence and

current recommendations. Different users should be able to access varying levels of evidence in order to justify the overall summary. New data is consistently being collected in low- and middle-income countries, so the issue of new evidence being added in a timely manner and being promptly incorporated into the recommendation was discussed. It was heavily stressed that the website needs to be able to handle the dynamic environment of global disease burden data while still providing reliable and valid estimates that have been authenticated by the WHO.

Questions to be addressed

- What are the priorities with regards to the key issues, the tasks, questions and frequencies the portal needs to address?
- Provide feedback on the quality assessment methods of the data/information in the portal
- Provide feedback on the visualisation of the data

Summary and recommendations

In 2014, IVIR-AC recommended that WHO facilitate a "hub" of work to assess the burden of disease and its economic impact, to include an associated network of experts. The WHO Secretariat commissioned the work through a competitive bidding process and presented the Committee with a preliminary draft which included the underlying tools used to synthesize the evidence.

Recommendations

- The VPD evidence synthesis tool should contain evidence vetted by WHO for decision-making criteria or parameters and should create and support discussion during country-level decision-making processes.
- The tool should be linked to the National Immunization Technical Advisory Committee (NITAG) Resource Center and other sites including the National Institute for Health Research SYSVAC,3 a database of systematic research on vaccines and immunization.4
- WHO should establish standard operating procedures to define how the emerging content will be vetted and updated to the portal (including timelines).
- Special attention should continue to be given so that common challenges of sustainability and comprehensiveness of the tool are anticipated and addressed.
- Main targets of the portal should be policy-makers and supporting staff, particularly those of NITAG including its secretariats and decision-makers.
- Follow-up meetings should be arranged to discuss and plan data visualization and communication efforts.

Session 4: Rotavirus mortality

Introduction

Rotavirus is a leading cause for diarrhoea amongst young children and infants globally. Following extensive trials to ensure safety and establish efficacy, the two currently available vaccines (Rotarix and RotaTeq) have been licensed and are now part of many childhood immunisation programmes. However, some countries, particularly those Africa and South East Asia, have yet to introduce Rotavirus vaccines.

While the mortality due to rotavirus can be minimized through appropriate clinical case management, in particular with rehydration, vaccination may present an opportunity to quickly reduce child mortality in some areas in low- and middle-income countries where case management or access to care is suboptimal. Therefore, establishing the burden of rotavirus mortality is critical in assessing the value of rotavirus vaccine introduction in these countries.

To date, three approaches have been published that estimate global rotavirus mortality. The respective model estimates for 2013 were 120,000, 160,000 and 220,000. IVIR-AC was presented a comparison that aimed to identify the drivers of such differences. The comparison showed that differences in the components of the estimates were relatively small but still visible on country level, and that they multiplied up to the reported twofold difference in estimates. Reasons for the differences include the use of different data sources, the use of different case definitions, the inclusion of vaccine coverage, the ways to account for missing data via covariates, and whether mixed infections were all attributed to rotavirus.

Review

The comparison was considered to be a worthwhile analysis that was thoughtfully completed. In communicating the results, the purpose of the study should be made clear. Drivers of the differences in model estimates include the use of different data sources, the assumption that the incidence of diarrhoea and rotavirus declines at similar rates, the inclusion of mixed infections, and the assumed proportion of acute watery diarrhoea among all diarrhoea deaths. While country-to-country variation is included by two of the models, considerable sub-national heterogeneity is ignored. The age of death was not included in the analysis, but using finer age strata than the presented group of children younger than 5 years of age may improve estimates. Agreement on key data sources may further enhance the interpretability of differences between model estimates. At present, only point estimates are compared. To make an appropriate assessment of differences in predictions, the uncertainty around each of the estimates will need to be taken into account. Furthermore, because most rotavirus deaths are preventable through appropriate clinical care, estimates could be used to assess the functionality of a healthcare system. Guidelines for reconciling mortality estimates are currently missing but would have helped this analysis.

Discussion

The presented work is part of a wider effort to evaluate the impact of rotavirus vaccination. The scope of the work was to identify drivers of the differences in mortality estimates (in contrast to the attempt towards consolidation into a single estimate). IVIR-AC suggested that alongside this work, it should be communicated that rotavirus deaths are preventable through appropriate clinical management. The children that die from rotavirus infection are likely predominantly those with poor access to healthcare and hence at risk of not being reached by vaccination efforts. The suggestion was made to disentangle the individual estimates for the three components for estimating rotavirus

deaths (the under-five mortality estimates, the proportion of those associated with diarrhoea, and the proportion of those associated with rotavirus) and evaluate them individually to get a more appropriate range of mortality estimates.

Question to be addressed

- IVIR-AC's advice on the review of the different modelling approaches for the rotavirus mortality estimates and the proposed best method to estimate rotavirus deaths in the future

Summary and recommendations

Rotavirus is a recognized cause of mortality from diarrhoea in children; however there is considerable disagreement on the number of deaths that occur each year. IVIR-AC was presented with a comparison of 3 sources of estimates (global, regional and national) of deaths from rotavirus in children aged <5 years5 for the year 2013 that aimed to identify the drivers of such difference.

Recommendations

- State directly that most deaths from diarrhoea reflect a lack of access to health care to provide rehydration which results from dysfunctional health-care systems. Assessment of basic health-care services should be incorporated into the presentation and analysis of mortality.
- Understand that estimates of mortality from rotavirus derive from the attribution of aetiology to total deaths from diarrhoea. Therefore, the same comparable sources for aetiology and mortality data should be used.
- Clarify that the purpose of this process is not to create one rotavirus mortality estimate, but to benefit from lessons learned from each estimate and to guide health decision-makers in their consideration of the sources and nuances of the data.
- Continue to improve data sources; consider how to address uncertainty of estimates; consider finer-age strata (important for impact assessment of on-time or delayed vaccination); evaluate the impact of different covariates in the model; and compare the implications of national and subnational data.
- Reliance on proprietary data limits the capacity of interested parties to understand rotavirus mortality estimates, and to conduct independent analyses. IVIR-AC should therefore examine and address strategies for optimally sharing databases and issue a recommendation regarding this at a future meeting.

Session 5: Guide for disease and economic impact model comparisons

Introduction

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

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

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

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

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

Review

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

Questions to be addressed

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

Summary and recommendations

As a follow-up to the IVIR-AC recommendation of 2015, the Committee emphasized the need for guidelines on the best practice for conducting disease and economic impact model comparison exercises. A preliminary framework of the model comparison was presented to the Committee for review.

Recommendations

- IVIR-AC considered that the framework proposed for model comparison was appropriate and that an IVIR-AC working group should be established to develop this.
- One of the goals of model comparison is to report and understand variability and uncertainty between models while taking into account parameter, structural and methodological uncertainty. In order to do this, model comparison exercises need to standardize reporting rather than modelling methods. To correspond with existing checklists, such as the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement, and to allow for results to be reproduced, modelling methods should be transparent.
- Reporting of a model quality assessment is encouraged.
- Pooling models through a weighting score should be considered in future model comparison studies.
- IVIR-AC noted that the informatics capacities now available for modellers and a wide array of scientists make the issue of how to approach transparent, open databases particularly germane and important to facilitate model comparison exercises, and for advancing implementation research in general. Other groups such as Chatham House, and leading

journals have been exploring this topic; IVIR-AC should obtain consensus opinions from other forums, and consider inviting appropriate participants who could provide relevant perspectives and input for discussions during a future meeting.

Session 6: Human papillomavirus (HPV) vaccine modelling in low- and middle-income countries

Introduction

In December 2015, IVIR-AC was first presented with a review of the ad-hoc expert consultation on human papillomavirus (HPV) vaccine research priorities that the WHO Secretariat had convened. The goal of the consultation was to identify implementation research areas that could be important in the near future to inform global HPV immunization policies. The specific objectives were:

(i) To assess evidence on alternative HPV immunization schedules and duration of protection with regard to cervical cancer prevention,
(ii) To review the global burden distribution of HPV-related cancers by viral type and sex and the potential for their prevention through immunization, and
(iii) To assess available evidence on HPV vaccination of boys (clinical, economic and programmatic).

Eleven experts from Africa, Australia, Europe, and North America, including an IVIR-AC member, contributed to the consultation. The four sessions reviewed immunization schedule and protection duration, burden of HPV-related cancers and diseases, male HPV vaccination, and modelling to inform HPV immunization policy-making in low- and middle-income countries. As output from the consultation, the experts recommended a series of actions to synthesize available evidence for immunization advisory groups. These actions include systematic reviews and meta-analyses on the burden of HPV-related cancers and anogenital warts, immunogenicity and efficacy measured in clinical trials of 2/4/9-valent vaccines, and impact evaluations of HPV immunization programmes. Modelling of effectiveness and cost-effectiveness of HPV immunization should be used to bring the information into evidence that can support immunization policy-making. The WHO Secretariat is implementing this work plan.

The three presentations that followed addressed the role of epidemiologic and economic modelling in support of HPV immunization policy-making. In a presentation from IARC focusing on HPV-related cancer control, it was highlighted that the global burden of HPV-related cancers mostly affects women due to the predominant burden of cervical cancer. The annual cervical cancer incidence is actually expected to increase by 56% (from 450,000 to 700,000 new cases each year) between 2012 and 2035 due to demographic and behavioural transitions in low- and middle-income countries. As such, a favourable and time-limited opportunity exists to introduce HPV vaccination in traditional populations in LMICs and also to leverage an anticipated central role of indirect protection (herd immunity). To determine the expected fraction of cancers preventable through vaccination, pre-vaccination HPV prevalence studies are needed. Studies in Bhutan and Rwanda showed that urine-based sampling is acceptable for young women and presents a promising, non-invasive methodology to survey HPV prevalence.

Next, the economic value of additional cancer protection from the 9-valent HPV vaccine in LMICs was presented, as estimated with the Papillomavirus Rapid Interface for Modelling and Economics tool (PRIME). While the impact of HPV immunization programme has been extensively modelled for high-income countries, the distinct benefit of PRIME is that it fills the scarcity of modelling in low- and middle-income countries specifically. The PRIME structure implies some limiting assumptions (i.e., no indirect effects, no non-cervical cancers and anogenital warts, and vaccine prices being based on GAVI, PAHO, and US prices), but the direction of the potential biases can be anticipated. In the future, PRIME should incorporate non-cervical cancers and back-of-envelope estimates of indirect effects as well as employ more recently published vaccine price assumptions.

Finally, evidence was presented from HPV transmission dynamic models and the key gaps that exist in adapting these models from high-income countries to developing settings. The HPV-ADVISE model in particular is an individual-based transmission-dynamic model with components for demography, sexual behaviour and HPV transmission, natural history of HPV-related diseases, cervical cancer screening and treatment, and economy. With regard to girls-only vaccination in LMICs, one can expect high population-level effectiveness and cost-effectiveness that are independent of the type of HPV vaccine used and the number of doses. Extended two-dose immunization schedules are likely the optimal strategy in terms of cost-effectiveness, as long as the longevity of protection of two-dose schedules is similar to that of the 3-dose schedule. Vaccination with the 9-valent vaccine is likely more cost-effective than vaccination with 2/4-valent vaccines. However, this conclusion is based on limited evidence and is dependent on both the distribution of HPV types associated with cervical cancer and the expected herd effects from cross-protection between vaccine and non-vaccine types. As for a gender-neutral HPV vaccination in LMICs, the incremental effectiveness and cost-effectiveness of adding boys to girls-only programmes is unknown. Data are needed on both the burden of HPV-related diseases among men in LMICs and the transmission dynamic models to predict herd effects. In the future, exploration of key issues related to HPV vaccine effectiveness in LMICS is undoubtedly needed. This work requires the adaptation of transmission-dynamic models, such as HPV-ADVISE, to examine the potential impact of sexual behaviour, sexual mixing, and cervical cancer screening patterns specific to LMICs on the predictions of population-level effectiveness and herd effects.

Review

During the review of the topic, the framework for further evidence elucidation and the presented modelling efforts were endorsed. Even though PRIME does not include population-level herd effects, it remains a useful tool in the short term. Data on background HIV prevalence and (though likely sparse) population mixing patterns in LMICs should also be considered in modelling. More details of the cost-effectiveness analyses should be made available, in particular on the drivers of cost-effectiveness; for instance, a cost-effectiveness plane may be helpful. The nature of the comparator for the economic analyses and the major uncertainty associated with the cross-immunity from vaccine to non-vaccine HPV type should be clearly indicated.

Discussion

The discussion highlighted some specific points. Models such as PRIME could be linked into transmission-dynamic models through a user interface. In particular, this interface would allow users to specify key model drivers. An alternative solution could be to train an emulator with the outcomes from individual-based models. Cervical cancer occurrence is the key driver of effectiveness analyses, although other cancers do have a non-negligible role. Some evidence indicates that the probability of progression from an HPV infection to an HPV-related cancer changes with age. This age-dependent risk may need to be considered in modelling. It was questioned whether models should consider the eventuality of HPV vaccines only offering a partial immunity (“leaky vaccines”). It was also suggested that if vaccinees might have a reduced chance of infection, vaccine protection could be exposure-dependent and long-term prediction results could vary. Nonetheless, there is little evidence for either issue; in particular, no leaky protection has been observed in clinical trials against HPV types 16 and 18 (although it may occur for cross-protection to non-vaccine high-risk types). Furthermore, methods to address the scarcity of data on mixing patterns in LMICs should be considered. Finally, it was noted that hospital costs are increasing faster than inflation and this situation may affect predictions. In LMICS, cancer treatments are gaining relevance, which is also leading to an increase in treatment costs exceeding inflation. Cost changes over time (either because

of increased inflation-adjusted hospitalization costs or improved treatment access) are not included in the models and thus cost-effectiveness analyses currently assume that all costs change in the same manner.

Questions to be addressed

- IVIR-AC members were asked whether the proposed approach is adequate and whether they had specific recommendations on modelling.

Summary and recommendations

As a follow-up to a WHO ad-hoc expert consultation in 2015 on priorities for HPV vaccine research in general disease and the economic impact, IVIR-AC proposed modelling activities specifically to compare 9-valent versus 2/4-valent vaccines; gender-neutral versus girls-only vaccination strategies; and 3-dose versus 2-dose schedules in low- and middle-income countries (LMICs). The modelling framework and plans to address the questions were presented to IVIR-AC for review.

Recommendations

- IVIR-AC endorsed the proposed framework to evaluate different HPV immunization strategies, particularly the intention to review systematically the burden of HPV-related cancers and anogenital warts, immunogenicity and efficacy of HPV vaccines in clinical trials, and effectiveness in post-introduction impact evaluations. Through modelling, the framework would also encourage the estimation of incremental effectiveness and cost–effectiveness of gender-neutral HPV immunization and catch-up vaccination compared with the currently recommended “girls-only” strategy.
- In the short term (within the second quarter of 2016), modelling with the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) tool should be conducted to contrast the cost– effectiveness of bivalent, quadrivalent and nonavalent vaccines in 179 countries of the strategy targeting girls only. The inclusion of population-level herd effects in PRIME is advised. With regards to the adaptation of transmission-dynamic models – which have been helpful to support policy-making in high-income countries – key issues relating to HPV immunization effectiveness in LMICS (such as variability of sexual behaviour, cervical cancer-screening patterns, and background HPV infection rates) should be characterized. Finally, the worldwide burden of anogenital warts, including by serotype, should be systematically reviewed to provide input data to further modelling.
- In the medium and long terms, transmission-dynamic models adapted to LMICs should examine the effectiveness and cost–effectiveness of different HPV immunization strategies comparing “no vaccination” and in combination with cervical cancer screening strategies, schedules and vaccine types. This work may start by re-calibrating the existing individual-based HPV model to the specific situation of 3–6 LMICs. Given the complexity of trans-mission-dynamic models, IVIR-AC suggests the use of one or more emulators that serve as user interfaces to simplify the evaluation of a variety of permutations, thereby facilitating in-country assessments and local ownership of effectiveness and cost–effectiveness analyses.

Session 7 Influenza-specific economic guidelines

Introduction

The products presented in this session comprise the "Guidance on the economic evaluation of influenza vaccination" developed at University of South Wales, Australia, as well as the "WHO Manual for Estimating the Economic Burden of Seasonal Influenza" developed at Monash University, Malaysia. Both products were reviewed in 2015 by an independent group of experts and again by a subgroup of IVIR-AC in two telephone conferences in 2016. The "WHO Manual for Estimating the Economic Burden of Seasonal Influenza" in addition had been piloted in the second half of 2015 in nine countries. Results were presented by countries at a WHO technical consultation in December 2015, confirming the feasibility and utility of the manual and tool. The two information products were put in context with the strategy from WHO to provide countries with the necessary guidance documents, tools, and information to make evidence-based decisions in the context of influenza vaccine introduction. The main questions of interest to IVIR-AC included a request for advice on what is needed to implement the guidelines in LMICs, and also which alternatives for fixed CE thresholds would be available to interpret cost-effectiveness results in LMICs.

The "WHO Manual and Tool for Estimating the Economic Burden of Seasonal Influenza" was presented as a hands-on tool complemented by a manual providing practical guidance on how to estimate the economic burden associated with seasonal influenza. It was stressed that the economic burden of influenza in low-resource settings encompasses multiple dimensions including both direct costs to the health service and households (e.g. hospitalization and outpatient care costs) and indirect costs due to productivity losses. Solid disease burden data was seen as prerequisite to ensure a valid analysis of the economic burden of influenza disease.

The "Guidance on the economic evaluation of influenza vaccination" was described as an influenza-specific guide outlining key theoretical concepts and best practices in economic assessment methodologies, focused on LMICs seeking to conduct, commission, or critically appraise cost-effectiveness analyses of influenza vaccination. The guide outlines the estimation of costs of vaccination programmes, impact assessment, incorporating herd protection effects, and key issues related to disease burden (e.g. challenges of estimating disease, economic impact of non-medically attended cases, choice of DALY versus QALY).

Review

The WHO influenza economic value chain analysis approach into country contexts was presented using epidemiological surveillance standards and the importance of working on guidance to optimize processes for dissemination of results was also stressed. For the guideline implementation, it was suggested that countries should share best practices experiences of using disease burden, economic burden, and cost-effectiveness information that helped to shape policy decisions. Other suggestions for success factors included securing sufficient funding for economic analyses and establishing local research teams to support the roll-out. WHO should provide technical support where needed and provide support to countries on how to use the evidence at global level and through regional hubs. Single or range thresholds, use of benchmark interventions, and league tables could be used to inform cost-effectiveness analysis agreement. Outcomes in either QALY or DALY should be transferred into monetary units (benefit-to-cost ratio, ROI) to strengthen decision making processes in countries.

Feedback was provided on the two information products. For the "WHO Manual and Tool for Estimating the Economic Burden of Seasonal Influenza" it was acknowledged that the necessary amount of detail in the table was based on differing information needs in countries and adaptations to local contexts. With regard to attribution of costs, it was questioned how an economic burden analysis could also account for who exactly bears the economic burden (individual, government, or third parties such as insurance companies) and what economic benefit from implementation of the roll-out could be expected, such as to vaccine manufacturers. The "Guidance on the economic evaluation of influenza vaccination" was endorsed, both the methodological recommendations and in particular the practical value of building costing into clinical trials where possible. It was suggested that influenza should be seen as three separate diseases (type A H1, type A H3, and type B), each with a separate epidemiology, age group, disease expression, mortality, and cost. It was also indicated the importance of vaccine acceptance and the value in modelling adjunctive control measures such as absenteeism vs presenteeism (voluntary self-isolation / paid sick leave).

Discussion

Following a discussion on the aspects raised by the reviewers, the IVIR-AC recommended that epidemiological surveillance standards should be included in the WHO influenza disease and economic value chain in order to support country level decision making. Furthermore, the underlying data should make use of local information from a variety of sources.

Existing country experiences should be supported by WHO by facilitating the sharing of information on the use of disease and economic burden formation in policy decision. This would help to generate policy demand for studies in other settings. Accordingly, the WHO influenza economic value chain should also include components to support communication of evidence and results from economic studies with decision-makers.

The original question to IVIR-AC on the use of fixed thresholds was considered to be beyond the scope of IVIR-AC. If countries do not have cost-effectiveness thresholds, IVIR-AC recommends the use of alternatives such as:

1) Benchmarking interventions at local level,
2) Cost-effectiveness league tables, and
3) Transferring outcomes (in either DALY or QALY format) into monetary units for benefit to cost ratio or return on investments.

Furthermore, economic burden outcomes should attribute and clarify who in society is bearing the costs of the disease in question. IVIR-AC also recommended that the influenza vaccine-specific economic evaluation guidelines should recognise the different effectiveness and cost-effectiveness of the different influenza types and subtypes.

Questions to be addressed

- Endorsement of the economic guidelines and what is needed to implement the guidelines in LMICs?
- IVIR-AC to propose alternative ways for fixed CE thresholds to interpret CE results in LMICs?

Summary and recommendations

IVIR-AC reviewed the WHO influenza disease and economic value chain – a set of guidance documents and tools that supports country-level decision-makers in assessing the economic and social benefits of introducing influenza vaccination or expanding existing vaccination to specific target groups, such as pregnant women, health workers and older people.

Recommendations

- IVIR-AC suggested that the WHO influenza disease and economic value chain should include epidemiological surveillance standards; that the underlying data should include local information from a variety of sources; and that the value chain should address how to communicate the evidence and results from economic studies with decision-makers.
- WHO should support the sharing of existing country experience regarding consideration of disease and economic burden in policy- and decision-making in order to generate policy demand for such studies in other settings.
- The original question to IVIR-AC on the use of a fixed cost–effectiveness threshold is beyond the scope of this Committee due to it being related to general cost–effectiveness in health rather than specifically to vaccines. However, if countries have not gone through the process of defining their cost–effectiveness thresholds, IVIR-AC recommends they use alternatives such as 1) benchmarking against the least cost–effective health interventions already funded by relevant jurisdictions; 2) using cost–effectiveness league table approaches; and/or 3) transferring outcomes (in either DALY6 or QALY7 format) into monetary units for benefit to cost ratios or return on investments.
- Economic burden outcomes should clarify who bears the costs of the disease in question.
- IVIR-AC recommends that the influenza vaccine-specific economic evaluation guidelines should recognize differences in the effectiveness and cost– effectiveness of various influenza vaccines based on presentation, formulation, and circulating types and subtypes that vary over time and place.

Session 8: Cholera disease burden

Introduction

In many low- and middle-income countries, cholera regularly causes morbidity high enough to severely disrupt health services. Cholera occurrence is highly spatially and temporally variable, and outbreaks cease quickly, often not permitting counter measures to be established. Risk factors associated with the likelihood of infection are thought to include limited access to clean water but vary widely between studies. The global oral cholera vaccine has made more than two million doses available, but limited supply means that vaccination efforts have to prioritise the populations most at risk for cholera infection and severe disease, such as those with limited access to health care.

IVIR-AC was presented with an effort to map estimates of reported sub-district cholera incidence with the prospect of inferring the global burden of cholera by extrapolating to areas with little or no data. The ongoing work has underlying data on reported cholera cases during the last five years on country, district, or sub-district levels. These are combined via Poisson regression using covariates including population density, access to drinking water, access to sanitation, and distance to the nearest major body of water in order to infer cholera incidence in the absence of data. At present, the work is focused on Africa but an extension to the rest of the world is planned.

Preliminary results show the potential of this work to identify areas at risk for cholera, characterised by a high predicted incidence, to estimate the impact of interventions or weather phenomena like El Niño through temporal comparison of estimates, and to identify data needs by identifying areas with high variance around estimates. Future plans for this work include moving from interpolation of the reported burden to a projection of the true burden of cholera by the inclusion of a parameter reflecting the regional reporting behaviour, validation of the approach through comparison with additional data, inclusion of additional covariates to improve prediction in areas with scarce data, and automation to allow regular updates with limited additional person-time.

Review

IVIR-AC noted that the underlying data will need more detailed assessment in order to allow for meaningful estimates of disease incidence. In particular, the case definition will need to account for whether a case was classified as suspected or confirmed, and data from outbreaks will need to be distinguished from data from routine surveillance systems that are more likely to provide temporally consistent information on the burden of cholera. Furthermore, cholera is more diverse than the currently considered maximal spatial resolution; hotspots are usually only parts of cities, so a finer resolution would be required if the work was to inform vaccination efforts or outbreak risks. Risk factors associated with cholera are geographically diverse, raising further concerns for the use of such systems to infer cholera incidence in areas with a lack of data. In particular, extrapolation to other continents with limited data, such as Asia, will need thorough validation in order to be useful. While this is difficult with the use of maps, it remains important to communicate uncertainty alongside the predictions.

Discussion

In the following discussion it was raised that the majority of data used in the analysis is from country-level surveillance on acute watery diarrhoea, and includes only suspected but few confirmed cholera cases. This could be made more explicit in communication of this work. IVIR-AC noted that any temporal comparison of model estimates to predict changes in the cholera burden as a result of interventions is prone to error from strong variations in cholera incidence with time and

location for yet poorly understood reasons. Changes in reporting may also distort estimates. Any such comparison will at least need to assess whether the change in cholera incidence exceeds the expected variability stemming from variable cholera epidemiology combined with prediction uncertainty. The prediction uncertainty in its current form is likely to be underestimated because the model does not account for over-dispersion. In particular, such predictions may not be meaningful in regions where the burden is extrapolated mainly from covariates.

It was commented that the standard deviation of the predicted incidence is a suboptimal measure of uncertainty when used to identify regions with the need for more data (as presented) because high variance may result from temporal changes in incidence rather than from an absence of good surveillance. Sharing a plan on how to estimate reporting rates that ultimately will allow the model to provide estimates of the true burden of cholera was encouraged, alongside further model validation potentially based on using only a subset of the available data for predictions. It was noted that phylogenetics present a potentially useful tool to better understand the transmission dynamics of cholera and to better define regions, and possibly overarching districts and countries, that present a more homogenous choice for epidemiologically similar zones with respect to cholera incidence.

Question to be addressed

- IVIR-AC's advice on modelling methodologies for estimating cholera incidence and regional distribution

Summary and recommendations

IVIR-AC reviewed an effort to map estimates of reported sub-district cholera incidence with the prospect of inferring the global burden of cholera including extrapolation to areas with little or no data available.

Recommendations

- The investigators should acknowledge more clearly that their model is descriptive rather than predictive. A predictive model for cholera is unlikely to be accurate in view of limited data and the diversity of transmission patterns and risk factors, which change over time and in various geographical settings. In addition, arbitrarily small geographical units, and the paucity of high-quality data on detection and incidence, limit the accuracy of predictive models for cholera.
- The model structure should start with questions posed (for example on the purpose of developing the model and graphs); confirmation of the target audience and how the model would be of benefit; confirmation of its potential use for advocacy, for immunization recommendations by NITAG secretariats, by the GAVI Alliance, for public health messaging or for impact assessment.
- The modelling effort at global level should focus on issues identified by the Global Taskforce for Cholera Control and the GAVI Alliance being key decision-makers on the use of vaccines.
- Data sources should be clearly identified, including the number of cases, the time period of acquisition, geography, source, and whether cases are suspected or confirmed.
- Outbreaks of cholera (e.g. variation from baseline) should be distinguished from endemic disease. Maps should include both since public health implications and interventions differ based on whether cholera is changing from baseline or is static.
- The model should distinguish confirmed cases from suspected cases, to determine whether, and to what extent, epidemiological patterns change, if at all.
- Uncertainty needs to be better acknowledged with regard to knowledge of the disease, the unpredictable spread of cholera due to the diversity of transmission patterns, and risk factors.

Session 9: Immunization e-registries

Introduction

Electronic immunization registries (EIRs) contain population-based individual data, including each individual's identification, contact information, characteristics, immunization history. This is collected and organized on a national or sub-national scale. The difference between EIRs and traditional systems is that central paper-based aggregation requires collection from each individual level, such as the community, vaccination provider, district, and province, whereas EIRs are constantly collecting information from all levels at once. EIR functions include patient and child registration, scheduling and registration of vaccinations, planning or defaulter tracking, reminders and recalls, and coverage information. Other uses include monitoring inequities and timeliness, cohort monitoring, decision support, including vaccines and supplies, and acting as a notice board. EIRs enable countries to consolidate immunization histories and better compare actual coverage to the aspired targets. However, EIRs are not perfect, given the denominator problem in which entries may be excluded or included incorrectly, resulting in inaccurate estimates. Many high-, middle-, and low-income countries have either established national registries, are scaling up sub-national registries, or are developing early pilots.

The role seen for WHO in EIRs is to develop global functional data standards, as well as regional implementation guides. WHO should provide methods for evaluation as well as advocacy for different countries in implementing EIRs. Several regions are actively supporting UN member states with planning, implementation, improvement, and evaluation of EIR. WHO should facilitate knowledge and experience sharing, as well as provide implementation guides to improve the capacity for operational research. There is a discernible lack of research on EIR data quality, cost studies, implementation barriers, and sustainability issues, particularly in low- and middle-income countries. EIRs are hugely beneficial because they can produce the data required for effective research into vaccine effectiveness and safety, vaccine hesitancy, equity, and program efficiency.

Barriers in EIR implementation in low-income countries include lack of infrastructure, inappropriate technology, implementation costs, lack of information technology (IT) and human resource (HR) support, lack of sustained financing, governance issues. Barriers that are also relevant in wealthier countries include a lack of e-health strategy, lack of legal frameworks, and low acceptability among both patients and providers. The proposed next steps in EIR implementation and monitoring include confirming priority and funding for different countries, and examining additional experiences in more countries. Carrying out a literature review to determine the current status of EIRs in LMICs will also be essential, in order to leverage ongoing projects (such as in Nepal) to implement key operational research. Priorities need to be established, like determining the most important barriers in low-income countries, and assessing which strategies have worked well to mitigate concerns.

Review

Several potential problems for both paper registration systems and electronic registries were noted. These issues included errors (both voluntary and involuntary) in recording vaccine doses, errors in data entry, inaccurate denominators (either incomplete or duplicate entries respectively reducing or increasing the denominator incorrectly), and not including doses given by private providers or other sectors (like social security). Only the paper registration system allows for errors in aggregation, but given the problems shared between the two systems, the aggregated digital answer can also be noticeably inaccurate. Good electronic information registries must ensure that the design includes all necessary variables, especially when vaccines or doses change. The necessary materials and equipment must be available and functional, and the quality of information should be reliable.

Providers need to track individuals for timely follow-up and maintain confidentiality. The denominator problem previously mentioned should be under constant surveillance in order to ascertain movement of entries in or out and determine a lack of connections to health services or devices.

WHO should be involved in electronic immunization e-registry development. WHO should identify the circumstances in which the registries can be successfully introduced, as well as what factors are necessary but not sufficient for success. The most important risks that guarantee failure in system introduction should be determined. WHO should also establish the physical, intellectual, communal, and financial resources that are needed to design, introduce, and maintain an electronic registration system. It should also be ensured that data will be used by providers in order to improve immunization services.

There are regarding the transfer of the experience from high-income countries to LMICs, and the lack of resources available for EIRs in developing countries. The possibility of cataloguing scenarios on the experience of LMICs was questioned to determine how to best implement EIRs based on the starting point in terms of existing country registries. This could help provide an idea of the best strategy for implementing EIRS based on the setting. Looking at the experience with EIRs, the difficulties in transitioning from paper to electronics were also noted, as well as the adjustment required in trusting the electronic system. There is a wealth of experience in the various problems that have come up in high-income countries, such as managing pharmaceutical supplies and linking it to various reports and prescriptions in hospitals. The issues in low-income countries might include making the electronic health immunization records available across facilities so that patients can be tracked to take advantage of that opportunity. There are dual interests in implementing EIR: firstly the improved coverage and the benefits to individuals by being able to track people and follow the experience. The second benefit is the ability to compile and aggregate national databases in order to determine whether strategies are working well. There is a potential impact of promoting the use of EIRs on reducing the missed opportunities for vaccination.

In terms of potential research questions, it was suggested that using these EIRs not only enables the monitoring of information coming through, but also provides the system for other vaccination issues. Countries do not necessarily have a single government system that has been uniformly implemented; developing and implementing a universal EIR will result in many direct and indirect benefits for vaccination programs. The denominator problem is being addressed, whether it requires additional surveys for effective integration and interpretation of the data. EIRs could contribute to addressing the research question of clinician vaccine hesitancy. The effort to promote vaccination record-keeping, either on paper or electronically, may be linked to enthusiasm for vaccination and strengthening of the immunization infrastructure.

Discussion

Electronic immunization registries have implications for program evaluation, supply chain management, pharmacovigilance, ensuring optimal individual vaccine coverage, vaccine effectiveness studies, and capturing hard-to-reach populations. The problem with creating EIRs in the United States was the lack of input from clinicians during implementation, resulting in a system that providers unanimously found excessively administrative and difficult to use. This resulted in a counterproductive system by failing to take clinical issues into account. The efforts taking place with EIRs in LMICs is motivated by a clear set of objectives in improving the system operation, and recognizes that input from immunization providers is critical. The EIRs also provide potential for communication across systems if they are seamlessly interlinked between facilities at a national level. The potential importance of financial incentives was also noted, given that linking vital

registration data to conditional cash transfers has proven to be highly functional and effective in India. If EIRs are used as a tool to capture hard-to-reach populations, particularly children and adolescents, then both registration drives and immunization programs can benefit. Three beneficiaries of EIR monitoring were noted: program management, service providers, and the community. In many cases, the benefits to the community and the service providers are great enough to justify the benefits of the registry, even if the national management system for monitoring and evaluation is suboptimal.

Questions to be addressed

- Comments on framework and document?
- Identify research gaps?

Summary and recommendations

Electronic immunization registries (IERs) facilitate coverage monitoring in terms of particularity, timeliness and accuracy. The Committee reviewed a conceptual framework to identify research barriers to implement IERs for monitoring immunization programmes.

Recommendations

- IVIR-AC appreciated the value of work presented and acknowledged its potential use within countries for supply chain evaluations, pharmacovigilance, vaccine coverage and effectiveness studies.
- IERs can be regarded as a tool for implementation research, for example by indicating the immunization status of hard-to-access populations and by linking IER with civil and birth registrations.
- The work on IERs should be linked to a similar study at PATH,8 funded by the Bill & Melinda Gates Foundation to identify barriers for implementing IERs in the United Republic of Tanzania and Zambia.
- The work on IERs should focus on country-level programme managers since some might be opposed to moving from paper to e-registries, particularly if both are used in a transition period.
- Paper registries have a long history of use in measuring immunization coverage and individual immunization status; countries choosing to implement IERs should ensure, demonstrate and disseminate that, in comparison with existing methods and relative to cost, IERs improve efficiency in terms of data accuracy, effectiveness and timeliness.
- IVIR-AC suggests WHO support the development of IERs in various ways such as by identifying circumstances in which they can be successfully introduced; identifying the “killer risks” to avoid failures; and identifying resources needed to ensure their long-term sustainability.
- IVIR-AC recommends that research and implementation of IERs should be prioritized and that WHO should find ways of making financial and human resources available.

Annex 1: Agenda

Annotated IVIR-AC Agenda 2016

Monday, 30 May 2016

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
08.30-09.00	Registration			
09.00-09.30	Welcome	Introduction and Charge of the Committee		R. Breiman
	THEME: Research to minimize barriers and improve coverage of vaccines currently in use			
09.30-11.00	***Session 1:*** Missed opportunities for vaccination	- To present the generic study framework and study experiences from African and Asian countries (T. Goodman)	- Do IVIR-AC members have any suggestions on the study protocol? - How generalizable is the study protocol to other settings?	IVIR-AC members: M. Amuyunzu R. Feilden WHO focal point: T. Goodman
11.00-11.30	***Coffee break***			

11.30-13.00	***Session 2:*** Comparison of modelling approaches to estimate global, regional and national estimates of rotavirus mortality.	- To present the Rotavirus Mortality Working Group Report with methods and estimates of rotavirus mortality estimates using different modelling approaches (A. Cohen)	- IVIR-AC members' advice on the review of the different modelling approaches for the rotavirus mortality estimates and the proposed best method to estimate rotavirus deaths in the future	IVIR-AC members: G. Kang D. Burke WHO focal point: X. Riveros-Balta
13.00-14.00	***Lunch***			
	THEME: Research to conduct impact evaluation of vaccines in use			
14.00-15.30	***Session 3*:** WHO Framework on VPD burden and impact assessment	- To present an update of the WHO portal on Vaccine Impact Assessment Data (S. Omer and M.Zook)	- What are the priorities with regard to the key-issues, the tasks, questions and frequencies the portal needs address? - Provide feedback on the quality assessment methods of the data/information in the portal - Provide feedback on the visualisation of the data?	IVIR-AC members: G. Kang M. Amuyunzu WHO focal points: R. Hutubessy
15.30-16.00	***Coffee/tea break***			

16.00-17.30	***Session 4:*** Non-specific immunological effects of vaccination	Summary of ad-hoc expert consultation on clinical trials for NSE held in February 2016 (B. Gessner*) - Proposed research questions (A. Pollard*, P. Fine and WHO secretariat)	- Should additional questions be considered? If so, why? - Does IVIR-AC have any comments on the proposed synopses and protocol drafts?	IVIR-AC members: Y. Teerawattanon P. McIntyre* WHO focal point: A. Vicari
17.30	**Cocktail**	***Venue TBD***		

* by phone

Tuesday, 31 May 2016

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
		THEME: Research to conduct impact evaluation of vaccines in use (continued)		
09.00-10.30	***Session 5:*** Vaccine impact model comparisons	- To present a literature review, framework and plan of activities (M. Jit and M. Brisson)	- To provide feedback on the overall objective and plan for future work	IVIR-AC members: P. Beutels W. Ndifon WHO focal point: R. Hutubessy
10.30-11.00	***Coffee/tea break***			
11.00-12.30	***Session 6:*** HPV vaccine models to assess the impact of various vaccination schedules in LMICs	- Summary of ad-hoc expert consultation on HPV vaccine research priorities held in December 2015 (J. Shiller*) - Burden of HPV-related cancers (I. Baussano) - Modelling effectiveness and cost-effectiveness of HPV vaccination in LMICs (Presenters M. Brisson and M. Jit)	- Are the proposed activities, products and work plan adequate? - Do IVIR-AC members have any recommendations to the modelling approach?	IVIR-AC members: Y. Teerawattananon P. Beutels WHO focal point: A. Vicari
12.30-13.30	***Lunch***			

* by phone

13.30-15.00	***Session 7:*** Influenza specific economic guidelines	- To present the influenza economic burden manual and cost-effectiveness (CE) guideline (P. Lambach and N. Chaiyakunapruk)	- Endorsement of the economic guidelines and what is needed to implement the guidelines in LMICs? Propose alternative ways for fixed CE thresholds to interpret CE results in LMICs.	IVIR-AC members: Y. Teerawattananon D. Burke WHO focal point: P. Lambach
15.00-15:30	***Coffee/tea break***			
15.30-17.00	Reports	Report from GAVI (20') Report from CDC (20')		H. Johnson K. Fox and A. Shefer*
17.00	**Adjourn**			
18.00	**Organized working dinner (AC members only)**			

* by phone

Wednesday, 1 June 2016

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
		THEME: Research to conduct impact evaluation of vaccines in use (continued)		
09.00-10.30	***Session 8:*** Cholera disease burden modelling	- To present preliminary estimates for (reported) cholera incidence and geographic distribution in Africa (W. Perea and S. Moore)	- IVIR-AC's advice on modelling methodologies for estimating cholera incidence and regional distribution	IVIR-AC members: B. Gessner M. Weiss WHO focal point: W. Perea
10.30-11.00	***Coffee/tea break***			
		THEME: Research to improve methods for monitoring of immunization programmes		
11.00-12.30	***Session 9:*** Research on barriers to implement e-registries for monitoring immunization programs.	- Presentation of overall framework and guidance document (J. Grevendonk)	- Comments on framework and document - Identify research gaps	IVIR-AC members: R. Feilden M. Weiss WHO focal point: J. Grevendonk
12.30-13.30	***Lunch***			

CLOSED SESSION

13.30-15.00	Discuss written reports with new studies and updates of ongoing studies reviewed by IVIR-AC	- Pneumo and Hib burden of disease and mortality numbers updates - Hepatitis B impact evaluation framework - Pertussis disease burden modelling and resurgence modelling project	- Optimal vaccine efficacy trials during public health outbreaks and how models can assist - Dengue vaccine update - SAGE April 2016 updates relevant to IVIR-AC - GATHER checklist
15.00-15.30	***Coffee/tea break***		
15.30-17.00	Discussion and write up of final IVIR-AC recommendations		
17.00	***Meeting closure***		

Annex 2: List of participants