REPORT ON THE IMMUNIZATION AND VACCINES RELATED IMPLEMENTATION RESEARCH (IVIR) ADVISORY COMMITTEE MEETING

Geneva, 26-28 June 2013
(Draft version 16 October 2013)

Immunization, Vaccines and Biologicals (IVB)

World Health Organization

Table of Contents

Abbreviations

CFR	Case-fatality rate
CDC	Centers for Disease Control
DALY	Disability Adjusted Life Year
GMP	Global Malaria Programme
HBsAg	Hepatitis B serum antigen
HBV	Hepatitis B vaccine
HPV	Human papilloma virus
IARC	WHO International Agency for Research on Cancer
IVB	WHO Department of Immunization, Vaccines and Biologicals
IVIR-AC	Immunization and Vaccines-related Implementation Research Advisory Committee
IVR	Initiative for Vaccine Research
JTEG	Joint Technical Expert Group on Malaria Vaccines in PivotalPhase III Trials and Beyond
LiST	Lives Saved Tool
LMICs	Low and middle income countries
MPAC	Malaria Policy Advisory Committee
QUIVER	Quantitative Immunization and Vaccines related Research
SAGE	Strategic Advisory Group of Experts
Swiss TPH	Swiss Tropical and Public Health Institute
WHO	World Health Organization
WPR	WHO Western Pacific Region

Executive summary

- WHO is funding a project to provide new data on hepatitis B disease, vaccination and infection measures in relation to vaccine implementation levels, in order to update evidence-based vaccine recommendations. The proposal was well-received by IVIR-AC, although the committee made some suggestions that will be taken into account in a revised proposal. Two IVIR-AC members have also agreed to join the project working group.
- A malaria vaccine (RTS,S/AS01) has shown efficacy over 12 months of follow-up in a large Phase 3 trial, with full trial results expected in late 2014. Five modelling groups have used preliminary trial data to explore the impact and cost-effectiveness of malaria vaccination. IVIR-AC will provide experts on health economics and health systems to advise on these issues to ensure that they are comprehensively captured in the models. IVIR-AC is also considering providing methodological guidelines around how projected demographic changes in LMICs (represented population mobility) should be handled in models. IVIR-AC will be available to review model findings and conclusions before they are presented to SAGE.
- A model to explore the case for investing in measles eradication has been revised to perform analyses at the country-level following feedback from IVIR-AC in 2012. However, IVIR-AC registers concern that the model does not capture within-country heterogeneities in coverage and transmission adequately. Hence, the current model may be insufficient to assess measles elimination goals. Further work that incorporates within country heterogeneity is critical to adequately assess elimination at country, regional and global levels. The modeling group agreed to build in sub-national heterogeneity in their model and will present this to the IVIR-AC subgroup on measles eradication.
- A model has been constructed to re-evaluate the burden of yellow fever in Africa, estimating 850,000-2 million infections with yellow fever virus, yielding 85,000-200,000 cases and 30,000-70,000 deaths per year. The case-fatality rate is higher than previously estimated. The remaining burden is concentrated in countries which were not targeted for investment by the GAVI Alliance. IVIR-AC felt that the model is adequate for yellow fever disease burden estimation across the Africa region.
- A model for varicella burden has been constructed in order to inform SAGE recommendations for varicella zoster vaccination in low and middle income countries. IVIR-AC finds the model to be appropriate although it could be strengthened by capturing uncertainties in data around seroprevalence, case-fatality ratios and morbidity estimates. Better data on disease incidence and outcomes in LMICs are needed before the model can be used to estimate global disease burden. Extending the work to calculate cost-effectiveness of vaccination across a range of possible estimates of disease burden would also be useful for priority setting.
- An exercise is being conducted by WHO in order to develop and prioritise a research agenda for implementation research. A bank of potential research questions was developed from a broad solicitation of experts and reviews of existing reports or reports from relevant advisory committees, for prioritization by an ad-hoc expert group. IVIR-AC is supportive of the effort to make priority setting for implementation research questions more systematic and believes that the overall analytical approach was well-designed. However, contextual variability and considerations will require that the findings not be used as the sole criterion for decision making. Input from a range of stakeholders at different levels besides global and regional will be beneficial in validating the exercise and defining the application of the results.

Introduction

(R. Breiman)

Dr. R. Breiman opened the second meeting of the WHO Immunization and Vaccines-related Implementation Research Advisory Committee (IVIR-AC). IVIR-AC evolved from WHO's Quantitative Immunization and Vaccines-related Research (QUIVER) advisory committee, expanding its remit to include implementation research. The key objectives of IVIR-AC are:

- To appraise methods to estimate disease burden and resolving differences in disease burden estimates.
- To characterise critical factors around vaccine demand and hesitancy.
- 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.

WHO's Department of Immunization, Vaccines and Biologicals (IVB) has conducted an analysis of areas where IVIR-AC has a comparative advantage compared to other WHO committees.

Hepatitis B impact evaluation framework

Introduction

(A. Hall)

Hepatitis B vaccine (HBV) has been available for 32 years but hepatitis B serum antigen (HBsAg) prevalence (reflecting exposure to HBV) in adult males has only recently decreased substantially, due to slow vaccine introduction and the long interval during which hepatitis B carriage can persist. The experience of early adopters in WHO's Western Pacific Region (WPR) suggests that vaccination can bring substantial herd protection against child-to-child transmission. Most cases of carriage acquisition in WPR are now from perinatal transmission. Countries in WPR have mostly advanced from monitoring vaccine coverage to estimating vaccine impact on HBsAg prevalence in children, to reach a target of <2% HBsAg prevalence in children under 5. However, some countries have expressed concern that they may lose funding if they report having controlled hepatitis B. There is also variability in schedules, especially for the birth dose, which affects perinatal transmission.

This project aims to provide new evidence on hepatitis B disease, vaccination and infection in relation to vaccine implementation levels, to provide evidence for updating vaccine recommendations. The project is intended to contribute to ongoing refinement of HBV programmes to minimise disease, as well as sustain political will in supporting these programmes. It has three parts:

- Global disease impact of HBV vaccination – estimating infection prevalence, vaccine coverage, economic measures and trends in liver cancer based on systematic reviews and modelling of health and economic outcomes. A report to SAGE will be prepared.
- Country-level impact of vaccination and strategy in selected countries – epidemiological data in early adopters with good data on HBV and liver cancer epidemiology, allowing between-country comparisons using a standard tool.
- Communication and data sharing – setting up an online database and journal publications to make all information accessible.

Management will be led by Prof. A. Hall, with representatives from IARC, WHO and CDC, as well as oversight by IVIR-AC. An outline of the steps in more detail will be prepared following the current IVIR-AC meeting, and the committee will report back to IVIR-AC and SAGE in 2014.

Review

(P. McIntyre)

The objective of the project is to conduct a comprehensive review of hepatitis B impact evaluation which may be worth narrowing down to a few key objectives, including identifying barriers to implementation. The country-level work should focus on a template for impact assessment or implementation. For instance, justification for delivery of birth dose in settings where this is logistically difficult may be important.

(G. Kang)
Prevalence needs to be defined more precisely – it can refer to acute disease, chronic infection or hepatocellular carcinoma. It is good to stratify countries in the analysis by time of vaccine introduction and performance of immunisation systems and that success in delivering the birth dose within 24 hours of birth as performance indicator for immunisation systems is included in the project proposal. In high income settings, treatment effects also have an impact on transmission.

Discussion

J. Edmunds declared a conflict of interest; he is currently bidding to do the modelling component of the work.

The value of the modelling work is that it allows the impact of HBV on carriage and liver cancer to be measured and demonstrated to decision makers. In many countries this is not obvious from monitoring liver cancer incidence, because increases in cancer incidence have occurred as a result of population growth and life expectancy improvements (allowing more people to reach the ages at which they may acquire cancer).

The main prevalence measure is seroprevalence, as used by WPR. There are no plans to evaluate catch up campaigns, but they may have limited impact if acute HBV is excluded since their effect on perinatal transmission is minimal. Treatment effects are limited outside high income settings. Liver cirrhosis is not being assessed because of poor surveillance data. Liver cancer is being estimated using data from countries with good registries; the strength of a country's registry is assessed through a partnership with IARC. Most regions have many countries with good registries apart from sub-Saharan Africa where there are only a few. It may be possible to explore within-country variations (eg rural vs urban).

WHO recommends that HBV is delivered as a birth dose, but many countries do not follow this, and those which do often have low birth dose coverage. Given the administrative and economic obstacles to birth dose vaccination, it may be worth examining the relative benefits and costs of a monovalent birth dose compared to a pentavalent dose. Other issues to examine are the number of primary doses needed after a birth dose, the impact of catch-up campaigns, particularly in children, and the cost-effectiveness and long-term budget impact of different vaccination strategies.

Summary and recommendations

IVIR-AC is broadly supportive of the framework, and welcomes in particular the assessment of the implementation of a birth dose and its potential impact of hepatitis B transmission. To improve the communication of the project's objective to the broader community it is important that some of the terms and objectives are further spelled out such as the definition of seroprevalence, immunization schedules to be evaluated, estimation of the contribution of hepatitis B to hepatocellular carcinoma, criteria for selection of countries and the project timelines.

IVIR-AC requested that the team incorporates the IVIR-AC suggestions and comments into the proposal, and then circulates to the committee by e-mail within one month, with a final statement within 6-8 weeks.

IVIR-AC suggests that two members of IVIR-AC (Philippe Beutels and Fernando de la Hoz Restrepo) join the project working group to ensure that IVIR-AC provides continued input into the project. Progress will be presented at the 2014 IVIR-AC meeting.

Malaria vaccine impact and cost-effectiveness

Introduction

(P. Smith, JTEG chair)

There is only one advanced malaria vaccine candidate (RTS,S/AS01), which is currently undergoing phase III trials and has demonstrated efficacy in children. Higher efficacy is seen when giving the vaccine to older children (5-17 months) compared to infants as part of the EPI schedule (6-12 weeks). Mathematical modelling using trial results with 12 month follow-up from the Phase 3 trial suggests that efficacy may also vary with local transmission intensity. By late 2014, all trial results will be available including a 30-month follow-up study with a booster dose at 18 months. Final results will help to address remaining unresolved issues such as the effect on vaccine efficacy of changes over time, transmission intensity, maternal antibodies, impact of co-administration of pentavalent vaccine, and prior administration of HBV vaccine. The results will inform discussion by SAGE and the Malaria Policy Advisory Committee (MPAC), ultimately leading to a WHO position paper to guide country-level decision making. Because trial results are also critical for licensure, the manufacturer (GlaxoSmithKline) has faced restrictions in altering its analytical plan in response to WHO requests.

Several models of malaria vaccination have been developed and will help to inform decision making in 2015 by giving an indication of the long-term impact of vaccination. WHO IVR and the Global Malaria Programme (GMP) have organised a Joint Technical Expert Group (JTEG) to evaluate the current status of the models, which met in May 2013. Five groups were represented: three with stochastic, individual-based, dynamic transmission models (Swiss Tropical and Public Health Institute (Swiss TPH), Imperial College and Intellectual Ventures), as well as two with static models (GlaxoSmithKline, and the Lives Saved Tool or LiST group). The first three groups have already published results on vaccine impact; the Swiss Tropical and Public Health Institute have in addition also published cost-effectiveness results.

The modelling groups have been given a standard set of input data in order to generate comparable impact and cost-effectiveness predictions for 2017-2030. The Swiss TPH and Imperial College were able to provide the full range of outputs requested. The most important remaining uncertainties include the duration of vaccine protection and site-specific efficacy for the two potential target age groups. Vaccine price is unknown, with analyses currently assuming the price of $5/dose based on the GAVI Alliance's vaccine investment strategy.

Models predict that vaccine efficacy against clinical malaria wanes more quickly in high transmission settings, so the most favourable cost-effectiveness is seen in medium transmission settings. However, vaccination is still cost-effective in high transmission settings at a range of $50-$200 per disability adjusted life year (DALY) averted in many African malaria-endemic settings. The greatest impact and most favourable cost-effectiveness can be seen in vaccinating children rather than infants (assuming no difference in delivery costs). Analyses suggest that investment in long-lasting insecticide treated nets is still more cost-effective than vaccination, so vaccination should be considered as an add-on to existing preventive strategies rather than a replacement.

The modelling groups were encouraged to further harmonise key parameters such as vaccine costs, vaccine efficacy, demographics and baseline disease burden as far as possible. Uncertainty around vaccine efficacy will be reduced after publication of full trial results in 2013-14. The next iteration of modelling will incorporate 18 month follow-up data, site-specific efficacy and booster dose data. WHO will then organise another meeting to enable comparative assessment of model predictions, which can inform the WHO policy process, post-marketing surveillance and tools for national decision-making. WHO policy recommendations for malaria vaccines in 2015 will focus on clinical trial data wherever available with the use of modeling as an adjunct to inform questions for which there are no clinical trial data available.

Review

(E. Sinanovic)

It would be useful to reach some general conclusions for policy makers as was recently done in WHO model comparison exercises for other vaccines such as HPV, rotavirus and pneumococcal vaccines. Besides epidemiological modelling, there is also a need to consider economic and health systems aspects such as indirect costs, affordability and possible impact of health systems. A budget impact analysis may also be useful to see if the vaccine is affordable as well as cost-effective, and if funding is sustainable after removal of donor support.

Discussion

JTEG currently lacks expertise on health economics and health systems, so it would be useful to have an IVIR-AC member with such experience to join the group. Models do not currently incorporate price maturity so it may be helpful to explore this in sensitivity analyses. Cost-effectiveness results compared to a GDP per capita threshold are not always useful for decision making in these settings; another useful type of evaluation may be to present net costs in terms of the total health care budget of a country. Indirect (herd) effects are not expected to be substantial because of the low target age range for vaccination and short duration of protection. However, the overall impact of vaccination is difficult to determine precisely, partly because many malaria-attributable deaths are due to the interaction of malaria and other diseases.

The current models also have different ways of capturing demographic change, which are difficult to accurately represent in sub-Saharan Africa because of high birth rates. IVIR-AC may need to take a general view on how methodological issues such as these should be handled.

Summary and recommendations

IVIR-AC looks forward to new vaccine trial data and their impact on the output of the models. IVIR-AC is available to review and comment on the results of the malaria models before they are presented to SAGE.

IVIR-AC is considering providing methodological guidelines around how demographic factors in low and middle income countries should be handled in these and other infectious disease models.

The WHO Policy process for malaria vaccines may benefit from having expertise in health economics and health systems from IVIR-AC. Aparnaa Somanathan and Edina Sinanovic have agreed to join the working group (in addition to the IVIR-AC Chair).

Measles investment case

Introduction

(K. Thompson)

Six WHO regions have committed to eliminating measles, and a further two regions have committed to eliminating rubella. The GAVI Alliance has offered investment for measles catch-up campaigns, with or without rubella. However, the world is currently not expected to meet Global Vaccine Action Plan targets for measles and rubella elimination.

WHO is funding a model to explore the case for investment in measles control, elimination and eradication. The model is an age-structured MSLIRV (maternal-susceptible-latent-infected-recovered-vaccinated) transmission model. Currently, it looks at six options for control, elimination and eradication and it integrates the economics and transmission dynamics of measles and rubella. The model assumes that countries will coordinate work towards their commitments from 2014 onwards with secure vaccine supply, financing and political will.

In 2011 and 2012, IVIR-AC emphasised the need to incorporate both between-country and within-country heterogeneity in the model. In response, the unit of analysis in the model has been changed from World Bank country income group to individual country. Results are then aggregated to regional and global levels. Population dynamics are matched to United Nations Development Programme estimates and projections for the years 1950 – 2100. The model is simulated from 1954 to 2013 using historical population and immunisation data, with the model at endemic equilibrium in 1954. Some coverage assumptions have to be made about historical coverage data. Stochastic importatations are incorporated; eventually these will be linked to regional and global levels of transmission.

For the rubella component, potential increases in the age of infection will be investigated. However, previous studies suggest that in most countries, the overall rubella burden will be reduced as long as coverage of about 80% is achieved, although the exact threshold is dependent on the birth rate. Work is also being done to develop a DALY weight for rubella. Development of the integrated economic and dynamic disease model for the investment case has taken longer than expected because of challenges associated with the data quality for some inputs (such as historical SIA coverage data) and the shift to a country-specific modeling, and further adaptation to include subnational modeling to account for heterogeneity will lead to some further delay.

Review

(J. Edmunds, S. Sow)

The reviewers received a set of papers that do not represent an investment case, so the review could only consider whether the main questions and guidelines for constructing such a case as presented are adequate. A large number of parameters are needed for every country in the world to parameterise a model, but most of them are unknown so there is a danger they will be filled in by extrapolation or assumption. Hence some kind of prioritisation around the list may be needed to ensure appropriate data collection activities for the most important parameters. Also, the total cost of investment may be more useful than cost-effectiveness, since the main need is to understand the resource and health systems implications of various measles vaccination strategies.

Within-country heterogeneity in contact patterns and vaccine coverage is crucial, particularly since the herd immunity threshold for measles is high (about 95%). The current model does not address this because it assumes mixing within a country is homogeneous. This is not of theoretical interest only; measles outbreaks in the Netherlands occurred in 1999/2000 and 2008 despite MMR1 coverage exceeding 95% in cohorts born since 1986, due to low coverage in particular subpopulations i.e. the “Bible belt”.

A further issue is the extent to which rubella dynamics need to be incorporated. In principle rubella should be eliminated before measles if the MR vaccine is used, since rubella has a lower R0 compared to measles. However, there is a danger that the burden of congenital rubella syndrome will increase at intermediate levels of vaccine coverage due to shifts in the average age of infection. Even if the overall burden does not decrease, health inequalities may worsen since the burden will be concentrated on the unvaccinated population. Hence if MR vaccination is used, there is a need to explore the use of broad immunization campaigns. The role of civil society in supporting eradication efforts also needs to be considered.

Discussion

Within-country heterogeneities could be handled by identifying groups with low coverage and considering appropriate social and behavioural interventions, rather than assuming they will never be reached. The affected groups are very diverse (migrants, underserved peoples, vaccine objectors etc.) The modellers indicated that they can incorporate heterogeneity explicitly in their model in the context of characterizing undervaccinated subpopulations, as they do for polio modeling. They indicated that they will add this capacity to the model, and expressed that this adds more complexity to the process of estimating input parameters (i.e., it adds parameters related to relatively poorly-characterized parts of the population).

The effect that measles eradication activities have on routine vaccination programmes (such as rotavirus and pneumococcal vaccines) is a key uncertainty. In countries like India, it is difficult to see how levels of coverage needed to maintain measles control can be achieved without compromising other services. On the other hand, India still experiences a high burden of measles which had led to intensified efforts to increase routine measles immunization coverage, add a routine second dose of measles vaccine and complete a catch-up vaccination in 14 low coverage States. The investment case also needs to take account of the cost of surveillance, contact tracing and outbreak response, and the model will need to comprehensively consider costs. The success of measles eradication activities is also dependent on events and trends that are difficult to predict such as changes in breastfeeding habits, political upheavals and natural disasters.

Summary and recommendations

IVIR-AC considers that the work as described cannot be recommended as the model does not sufficiently capture all the uncertainties and risks of measles eradication. Concerns that IVIR-AC outlined at its previous meetings in 2011 and 2012 still exist in particular with respect to within-country heterogeneities in coverage and transmission. Variability in coverage can occur within sub-populations with substantial implications for eradication, making a global model using country-level data only problematic.

Additional work that addresses the key concerns and incorporates subnational heterogeneity in the model is required prior to its use for assessing global measles eradication. The modellers have agreed to incorporate these IVIR-AC suggestions and comments and will submit the updated approach for discussion with some IVIR-AC members in about 4-6 weeks.

Estimating the burden of yellow fever across Africa

Introduction

(N. Ferguson)

In 1990, it was estimated that there were around 200,000 cases and 30,000 deaths due to yellow fever. In October 2011, QUIVER recommended revisiting these estimates in order to inform investment decisions about yellow fever vaccination by the GAVI Alliance. An expert committee convened by WHO commissioned a group led by Imperial College to carry out this assessment.

Work began in 2012 with an initial review of data, with a decision to focus on sub-Saharan Africa in the initial assessment. A list of available data on seroprevalence, outbreaks, surveillance database trends, vaccine coverage, population estimates and environmental variables was compiled. A model was then fitted to incidence data (with environmental and other variables as covariates) to estimate transmission intensity and hence overall disease burden.

In most countries, an age-independent force of infection fits data well. Overall burden estimates are similar to previous ones (850,000-2,000,000 infections, 85,000-200,000 cases and 30,000-70,000 death). However, the CFR is higher than previously estimated (35% compared to 15%). GAVI Alliance support for vaccination is estimated to have reduced incidence by 26% across Africa, and 56% in the targeted countries. The largest remaining burden is in countries not targeted by GAVI (particularly Nigeria). High infant vaccine coverage needs to be maintained in the targeted countries in order to maintain current levels of disease reduction.

Key limitations include uncertainties in demographics, vaccine coverage reports and interpretation of serosurveys. It is also not possible to distinguish between sylvatic, intermediate and urban transmission. Also, vaccine impact estimates are conservative because they do not take into account indirect protection. Key strengths are the use of a coherent framework making use of available data, quantification of uncertainty and ability to evaluate vaccine impact (including prospectively).

Discussion

The model suggests that the burden of yellow fever increases across Africa from east to west; the mechanism behind this effect is unclear. Models without longitude fit data more poorly. It is possible that this is due to different regions having different vectors, but there are insufficient data on vectors to investigate this hypothesis. The CFR varies depending on the vector cycle and level of endemicity. Also, it may be inflated if only severe cases are detected. However, the historical range is around 20-65%. Changes in forestation levels affect the population of animal vectors but could not be taken into account, partly due to poor quality of data sets in the past.

The GAVI Alliance will need to make a decision about yellow fever vaccination by the end of 2013. The work will be important to inform decisions about continued investment in the targeted countries, extension to new countries and use of mass campaigns. The model needs to be sustainable because the GAVI Alliance may need to know in the future whether investment has made an impact.

Summary and recommendations

IVIR-AC requested further clarification about how the generalised linear model captures the effect of vaccination. In follow up discussions after the meeting through a conference call with IVIR-AC chair, two members and the project team, outstanding issues were satisfactorily addressed, and discussed hence IVIR-AC felt that the model was adequate for yellow fever disease burden estimation across the African region.

Varicella and zoster vaccination in low and middle income countries

Introduction

(M. Brisson)

There are three concerns around varicella vaccination: (i) high rate of breakthrough cases among vaccinees, particularly if they only receive one vaccine dose, (ii) shifts in the age of infection to adults in whom disease severity is greater, and (iii) vaccine induced reduction of wild virus circulation in the population with consecutive decrease in natural boosting of immunity might increase the risk of reactivation of latent varicella-zoster-virus. These concerns are particularly pronounced in LMICs because of poor data and greater risk of age shifts due to likely mixing and coverage patterns. A SAGE working group is developing recommendations for varicella and zoster vaccination in low and middle income countries. Conclusions will be presented to SAGE for discussion.

Modelling has been conducted to inform SAGE deliberations. This uses a previously described transmission dynamic model (Brisson et al, 2000, 2010)[1] fitted to age-specific seroprevalence from countries representing a range of seroprevalence values and geographical regions. However, the validity and generalisability of the available serological data is unknown, as the data are not always nationally representative. Empirical contact matrices from Europe (POLYMOD) did not fit LMIC data well so a range of parameterised matrices were used instead. CFRs by age were extrapolated from Brazilian data.

Results suggest that at post-vaccination equilibrium, breakthrough cases occur most frequently in countries with medium to high seropositivity and intermediate coverage. In these countries, at intermediate levels of coverage the number of varicella deaths will increase after vaccination. In low seropositivity countries, deaths will decrease as vaccine coverage increases. Brazil and Singapore are outliers where the number of breakthrough cases always seems to increase with increasing coverage.

Remaining work to be done includes conducting sensitivity analyses on assumptions about contact patterns and vaccine efficacy, exploring the effect of varicella vaccination on herpes zoster, examining 2-dose vaccination, modelling African countries and estimating global burden.

Review

(P. Beutels)

The current work offers a good pragmatic approach but should be considered a prelude to a more elaborate analysis. Key parameters that drive results are seropositivity and CFR. It would also be useful to show the cost-effectiveness and affordability of varicella vaccination compared to other vaccination programmes.

Fitting to seroprevalence data could be improved by considering the sample size of each data point, so that older age groups (which are typically undersampled) are given less weight. It would also be useful to fit to the original datasets; the IVIR-AC secretariat could write to the authors to request these. There may be other serological studies which are unpublished or in the gray literature which WHO regional offices could try to obtain. The functions used for fitting to seroprevalence data (gamma and Farrington) are unimodal; POLYMOD-like contact patterns often require multimodal functions. The assumption of time homogeneity may also be an issue in multiple time point seroprevalence studies that needs to be examined. Also, it is important to allow the status of immune

[1] Brisson et al. Vaccine. 2010 Apr 26;28(19):3385-97; Brisson et al. Epidemiol Infect. 2000 Dec;125(3):651-69

individuals to vary continuously with age rather than to summarise seroprevalence data to binary outcomes.

The most important concern with varicella vaccination is the potential shift in the average age of infection; this is well represented in the model. However, the importance of this age shift relies on estimates of CFR which depend on an evaluation of varicella primary cause deaths in Brazil. This is subject to uncertainties in both the numerator (varicella and zoster deaths may have been mixed up in adults) and denominator (the total number of varicella cases over the time period may be small in some age groups). However, the most important use of the analysis is simply to get the overall shape of the age-dependent CFR curve. For this purpose, the pragmatic approach taken seems acceptable. Also the age profile appears fairly similar to UK and Canadian data.

Another concern is a potential increase in zoster. However, there is a poor understanding of the underlying mechanism for such an increase. Post-vaccination observational data, modelling work and immunological studies investigating this effect have shown mixed results. Demographic change in LMICs may play a critical role, but there was not time to investigate this within available timelines. Lastly, breakthrough varicella cases may be important since vaccine efficacy in LMICs is poorly documented.

(J. Edmunds)
Overall the model uses an appropriate approach to address the question. The shapes of the force of infection and morbidity curves are probably the most important inputs to the model. They are likely to show similar patterns to those in high income settings, but it is possible that varicella is more serious in older adults in LMICs. Meta-analyses combining available data sets may offer a means to increase statistical power. To obtain a reliable global burden estimate requires more than simply extrapolating data from Brazil and high income settings.

Discussion

Vaccine effectiveness data from China was used; this has performed at the same effectiveness level as vaccines in high income countries and uses the same Oka strain.

LMICs are not homogeneous; a model designed for Brazil or China cannot always be extrapolated to other countries. In low income countries, there are a number of barriers to vaccine introduction: lack of data, cost-effectiveness issues, competing demands on health care resources and the potential for negative outcomes. Hence it may be useful to focus the exercise mainly on middle income countries, where private sector use is important (and may on its own bring coverage to intermediate levels where the potential for harm is greatest), and WHO guidance is likely to be most influential. For low income countries, due to the potential for harm, it may be better to focus on improving access to care.

Despite data uncertainties, it is unlikely that overall mortality due to varicella is high compared to more severe vaccine-preventable diseases like measles. The incidence of varicella deaths is likely to range between 1-10 deaths per million, based on data from the two outlier countries in terms of CFR (Brazil and Sri Lanka). It would be useful to see cost-effectiveness results for different CFR assumptions. In terms of guidance, SAGE has already recommended that vaccination programmes should only be introduced if coverage of at least 80% is achievable. It would be useful to incorporate into guidance the level of private sector uptake that would trigger a cause for concern.

Summary and recommendations

IVIR-AC believes that the model is suitable and appropriate for varicella vaccine impact modelling and to examine potential concerns prior to vaccination with regard to breakthrough cases and shifts in the age of infection in LMICs. However, some minor technical improvements can be made such as around the functional forms used to represent the force of infection and mixing patterns. A better

acknowledgment of the uncertainties in the data that are used in the model such as seroprevalence, CFRs and morbidity estimates is also recommended.

IVIR-AC believes that more data are needed about the burden of varicella in low and middle income countries for the model to be of optimal use. IVIR-AC considers that the model is not designed to estimate global burden of varicella. If additional modelling exercises on varicella burden of disease are undertaken, IVIR-AC would like the opportunity to review and provide comments.

Extending the work to calculate cost-effectiveness of vaccination across a range of possible estimates of disease burden will have substantial utility for priority setting.

Implementation research priority setting framework

Introduction

(J. Clemens)

Barriers to increasing vaccination coverage are often not technical. Implementation research focuses on understanding bottlenecks and barriers that impede uptake of new vaccines or improved coverage for existing vaccines, and finding solutions to overcome them. In early 2012, WHO started work to develop a systematic process for formulating an implementation research agenda to increase vaccine uptake. In September 2012, IVIR-AC made some suggestions for methodological improvements which have been incorporated. Preliminary results were presented pending completion of the prioritization exercise and a final report.

An ad-hoc working group was convened with 21 independent experts to develop a prioritisation framework to review a list of candidate research questions from a broad solicitation of experts and existing reports in order to help define the final list of questions to undergo a systematic prioritisation.. Input from the group and from a pilot prioritization criteria was used to formulate pilot questions, which were then narrowed down to a final set of 84 questions. An additional 21 members were later added following IVIR-AC recommendations.

For the prioritisation framework used, adapted from the Essential National Health Research (ENHR) methodology incorporates four categories (appropriateness, relevance, chance of success and impact), consisting of nine criteria with three response levels each. Responses are weighted to derive an additive numerical score across the nine criteria using the PAPRIKA (Potentially All Pairwise Rankings of All Possible Alternatives) method and software developed by 1000 Minds[2].

The preliminary results from (from 26 raters who completed ratings for weights to the criteria and 15 who completed the rating of candidate questions) showed that the most important criterion identified was whether a study can be conducted ethically. The prioritization criteria and PAPRIKA methodology were found to be feasible and relevant, although the final rating of questions was limited by low response rate and small numbers of raters per domain.

The next steps will be to try to achieve a higher response rate (using phone reminders and trying to determine reasons for dropouts), analyse the final dataset and share it for stakeholder comments, and finally to disseminate a list of priorities to relevant stakeholders. IVIR-AC guidance was sought on the robustness of the method and analytical strategies,

Review

(M. Weiss)

The method used has appeal because it is based on an accepted decision theory framework, taps the authority of experts and simplifies complex multiple comparisons to binary choices. While the process uses explicit criteria to guide decision making, it is important that it does not displace the decision makers. It should be used as a hypothesis generating exercise; the next step is to shift from the technical process of conducting the exercise to reflecting on the priorities it produces and their implications.

[2] See Hanssen et al. J. Multi-Crit. Decis. Anal. 15: 87–107 (2009)

Discussion

In general, the exercise was well conducted and the methodology appears sound. But the results need to be brought back to decision makers and re-evaluated for face validity. It is also important to have more grassroots input; although regional representation has now been included in the exercise it may be necessary to get feedback from national and district levels officers as well. There are different kinds of potential users of the results, but each will have a different set of priorities. Local or regional exercises producing lists of priorities tailored to local needs may be more useful, but may require a lot of work.
Preliminary results show higher priority for research questions that are widely applicable and generalisable, and less priority for topics in specific areas. However, it was noted that the exercise was geared toward broadly generalisable research questions while specific questions and research topics may still have relevance for particular conditions, vaccines and geographical areas. The experts who rated the questions were mainly generalists; disease-specific experts may have given a different set of rankings.

One immediate use of the results is to prioritise the agenda of IVIR-AC. However, the list of priorities is unlikely to have wider impact unless if affects priorities of funders. Most funders are interested in funding disease-specific projects rather than the broader set of topics that were highest rated.

For the GAVI Alliance, specific questions on research priorities to fill critical information needs are more helpful than general questions. While a lot is known about general barriers to vaccine uptake, it is important to understand particular pathways more precisely.

Summary and recommendations

IVIR-AC is supportive of the effort to make priority setting for implementation research questions more systematic. IVIR-AC believes that the overall analytical approach is well-designed. While the findings provide a basis for decision making, IVIR-AC recognizes that contextual variability and considerations will require that the findings are not used as the sole criterion for decision making. Input from a range of stakeholders at different levels besides global and regional will be beneficial in validating the exercise and defining the application of the results. IVIR-AC recommends that IVB develop a well-formulated strategy for the next steps in priority setting.

Annex 1 Agenda

WEDNESDAY, 26 JUNE 2013

Time	Session	Purpose of session, target outcomes and questions for IVIR	Time allocation
08.30-09.00	**Registration**		
09.00-09.30	**Welcome - introduction and Charge to the Committee** R. Breiman, Chair of IVIR		30 min.
09.30-10.30	**Hepatitis B impact project – Session 1** Introduction A. Hall, 20 min IVIR review: P. McIntyre, G. Kang, 20 min. Discussion, 20 min.	**FOR DECISION** Outcomes IVIR-AC to provide recommendations on the proposed framework and methods for Hepatitis B impact evaluation Questions Does IVIR consider that the Hepatitis B impact evaluation framework is a robust/appropriate method?	1 hour
10.30	**Coffee/tea break**	**Break**	**30 min**
11.00-11.30	Review and discussion cont'd, 30 min.		30 min.

11.30-12.30	**Malaria vaccine impact and cost-effectiveness – Session 2** Introduction P. Smith (by phone), 20 min. IVIR review: R. Breiman, E. Sinanovic, 20 min. Discussion: 20 min.	**FOR INFORMATION** Outcomes: Update IVIR-AC on outcomes of a recent meeting held on malaria vaccine impact and cost-effectiveness analysis	1 hr
12.30	**Lunch**	**Break**	1hr min.
13:30-15.00	**Measles investment case (IC) for eradication – Session 4** Introduction: A. Dabbagh, K. Thompson, 30 min. IVIR review: J. Edmunds, S. Sow, 20 min. Discussion: 40 min.	**FOR DECISION** Outcome: IVIR-AC to provide comments and recommendations to the preliminary results of the measles/rubella IC eradication Questions: • Are the main questions for the investment cases adequate? • Will the proposed modeling approach for managing population immunity for measles and rubella at the national level capture heterogeneity sufficiently well to support the global estimates developed in the investment cases? • Should considerations of the dynamics and economics of rubella impact national and global vaccination strategies?	1hr 30min.
15.00	**Coffee/tea break**	**Break**	**15 min.**

15.15–17.00	**Yellow Fever Burden of Disease – Session 3** Introduction: N. Ferguson, 20 min. (by phone) IVIR review: F. De La Hoz, P. McIntyre, 20 min. Discussion: 50 min.	**FOR DECISION** Outcome: IVIR-AC to provide comments and recommendations to the preliminary results of the Yellow Fever burden estimates Questions: • Are the methods applied adequate? • Can WHO use the updated YF estimates and replace the previous one?	1hr 30min
17.00	**Adjourn**		
17.15	**Cocktail**		

THURSDAY, 27 JUNE 2013

Time	Session	Purpose of session, target outcomes and questions for IVIR	Time allocation
8.30-10.00	**Varicella and Zoster burden of disease – Session 5** Introduction: M. Brisson, J. Seward, 30 min. IVIR review: J. Edmunds, P. Beutels, 20 min. Discussion, 40 min.	**FOR DECISION** Outcomes: IVIR-AC to provide comments and recommendations on the methods and preliminary results of the impact modeling of varicella/zoster vaccine Questions: • To comment on vaccine impact on population-level incidence & morbidity • To examine potential concerns prior to vaccination, and conforming models to data with respect to: ○ Breakthrough cases and waning protection with 1 dose	1hr 30 min.

		○ Shift in age at infection by level of vaccine coverage (particularly relevant for LMIC)	
10.00	**Coffee/tea break**	**Break**	**30 min**
10.30-12.00	**Implementation Research priority setting framework - Session 6** Introduction: A. Bentsi-Enchill, J. Clemens 30 min. IVIR review: M. Weiss, D. Bloom, 20 min. Discussion: 40 min.	**FOR DECISION:** Outcomes: • To present the preliminary results of the prioritization exercise and draft immunization implementation research agenda Questions: • Are the methods used robust enough? • IVIR-AC's comments on the preliminary results and recommendations for additional analysis?	1hr 30 min.
12.00-12.30	**Meeting summary and closure**		30 min.

Thursday afternoon 27 June and Friday morning 28 June closed sessions for IVIR-AC members only

Annex 2 List of participants

Advisory Committee Members

Professor Philippe Beutels, Associate Professor, Health Economics, Health Economics and Modeling Infectious Diseases Unit, University of Antwerp, Centre for the Evaluation of Vaccination, Universiteitsplein 1, Antwerp 2610, **Belgium**

Professor David E. Bloom,** *Department of Global Health and Population, Harvard School of Public Health, 665 Huntington Avenue, Boston MA 02115 9957,* **United States of America

Professor Robert F. Breiman (Chair), Director, Emory Global Health Institute, Emory University, 1599 Clifton Road, Suite 6.101, Atlanta, GA 30322, **United States of America**

Dr Donald Burke,** *Center for Vaccine Research, University of Pittsburgh 9014, Biomedical Science Tower 3, 3501 Fifth Avenue, Pittsburgh, Pennsylvania 15261,* **United States of America

Professor John Edmunds, Head, Department of Infectious Diseases and Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, **United Kingdom of Great Britain & Northern Ireland**

Ms Rachel Feilden,** *FBA Health System Analysts, Tellisford Mill, Tellisford, Bath Somerset BA2 7RL,* **United Kingdom of Great Britain & Northern Ireland

Professor Fernando Pio de la Hoz Restrepo, General Director, Colombian National Institute of Helath, Carrera 45 No 26-85, Edificio Uriel Gutiérrez, Bogotá D.C., Colombia Carrera 45 No 26-85, Edificio Uriel Gutiérrez, Bogotá D.C., **Colombia**

Professor Gagandeep Kang, Head, Department of Gastrointestinal Sciences, Christian Medical College, Ida Scudder Road, 632004 Tamil Nadu, Vellore, **India**

Professor Peter McIntyre, Director, National Centre for Immunization Research & Surveillance, University of Sydney, Cnr Hawkesbury Road and Hainsworth Street, Westmead, **Australia**

Dr Edina Sinanovic, Senior Lecturer in Health Economics, Health Economics Unit, University of Cape Town, **South Africa**

Dr Aparnaa Somanathan, Health Economist, Human Development, East-Asia and Pacific Region, World Bank, Room MC8-428B; MSN MC8-813, 1818 H Street NW, Washington DC 20433, **United States of America**

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

Professor Mitchell Weiss, Professor & Head, Swiss Tropical & Public Health Institute (Swiss TPH), Socinstrasse 57, CH-4002 Basel, **Switzerland**

Participants

Dr Marc Brisson, Research Unit, Population Health, University of Laval, Centre de recherche FRSQ du CHA universitaire de Québec, Hôpital du Saint-Sacrement, 1050, chemin Ste-Foy, Québec G1S 4 L8, **Canada**

Dr James Goodman, Global Immunization Division, Centers for Disease Control and Prevention, Atlanta, GA 30333, **United States of America**

Sir Andrew Hall, Retired Epidemiologist, 1 b Surbiton Hill Park, Surbition KT5 8EF, **United Kingdom of Great Britain & Northern Ireland**

Dr Joerdis J. Ott, Epidemiologist, Department of Epidemiology (EPID), Helmholtz Centre for Infection Research, Inhoffenstraße 7, Braunschweig 38124, **Germany**

Dr Etienne Racine, Research assistant, University of Laval, Centre de recherche FRSQ du CHA universitaire de Québec, Hôpital du Saint-Sacrement, 1050, chemin Ste-Foy, Québec G1S 4 L8, **Canada**

Dr Jane Seward, Deputy Director, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333, **United States of America**

Dr Mona Marin, Medical Epidemiologist, Epidemiology Branch, Division of Viral Diseases

National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333, **United States of America**

Professor Peter Smith, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, **United Kingdom of Great Britain & Northern Ireland (via teleconference)**

Dr Kimberly Thompson, President, Kid Risk, Inc., P. O. Box 590129, Newton, MA 02459, **United States of America**

Dr Trudy Murphy, Division of Viral Hepatitis, Epidemiology Branch, Division of Viral

Diseases, National Center for HIV, Viral Hepatitis, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA 30333, **United States of America**

Dr David H. Sniadack, Senior Program Advisor for Measles, Disease Eradication & Elimination Branch, Global Immunization Division, Center for Global Health, Centers for Disease Control and Prevention, **United States of America**

Dr Karla Soares-Weiser, CEO, Enhance Reviews Ltd, Cobweb Buildings, The Lane Lyford, Wantage, **United Kingdom of Great Britain & Northern Ireland**

Observers

Professor Neil Ferguson, Professor of Mathematical Biology, Faculty of Medicine, Imperial College London, South Kensington Campus, London SW7 2AZ, **United Kingdom of Great Britain & Northern Ireland (via teleconference)**

Mrs Sandra Gavart, Global Market Access Leader, Infectious Diseases & Vaccines, Global Market Access & Commercial Strategy Operations, Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse, **Belgium**

Professor Peter Hansen, Director, Monitoring and Evaluation Policy & Performance, GAVI Alliance Secretariat, c/o UNICEF, Palais des Nations, Genève 10 CH-1211, **Switzerland**

Dr Hope Johnson, Head, Programme Outcomes and Impact, Monitoring and Evaluation Policy & Performance, GAVI Alliance Secretariat, c/o UNICEF, Palais des Nations, Genève 10 CH-1211, **Switzerland**

Dr Maria Van Kerkhove, Research Associate, School of Public Health, Norfolk Place, St Mary's Campus, Imperial College London, South Kensington Campus, London SW7 2AZ, **United Kingdom of Great Britain & Northern Ireland**

Dr Camille Morlière, Intern, Agence de Médecine Préventive, Department of Supporting National Independent Immunization and Vaccine Advisory Committees (AMP/SIVAC) Paris, **France**

Dr Baudouin Standaert, Director Health Economics, GlaxoSmithKline Vaccines, Avenue Fleming, 1300 Wavre, **Belgium**

Regional Offices

AFRO – no response

AMRO - regretted

EMRO - regretted

EURO - regretted

SEARO - regretted

WPRO – no response

WHO Consultants

Professor John Clemens, Professor of Epidemiology and Founding Director, Center for Global Infectious Diseases, UCLA School of Public Health, **United States of America**

Dr Mark Jit, Mathematical Modeller, Modelling and Economics Unit, Health Protection Agency, 61 Colindale Avenue, London, NW9 5HT, **United Kingdom of Great Britain & Northern Ireland**

WHO Secretariat

Dr Adwoa Bentsi-Enchill, Medical Officer, Immunization for All Ages, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

Dr William Perea Caro, Coordinator, Control of Epidemic Diseases, Health, Security and Environment, World Health Organization, Switzerland

Dr Alya J. Dabbagh, Scientist, Expanded Programme on Immunization, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

Dr Philippe Duclos, Senior Health Adviser, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

Dr Fruth Uli, Technical Officer, HIV Vaccine Initiative, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

Dr Ana Maria Henao-Restrepo, Scientist, Implementation Research, Initiative for Vaccine Research, World Health Organization, Switzerland

Dr Raymond Hutubessy, Economist, Initiative for Vaccine Research, Implementation Research, World Health Organization, Switzerland

Dr Jeremy Lauer, Economist, Costs, Effectiveness, Expenditure and Priority Setting, World Health Organization, Switzerland

Dr Vasee Moorthy, Technical Officer, HIV Vaccine Initiative, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

Dr Robert Perry, Medical Officer, Expanded Programme on Immunization, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

Ms Ximena Riveros, Technical Officer, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

Dr Peter M. Strebel, Medical Officer, Expanded Programme on Immunization, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland