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

Advisory Committee Meeting
Geneva, 25-26 September 2012

Immunization, Vaccines and Biologicals (IVB)
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1 Executive Summary

- The sixth meeting of the IVIR advisory committee was held 25-26 September 2012 in Geneva, Switzerland. The name of the advisory committee has now been changed from QUIVER (Quantitative Immunization and Vaccines Related Research) to IVIR (Immunization and Vaccines related Implementation Research) so that it can incorporate immunization systems issues as well as quantitative methods in evaluating vaccine performance.

- WHO is in the process of developing an Implementation Research priority setting framework. They have set up an ad hoc working group and are in the process of prioritizing the research questions. IVIR is positive about the priority setting approach and methods used. However, the members feel that more thought should be given to whether or not to shorten the list of proposed research questions to be prioritized (currently 86 priority questions) and reformat the questions to reduce the burden on the respondents. In addition, IVIR believes that a wide number of stakeholders should be involved, particularly from the countries and each of the six WHO regions.

- The Johns Hopkins School of Public Health International Vaccine Access Center is using Value of Statistical Life (VSL) to value a fatality or injury prevented through vaccination in monetary terms. IVIR members believe that Cost Benefit Analysis (CBA)/Value of Statistical Life (VSL) and Cost-Effectiveness Analysis (CEA) address different questions and that VSL has not been as widely used in the health sector. They believe that there are technical challenges to the measures that have not been fully addressed. The committee believes that VSL may provide valuable complementary information, but should not be used as the primary basis for priority setting in vaccines at this time. In theory, the VSL method is appropriate to decide whether a vaccine should be introduced, but empirical evidence is lacking, particularly in low- and middle-income countries (LMICs). The IVIR-AC recommends conducting case studies using both CBA/VSL and CEA for economic evaluation of vaccine introduction using similar datasets in LMICs.

- WHO established a working group to assess yellow fever disease burden. Improving evidence on yellow fever will help inform decisions about vaccination as well as GAVI decisions about investment. The working group is tasked with providing information on published and unpublished sources of yellow fever data and to provide input into the methods used to estimate burden in Africa. Imperial College London was commissioned to coordinate and carry out the work. The working group proposed two approaches to estimate burden of disease: (1) estimate the annual risk of infection from the age distribution of observed cases; and (2) estimate the basic reproduction number from reported outbreak sizes. Preliminary estimates are expected to be presented to WHO and partners in late October with final estimates by the end of 2012. Next steps will be the evaluation of yellow fever control strategies, support policy-making, and peer-review publication. It was noted that it will be important to distinguish between yellow fever and jaundice possibly due to other causes.

- Work on the broader benefits of vaccination addresses requests from external stakeholders as well as in-country decision-makers, such as Ministers of Finance, for outcomes of economic evaluations beyond traditional measures (e.g., cost per QALY/DALY). The intended outcome is to develop tools and methods that could capture broader impacts of vaccination in a way that is useful to stakeholders and feasible to measure. So far, this work has involved two expert consultations (Toronto 2011 and Geneva 2012), a stakeholder survey, and a literature review. In addition, four groups have responded to a request for proposals to develop innovative tools and have begun conducting their proposed packages of work. IVIR
members recognize that measurement of broader economic impact of vaccines is important to estimate and thinks that the proposed theoretical framework is appropriate. However, it is more difficult to estimate indirect effects of vaccines – i.e., the specific mechanisms to deal with confounding have not yet been worked out and there are deficiencies in basic data. IVIR recommends that there should be a continued effort to try to find better mechanisms to measure these causal relations. It is also important to think about including variables that measure broader impact in the design of RCTs to improve the likelihood that indirect effects can be evaluated.

- WHO is continuing to support an investment case for measles and rubella eradication. IVIR is encouraged by the investment in properly modeling eradication before the measles eradication game is reached. However, they continue to emphasize the need to consider heterogeneity in vaccine uptake, which is a key driver during the eradication phase. This requires models that do not simply aggregate entire populations, as well as exploration of the behavior of vaccine refusers and hard-to-reach groups within individual countries. It is also important to conduct an assessment of risks associated with evaluation campaigns, issues associated with first dose vs. second dose, and costs of outbreaks. IVIR suggests that data from the experience of the Americas in eliminating measles and rubella could be evaluated and used for some of these risk assessment analyses.

- WHO has developed a cervical cancer prevention and control costing (C4P) tool. IVIR reviewers believe that the methods used in the WHO C4P tool are appropriate. They feel that the costing tool could be very helpful for national program managers in planning for the introduction of HPV vaccination, as well as screening and treatment once that module is completed. They suggest some modifications that could further enhance the tool: (1) include an optional module for capturing societal costs (user and indirect/productivity costs); (2) provide a sensitivity or scenario analysis, including allowing for different vaccination schedules; (3) include more monitoring and evaluation costs, particularly for cancer registries for the screening and treatment module; (4) include an optional module for local data collection for countries that have decentralized health systems; and (5) add more information on cost calculations to the user guide.

- A proposal to use emulation in order to incorporate transmission dynamics (herd immunity) into static models of immunization (such as WHO-CHOICE’s PopMod, PAHO’s TriVac, and LiST) was presented. The plan is to use PopMod as an exemplar, and incorporate herd effects from a dynamic model of rotavirus vaccination into PopMod. An emulator would then be used to allow PopMod to model parameter sets that had not been explicitly used in the original dynamic model. IVIR members believe that both static and dynamic models have benefits and drawbacks. The proposed approach is to merge the emulator with the static model. This approach has promise but also has some drawbacks. IVIR members suggest that the model be pilot tested. They also feel that there should be some exploration of what would be required to provide the kind of modeling tool that will incorporate the benefits of static and dynamic modeling.

- WHO commissioned a study on the burden of disease of varicella and herpes zoster. IVIR members believe that the proposed methods to investigate the burden of disease of varicella and herpes zoster are appropriate but are concerned about the lack of data, especially in African countries. For this reason, they suggest that the working group evaluate other existing seroprevalence data, as well as data from Latin American countries that have introduced varicella vaccine. Even in the absence of hard data, modeling can play a role in estimating the impact of vaccination. IVIR members also suggested some medium-term
solutions to the lack of data: (1) include zoster in existing surveillance systems; and (2) test for varicella antibodies in existing serum samples in Kenya and other countries.
2 Introduction and charge to the committee

Dr. J-M. Okwo-Bele introduced the sixth meeting of the IVIR (formerly QUIVER) advisory committee. Briefly, QUIVER was set up as a technical committee advising the Strategic Advisory Group of Experts on Immunization (SAGE) due to increasing demand for the use of quantitative methods in evaluating vaccines. Its mandate has now been expanded to include both the evaluation of immunization systems and the use of quantitative methods for evaluating vaccination and vaccine performance. Dr. Okwo-Bele noted that a recent review evaluation of Immunization, Vaccines, and Biologicals (IVB) committees found that QUIVER was one of the best functioning committees and that it aids in oversight of research and allows inputs from outsiders.

Dr. Okwo-Bele gave a certificate of appreciation to Dr. A. Hinman, who is leaving his position as chair. He also welcomed the incoming chair, Dr. R. Breiman as of January 2013. The chair, members, and rapporteur of IVIR were thanked for their contributions, along with the WHO secretariat and the Bill and Melinda Gates Foundation for financial support.
3 WHO Implementation Research priority setting exercise

Overview
(J. Clemens and P. Namgyal)

Starting in early 2012, the WHO Initiative for Vaccine Research (IVR) initiated a consultation process for the prioritization exercise and set up an ad hoc working group composed of 20 individuals representing diverse areas of expertise. Dr. Clemens, Chair of the ad hoc Working Group, presented the background, the process, and the progress of the work to identify important implementation research issues in immunization. Consultations have been held with staff within the immunization department, the WHO regions, and countries, as well as individual experts, to obtain suggestions for potential implementation research questions. At the same time, reviews of key documents such as meeting reports (2007-11) of WHO’s Strategic Advisory Group of Experts (SAGE), reports of work on the Epidemiology of the Unvaccinated Child, Gender and Immunization, EPI reviews, post-introduction reviews, national research priorities posted on Web, etc., were undertaken to extract possible implementation research questions. Based on these background documents and, more importantly, based on their own experience and knowledge, the members of the ad hoc working group were asked to suggest research questions. These steps collectively generated more than 400 research questions. The ad hoc working group developed the framework and the guiding principles. The group met face-to-face on 29-30 June 2012 and reviewed the suggested questions, re-worded them where necessary, removed duplications, and shortened the list. A subgroup was formed and developed a survey tool, based on the Essential National Health Research (ENHR) strategy for research priority setting. Following the workshop, further revising of the topics was carried out, several rounds of discussions were held with various units within the department, and a final list of about 86 research topics was developed as the proposed list for scoring. It was noted that the current implementation research priority setting is consistent with the Global Vaccine Action Plan (GVAP) of the Decade of Vaccines (DoV).

Discussion

• Overall the IVIR-AC members welcomed the initiative and acknowledged the tremendous work that the ad hoc working group has made.
• Despite shortening the list of research questions from over 400 to about 86, the committee still felt that it is too long for a questionnaire, especially since there are four attributes with ten sub-attributes for each question to be rated.
• A methodology needs to be found to further reduce the number of research topics before any scoring is attempted; in addition, while the framework and the guiding principles state the focus to be more generic, there are several questions that appear too specific. Further editing may be required.
• The importance of wider feedback from key informants and stakeholders (e.g., EPI program managers, regional EPI focal persons, and other stakeholders) was emphasized, including a recommendation by IVIR to have a minimum number of countries from each region (not selected by the regional office to avoid bias) included in the scoring process. For example, a process could be devised to ask these stakeholders to identify their top five or top ten and bottom five or bottom ten research topics, without any scoring but within broad parameters explained in accompanying notes.
• Other methodological approaches for ranking were suggested for further exploration – e.g., for the working group to be split into four subgroups with each subgroup scoring all questions on one attribute only, followed by a composite evaluation of those results in a single matrix.
• Several suggestions were made about the best way to conduct the scoring of the questions:
It was agreed that, if the working group is to be involved in the scoring, all members should score all the questions. If research topics are grouped into common domains and scored by groups of experts related to the domains, the number of experts (scorers) may have to be expanded because there will not be sufficient numbers for all the different domains from among the 20-member working group.

A comprehensive and clear analysis plan needs to be carefully developed before the actual scoring exercise.

One suggestion for dealing with "X" & "Y" responses was to see if such responses (for a specific question) exceed a pre-determined threshold and, if so, the scoring may be repeated with another group with more appropriate expertise to deal with such questions.

- Piloting would be necessary before the final scoring.
- There is a need for closer linkages with IPAC (Immunization Practices Advisory Committee) and IVIR members suggest that chairs of both advisory committees should attend both IPAC and IVIR meetings.
- Even those questions for which work is already ongoing should be kept in the priority list (as either annex or as a separate file for record), but should be identified as such so that their importance is understood.
- Removing cold chain and logistics management takes away the importance of this subject; the questions in that domain should be maintained as stated in the previous bullet.

Summary and recommendations

- IVIR is positive about the priority setting approach and methods used.
- More thought should be given to shortening the list of questions and to editing some questions in order to facilitate question-scoring. A wider representation of stakeholders should be involved in scoring, particularly from the countries and six WHO regions.
- Even though substantial work on cold chain and logistics is ongoing through projects such as Project Optimize, not including these issues in the prioritization would be ignoring an important area of immunization systems. Therefore, the domain on cold chain and logistics management should be retained, but efforts already in place should be indicated so the related research questions would not need to be considered in the final prioritization exercise.
4 Value of Statistical Life

Overview
(S. Ozawa, R. Laxminarayan)

Dr. Ozawa of International Vaccine Access Center presented on the Value of Statistical Life (VSL) methodology for the Decade of Vaccines (DoV). First, she noted that all decisions about health spending implicitly weigh the value of lives, including decisions made without economic analysis, or decisions that consider CEA or CBA/VSL. For example, when country-level decisions about health spending are made using either CEA or CBA/VSL, the value of health varies based on decision-maker preferences. Second, VSL – an old methodology but a new application in health in LMICs – uses weights to value an incremental decrease in mortality risk caused by an intervention. Third, the use of VSL for the Decade of Vaccines can facilitate comparisons with non-health investments. In addition, CBA/VSL has been used by governments and international organizations and can present the return on investment in dollar units.

Prof. Laxminarayan also made a presentation on CBA/VSL. He noted that this technique is used by governments: US, UK, Australia, Japan, and Canada, and international agencies – the World Bank, the European Commission, the UN Intergovernmental Panel on Climate Change, and WHO. Some examples of VSL variations are comparisons of smokers and nonsmokers, black-white VSL differences, and Mexicans vs. other immigrants or Native Americans. One example of a WHO study that uses this technique for water and sanitation can be found at http://www.who.int/water_sanitation_health/publications/2012/globalcosts.pdf.

There are relatively few VSL studies in low- and middle-income countries. CBA/VSL studies use revealed preference and stated preference methodologies. He noted there are many challenges in using VSLs in LMIC settings, but the same challenges are found with QALYs or DALYs for CEAs. VSLs can complement existing cost-effectiveness methods, particularly since these studies face their own methodological challenges.

WHO’s perspective on the use of VSL for CBA
(D. Evans)

Dr. Evans stated that WHO audiences such as MoH policymakers are familiar with concepts of DALYs and QALYs and are less familiar with CBA/VSL. They understand the concepts of scarce resources and cost per improvement in health. He noted that researchers can compare net values but not cost benefit ratios. Another problem is that currently researchers do not have enough data from low- and middle-income countries. In addition, wage markets in LMICs are imperfect and can be limiting for analyses. Thus, VSL is not currently recommended by WHO.

Review
(J. Edmunds)

Prof. Edmunds felt that the arguments for the use of CBA/VSL in vaccine decision-making are not new and have been around for decades. He agreed that CEA does put a value on life and uses a decision rule that puts a value on health, and stipulated that WHO/World Bank use arbitrary cut-offs for these. CBA/VSL is used in environmental analyses and fits in better with welfare economics. He noted that the human capital approach uses wage rates and undervalues life, leading to equity concerns. This approach is not consistent with welfare economics since it should be based on what
people are willing to sacrifice. The second approach, revealed preference, has huge technical and practical challenges since the most dangerous jobs are often not the most well-paid. He noted that studies find a negative relationship between risk and wage, and it is unclear how well people in risky jobs are aware of those risks. He also noted that there is selection bias and estimates vary widely. The third approach, price risk studies, evaluates how much people are willing to pay for a lowered risk. However, people do not always put a higher value on safer products – e.g., smoke detectors. The fourth approach, contingent valuation, uses surveys to set up hypothetical situations. However, people are often unfamiliar with the hypothetical market and may not want to pay for health care, can protest valuations, are sensitive to payment vehicle (e.g., out of pocket vs. tax rate), and are sometimes insensitive to risks. Edmunds noted that decision rules should be consistent across broad areas and the value in sticking to one decision rule over time is that it builds up understanding. Overall, he noted that the CBA/VSL method has theoretical benefits, captures non-health benefits, and can aid comparison with other programs. On the other hand, it has practical difficulties, ethical concerns, and does not promote having one decision rule.

Review
(D. Bloom)

Prof. Bloom has two concerns that fall into two categories: conceptual and applied. The conceptual concerns are the following: (1) VSL measures reflect private value, which are not a good guide to social value, especially when there are herd effects associated with communicable disease or when there are third-party payer insurance schemes or compensation practices that include a provision for paid leave (when people miss work to take care of a sick child); and (2) VSL measures lump together many components of the value of life including income (presumably net of some sizable portion of taxes), utility from own consumption, interdependent utility, the value of pain and suffering, and out-of-pocket medical spending. Information on the components of VSL would be useful as well as the implications of an immunization program for health sector budgets, tax revenues, pension liabilities, labor productivity, savings, economic growth, and the poverty rate since these are the factors for which public decision-makers are accountable.

The applied concerns are the following: (1) revealed preference often involves linear extrapolation of the estimated wage premia associated with occupations that have different risks of death; and (2) contingent valuation, in which people are asked to specify a willingness to pay to avoid certain risks, is likely to suffer from the fact that there is often a wide gulf between what people say and what they do (see Diamond and Hausman’s 1994 article on contingent valuation in the Journal of Economic Perspectives). Bloom also notes that there are no VSL studies for children, and inferring VSL for children from parents’ stated preferences (for child health) is problematic given inter-generational conflicts of interest, which are accentuated for girls compared to boys in many settings. Moreover, VSL measures derived from parents’ stated preferences for their children’s health do not naturally account for a major benefit of childhood vaccination – the higher productivity and earnings of vaccinated children when they reach adulthood. There are also no VSL studies for African countries and very few VSL studies for low- and middle-income countries overall. As a practical matter, this requires investigators to adjust VSL estimates from rich countries to apply to poor countries. The validity of these adjustments is difficult to evaluate. According to Bloom, in terms of their magnitudes, VSL estimates often seem to fail the “sniff test,” which is not surprising given that their values are not naturally bounded or constrained by other parameters of one’s economic circumstances (e.g., ill-informed individuals may make choices that are not in their best interests). Alternatively, even well-informed individuals may be immobile or not empowered to make choices. Bloom concluded that VSL measures can yield numbers that have considerable shock value with respect to the value of vaccination and this is their main use in this space. By contrast, their scientific value in the rational allocation of resources to and among immunization programs is not great.
Discussion

Some individuals pointed out that the Decade of Vaccines is interested in using VSL for advocacy and not for priority setting. Also, the Johns Hopkins analysis is estimating VSL as a complementary analysis of Decade of Vaccines in addition to CEA. Several persons felt that VSL could potentially be valuable as a complementary analysis to CEA – Ministries of Finance are often more familiar with CBA ratios than incremental cost-effectiveness ratios. Also, CEA ratios are often incorrectly calculated and results are not very useful. On the other hand, the valuations of VSL studies appear to be too high and present equity concerns.

Summary and recommendations

- CBA/VSL and CEA address different questions. CEA is well established as a mechanism for priority setting in health. VSL has not been as widely used in the health sector and there are technical challenges to the measures that have not been fully addressed. The committee believes that VSL may provide valuable complementary information but should not be used as the primary basis for priority setting in vaccines at this time. In theory, the VSL method is appropriate to decide whether a vaccine should be introduced, but empirical evidence is lacking, particularly in low- and middle-income countries (LMICs). The IVIR-AC recommends conducting case studies using both CBA/VSL and CEA for economic evaluation of vaccine introduction using similar datasets in LMICs. IVIR members also recommended collecting more empirical VSL data in LMICs.

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<tr>
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<th>CBA/VSL</th>
<th>CEA</th>
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<tr>
<td>Advantages</td>
<td>• Used to compare health interventions to non-health interventions</td>
<td>• Includes quality of life measures</td>
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<td></td>
<td>• CBA results are additive</td>
<td>• Can make relative comparisons across vaccines</td>
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<td></td>
<td>• Easy to communicate results to MoF and used for regulatory decision-making</td>
<td>• Easy to communicate to MoH and useful for health policy</td>
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<tr>
<td>Disadvantages</td>
<td>• Methodological challenges (see comments above)</td>
<td>• Methodological challenges</td>
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<tr>
<td></td>
<td>• Ethical considerations since may overvalue benefits based on wages</td>
<td>• Ethical considerations since implicitly decision makers put a value on life</td>
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<td></td>
<td>• Empirical VSL evidence is lacking in children and LMICs</td>
<td>• Not based in Welfare Economics (extra-Welfarist) hence does not allow comparison with non-health interventions</td>
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<td></td>
<td>• Wage markets are imperfect hence VSL does not fully reflect value of life</td>
<td>• WHO CE-thresholds are arbitrary</td>
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5 Yellow fever burden of disease

Overview
(N. Ferguson, T. Garske, M. Van Kerkhove)

During its meeting held beginning of October 2011, the then-QUIVER Advisory Committee recommended that WHO establish a working group to explore modeling techniques and review data from surveillance systems to measure the yellow fever disease burden in Africa. Following discussions with the QUIVER Secretariat, it was suggested that the working group be composed of at least two members of QUIVER, two yellow fever experts, one expert on mathematical modeling, one observer from GAVI, and one WHO yellow fever disease focal point. The members of the Yellow Fever Disease Burden Working Group include: Erin Staples, CDC Forth Collins; Rosamund Lewis, Public Health Agency Canada; Bryan Grenfell, Princeton University; Donald Burke, Pittsburgh University; Fernando De la Hoz, Instituto Nacional de Salud, Colombia; and Peter Hansen, GAVI.

The expert committee is tasked with providing information on published and unpublished sources of yellow fever data and to provide input into the methods used to estimate burden in Africa. Imperial College London (Tini Garske, Maria Van Kerkhove, and Neil Ferguson) was commissioned to coordinate and carry out the work and WHO formed the secretariat (Raymond Hutubessy, IVB/WHO and William Perea and Sergio Yactayo, GAR/WHO). Additional input was sought from Emily Jentes and others from US CDC. All parties met at a face-to-face meeting in January 2012 in Geneva and communication with the expert committee has been ongoing via periodic teleconferences.

The agreed-upon work plan includes two stages: (1) identification of potential published and non-published data sources including publications in peer-reviewed journals and the Weekly Epidemiological Record (WER), outbreak data since 1980, the AFRO case database, vaccination coverage over time, seroprevalence studies since 1980, and other sources; and (2) development of model structure to estimate burden in Africa. We propose two approaches to estimate burden of disease: (1) estimate the annual risk of infection from the age distribution of observed cases; and (2) estimate the basic reproduction number from reported outbreak sizes. Preliminary estimates are expected in late October with final estimates by the end of 2012.

Review

The discussion focused on the limitations of the data to make estimates of yellow fever burden of disease. It was noted that it will be important to distinguish between yellow fever and jaundice. Improving evidence on yellow fever will help inform decisions about vaccination as well as GAVI decisions about investment.
6 Broader economic impact on vaccines and immunization programs

Overview
(M. Jit)

Dr. Jit presented an overview of WHO’s work on the broader economic impact of vaccines and immunization programs (BEIV). This work addressed requests from external stakeholders as well as in-country decision-makers, such as Ministers of Finance, for outcomes of economic evaluations beyond traditional measures (e.g., cost per QALY/DALY). The intended outcome is to develop tools and methods that could capture broader impacts of vaccination in a way that is useful to stakeholders and feasible to measure. So far, this work has involved two expert consultations (Toronto 2011 and Geneva 2012), a stakeholder survey (by Van der Putten et al. in preparation), and a literature review (by R. Deogaonkar et al. BMC Public Health 2012, 12:878). In addition, four groups have responded to a request for proposals to develop innovative tools and have begun their proposed packages of work. A draft conceptual framework to explore the possible causal pathways between immunization and different outcome measures (such as cognition, productivity, fertility, tax revenue, and GDP growth) has been developed. Further work on strengthening the evidence (or lack thereof) behind these links in the framework is planned by WHO and others. This may possibly require a mixture of new RCTs, retrospective analyses alongside existing RCTs, statistical analyses, and model-based sensitivity analyses.

Review
(P. Beutels)

Dr. Beutels chaired the last technical WHO meeting on BEIV and indicated that that meeting led to a slightly adapted categorization of benefits and conceptual pathways between impact indicators. At that meeting, there was general consensus that further explorative research on estimating the broader economic impact is very useful in the field of vaccination. However, it would be fundamentally wrong to limit it just to the field of vaccination, because many of these broader impact aspects are also relevant for other broad scope public health interventions. Dr. Beutels proceeded to discuss the thirteen benefit categories one by one (as provided in “Table 1: Classification of Benefits” in the document), and indicated for each their essential characteristics and major pros and cons. He pointed out in general that as one went down in the table of the BEIV framework there is lower strength of evidence to produce estimates of these benefits, and therefore there is more uncertainty about each successive category of benefits. Subsequently, much attention in applied studies needs to go to estimating the uncertainty of the broader impacts. He signaled that since this list has many categories, and that for many of these categories there are different methodological options to produce estimates, there is a danger of “cherry picking” from the list for those who want to use the framework for advocacy. It was very useful and necessary that the BEIV framework indicated which methods should be used to estimate each benefit. There is a clear responsibility that comes with recommending the further exploration of this framework in applied studies. Hence, not only should users of this framework outline the reasons to include certain broader impact categories, as well as the preferred method to demonstrate the impact, but also why they would exclude other categories. Different vaccines will impact differently on the various economic impact categories.

The conceptual pathways in Figure 1 of the document, which represent the core reasoning for exploring the broader economic impact, show an intuitively appealing framework, but the direction of the causality is not as clear-cut as it may seem. The specific contribution of a single factor in this
process (e.g., vaccination of children) is extremely difficult to single out from other explicit or implicit factors in the process.

Trying to document what decision-makers in health and finance actually want to base their decisions on is a pivotal part of the information needed to further shape the framework. So far, the survey yielded too limited information because of low numbers and a too basic statistic approach. Expanding the surveys and particularly the qualitative interview-based research is very useful. Dr. Beutels also suggested other approaches, such as discrete choice experiments, should be considered. Of the four applied studies that have started, he mentioned that only two studies estimate aspects of broader economic impact (Category D in Table 1) – one study estimates benefits up to community externalities and is limited to literature reviews when it comes to wider impacts beyond category B2. This may indicate that the theory behind the framework, however appealing, is highly difficult to put into practice.

He concluded by saying that the framework is useful for policymakers, that he has concerns about its robustness, that it should not only be applied to vaccines if it is meant for prioritization, and that better research on underlying causal pathways is needed to strengthen the evidence behind the framework.

Review
(A. Somanathan)

Dr. Somanathan felt that the systematic review is comprehensive and methods used to include and exclude data are robust. However, the review did exclude evidence from high-income countries that may contain innovative methods for BEIV evaluation. From this perspective, it might also be useful to consider high-income country data, too.

A framework that captures the full range of costs and benefits of vaccines is essential for further research in this area. In a way, it is similar to the Mosley and Chen framework for understanding the determinants of infant mortality, which was the basis for a large body of work on infant mortality. Such a framework has been developed over the past 18 months or so, building on work done at Harvard and other places. This is an evolving body of work and likely to be modified as new evidence comes into play. Also, over the past 18 months, the framework has been revised to identify and compare impacts that will be assessed using RCTs vs. observational studies. However, this is still a framework that will drive the research rather than a research methodology in itself. So, it is not possible to comment on whether the framework provides a robust and appropriate method for evaluating the broader economic impact of vaccines.

Attribution will be a key challenge in the effort to measure the broader economic impact of vaccines. As the range of benefits becomes broader and the time horizon longer, the greater the number of other variables besides the vaccine will be involved. The framework acknowledges the existence of other factors, but does not get into how to control for other factors in measurement. For instance, the systematic review looked at studies that measured long-term productivity gains. But, it is not clear to what extent these studies were able to separate out the impact of vaccines from other interventions/factors.

IVIR members noted that limited data are available for productivity-related benefits and community externalities. They also noted the importance of improving methods of estimating indirect effects of vaccines.
Summary and recommendations

IVIR recognizes that measurement of broader economic impact of vaccines is important to estimate and thinks that the proposed theoretical framework is appropriate. WHO has used an approach for several years that quantifies direct effects. It is also important to estimate the broader economic impact, but it is more difficult to estimate indirect effects of vaccines – i.e., the specific mechanisms to deal with confounding have not yet been worked out and there are deficiencies in basic data. In category A, on health-related benefits, there is quite a bit of evidence. However, in other categories, productivity-related benefits and community externalities, the evidence on the causal links is much weaker. IVIR recommends that there should be a continued effort to try to find better mechanisms to measure these effects. It is also important to think about including variables that measure broader impact in the design of RCTs to improve the likelihood that indirect effects can be evaluated.
7 Measles investment case for eradication

Introduction
(A. Dabbagh)

Dr. Dabbagh reported that several significant events occurred during the past year with respect to measles and rubella. First, the Measles and Rubella Initiative released a strategic plan for 2012-2020 that fully integrated efforts for measles and rubella and outlined goals and key strategies to support their achievement. Second, the GAVI Alliance created new funding opportunities to support an increased use of measles- and/or rubella-containing vaccines in eligible countries over the next five years. Third, the Global Vaccine Action Plan included the goal of eliminating both measles and rubella in five WHO regions by 2020. Finally, efforts made by countries and WHO regions toward the existing goals shows many signs of progress, but, at its recent meeting, which included presentations by all six WHO regions, the SAGE Working Group on Measles and Rubella noted that the regions are not currently on track globally to achieve the existing goals. All of these changes led to iteration throughout the year on the options for inclusion in the investment cases for measles and rubella.

Progress on work plan
(K. Thompson)

Dr. Thompson and her project team, using an analytic-deliberative process, identified and iteratively developed the complete set of topics for inclusion in the measles and rubella investment cases and developed a draft manuscript shared with the IVIR for comment. In addition, the team identified all of the national and global options for coordinated management of measles and/or rubella and the analyses needed to evaluate the risks, costs, and benefits associated with the measles and rubella aspects of the Global Vaccine Action Plan. The team shared draft manuscripts on these topics with IVIR for comment and summarized the options that will be characterized in the investment cases. The team also presented its overall framing and cost and disease model assumptions, and, subsequently, requested input on its plans to present the results of both incremental cost-effectiveness ratios and incremental net benefits. The team will focus on providing insights relevant to the global coordination of efforts and global commitments, but stratify the analyses appropriately to capture the real heterogeneity that exists between income levels and WHO regions. The team noted significant heterogeneity among the WHO regions, with particular concern that the European Region does not remain on track to meet its existing goal of achieving elimination of measles and rubella by 2015. The modeling used to consider the investment case option will strive to provide realistic assessments of the full costs, including the costs associated with delays, and full discussion and consideration of the risks and challenges associated with achieving global goals. In addition, the investment cases will serve to synthesize the existing evidence, characterize uncertainties, and identify key areas for additional research.

Discussion

IVIR is encouraged by the investment in properly modeling eradication before the measles end game is reached. However, they continued to emphasize the need to consider heterogeneity in vaccine uptake, which is a key driver during the eradication phase. This requires models that do not simply aggregate entire populations, as well as exploration of the behavior of vaccine refusers and hard-to-reach groups within individual countries. It is also important to conduct an assessment of risks associated with elimination campaigns, issues associated with first dose vs. second dose, and costs of outbreaks. IVIR suggests that data from the experience of the Americas in eliminating measles and rubella could be evaluated and used for some of these risk assessment analyses.
8 Cervical Cancer Prevention and Control Costing Tool

Overview
(A. Levin)

Dr. Levin presented on the WHO Cervical Cancer Prevention and Control Costing (C4P) Tool. This tool is designed for use by national program managers for planning and costing for the introduction of HPV vaccination, as well as cervical cancer screening and treatment. Planning for this vaccine is important since it targets a non-traditional population – adolescent girls between nine and 13 years old – and is usually conducted at venues where adolescent girls are found (e.g., schools and/or pulsed campaigns). Because the vaccine has three doses and is typically delivered through outreach or campaigns, it is more costly to provide than other vaccines. The costing tool has two modules: (1) introduction of HPV vaccination; and (2) scaling-up of cervical cancer screening and treatment. The tool is Excel-based, uses an ingredients approach to costing, and calculates both financial and economic costs. The tool was field tested in Tanzania and validated with PATH demonstration projects. It has also been used in Rwanda and Kyrgyzstan to estimate the costs of introducing HPV vaccination. Future plans for the C4P tool are to finalize development of a generic version of the module for cervical cancer screening and treatment, use the tool to conduct costing/financial analysis in low-income countries, and costing and cost-effectiveness analysis in middle-income countries. The tool will also be integrated into the OneHealth tool (Unified UN health sector costing and planning tool).

Summary and recommendation

IVIR reviewers believe that the methods used in the WHO C4P tool are appropriate. They feel that the costing tool could be very helpful for national program managers in planning for the introduction of HPV vaccination, as well as screening and treatment once that module is completed. They suggest some modifications that could further enhance the tool: (1) include an optional module for capturing societal costs (user and indirect/productivity costs); (2) provide a sensitivity analysis, including allowing for different vaccination schedules; (3) include more monitoring and evaluation costs, particularly for cancer registries for the screening and treatment module; (4) include an optional module for local data collection for countries that have decentralized health system; and (5) add more information on cost calculations to the user guide.
9 Proposed dynamic method of static models

Overview
(M. Jit)

Dr. Jit presented a proposal to use emulation in order to incorporate transmission dynamics (herd immunity) into static models of immunization (such as WHO-CHOICE’s PopMod, PAHO’s TriVac, and LiST). The plan is to use PopMod as an exemplar, and incorporate herd effects from a dynamic model of rotavirus vaccination (published in Atchison et al., Vaccine 2010; 28:3118) into PopMod. An emulator would then be used to allow PopMod to model parameter sets that had not been explicitly used in the original dynamic model. The work would be done in collaboration with the PopMod team at WHO (Jeremy Lauer, Raymond Hutubessy, and Tessa Tan-Torres) as well as John Edmunds at LSHTM and Mira Johri and the University of Montreal (who joined the session by telephone). If the rotavirus example is successful, then it could be expanded to other antigens (e.g., pneumococcal, measles) and models (e.g., TriVac, LiST).

Review
(D. Burke)

Dr. Burke stated that an emulator is useful if researchers want to conduct the analysis more quickly since the values of its use are increased efficiency and reduced complexity. He thinks that the methods are appropriate, but there are a lot of alternatives available. However, this proposal is acceptable.

Review
(B. Grenfell)

According to Dr. Grenfell, allowing for nonlinear dynamics in existing linear approaches is an important development, since nonlinearities can produce very counterintuitive results that static approaches sometimes cannot capture. The proposed approach to provide input to models like PopMod is well thought out and appropriate. Some suggestions are: (1) WHO “users” and external modeling groups need to pre-agree on a range of parameters (e.g., vaccination rates) since incautious extrapolation beyond these limits could be dangerous (e.g., if dynamics change qualitatively); and (2) as these collaborations develop, an ultimate aim should be to incorporate the dynamic models explicitly.

Discussion

Some IVIR members felt that there would be advantages and disadvantages to using an emulator with a static model vs. a dynamic model. However, it was emphasized that the use of an emulator would add flexibility and has some time savings.

Summary and recommendations

IVIR believes that both static and dynamic models have benefits and drawbacks. Some of the current models being used lack a dynamic component for infectious diseases. The proposed approach is to merge the emulator with the static model. This approach has promise but also has some drawbacks. IVIR members suggest that the model be piloted. They also felt that there should be some exploration of what would be required to provide the kind of modeling tool that will incorporate the benefits of static and dynamic modeling.
10 Burden of disease of Varicella and Herpes Zoster

Overview
(J. Seward, M. Brisson)

Varicella zoster has lower case severity than measles, including long-term issues (e.g., even with lower morbidity, the total number of complications including death is potentially high). Differences in varicella epidemiology are described in temperate vs. tropical climates. In addition, the disease is acquired later in childhood and a higher proportion of adults are susceptible in tropical climates. Most population-based data on disease burden are from developed countries. Seventy-two studies were found from the US, UK, and Europe, while five were from South America, nine from the Eastern Mediterranean, and 12 from Asia. The risk factors for varicella are age, pregnancy, immunocompromised, and lack of access to health care, with incidence varying by age. While it is known that incidence of varicella in the US pre-vaccine introduction was 2.6 per 100,000, data from low- and middle-income countries are extremely sparse. Three studies were described. Due to the lack of data, the team is estimating that the number of hospitalizations and deaths be multiplied by ten times in low- and middle-income countries to get 140 million cases, 4.2 million hospitalizations, and 42,000 deaths. The largest data gap is for the number of hospitalizations and the case fatality rate.

Congenital and neonatal varicella are severe and have high mortality. Varicella in aboriginal and Torres Strait Island populations had significant reductions with vaccination – from 25 to 12.7 per 100,000.

Modeling Herpes Zoster
(M. Brisson)

Most data on the incidence of herpes zoster and mortality data are from Europe, North America, and Australia. It is possible to model the global incidence of zoster using estimated country-specific varicella incidence rates and estimated age-specific rates from varicella to herpes zoster, adjusting for HIV prevalence. The difficulty is that the impact of vaccination on zoster is unknown. The scarcity of data from low- and low-middle-income countries and the validity of using extrapolations from high-income countries is very questionable.

Summary and recommendations

IVIR members believe that the proposed methods to investigate the burden of disease of varicella and herpes zoster are appropriate, but are concerned about the lack of data, especially in African countries. For this reason, they suggest that the working group evaluate other existing seroprevalence data, as well as data from Latin American countries that have introduced varicella vaccine. Even in the absence of hard data, modeling can play a role on the impact of vaccination. IVIR members also suggested some medium-term solutions to the lack of data: (1) include zoster in existing surveillance systems; and (2) test for varicella antibodies in existing serum samples in Kenya and other countries.
11 Grading evidence

Overview
(A. Portnoy, R. Hutubessy)

The IVIR Advisory Committee currently has two forms for review of (1) vaccine mathematical models and (2) vaccine economic models. These forms are not adequate for new studies that may be evaluated by the committee in the future and so there is need for new IVIR review forms. Philippe Duclos, the WHO focal point for SAGE, requests that the committee could use the GRADE approach, which has been adopted by SAGE.

Discussion

Dr. Duclos feels that IVIR-AC should use GRADE as a WHO committee. The most debated part of GRADE is scoring, since prominence is given to RCTs. The GRADE working group has made adjustments to the tables when it does not work well in practice and is open to future adjustments based on the committee’s needs. The current forms have made a clearer inclusion of observational studies, post-surveillance studies, and other non-RCT studies. They have also added more narrative requirements to the forms and are more accepting of observational studies when it is not possible to do RCTs. Dr. Duclos also noted that many analyses are not GRADE-able, e.g., burden of disease. It is only possible to use GRADE for published studies since WHO needs study support in order to justify new guidelines. He also noted that cost-effectiveness analysis has been one of the weaknesses of GRADE.

Others noted that there are not as many opportunities for RCTs in public health, but countries such as the US use RCTs as the “gold standard.” It may be necessary to establish a working group on this subject that could identify the limitations of using the GRADE approach for different cost-effectiveness studies. In six years, QUIVER/IVIR has been primarily reactive and it is time to think about what the committee wants its role to be. It would be useful to add another day to discuss IVIR-AC’s role and discuss process and grading at a future committee meeting. In the past, QUIVER/IVIR has been unsuccessful in reaching consensus about burden of disease and coverage when data are questionable.
12 Annex A: Meeting Agenda

Final Agenda
Immunization and Vaccines-related Implementation Research (IVIR)
Advisory Committee (AC) Meeting
Salle D, WHO HQ, Geneva, Switzerland
25-26 September 2012

TUESDAY, 25 SEPTEMBER 2012

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Purpose of session, target outcomes and questions for IVIR</th>
<th>Time allocation</th>
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<tbody>
<tr>
<td>08.30</td>
<td>Registration</td>
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<tr>
<td>09.00</td>
<td>Welcome - introduction and Charge to the Committee A. Hinman, Chair of IVIR</td>
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<td>30 min.</td>
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<tr>
<td>09.45</td>
<td>WHO Implementation Research priority setting framework – Session 1</td>
<td>FOR DECISION</td>
<td>45 min.</td>
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<tr>
<td></td>
<td>Report of the WHO prioritization process and list for an immunization implementation research, P. Namgyal, 5 min. J. Clemens, 20 min</td>
<td>Outcomes: IVIR’s proposal to SAGE on the priority setting process, method and next steps in the finalization of the implementation research topics list.</td>
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<td></td>
<td>IVIR review, R. Breiman, A. Hall, 15 min each</td>
<td>Questions: - Is the IR priority setting method appropriate given the purpose of the exercise? - Does IVIR consider that the proposed implementation research topics list is appropriate and relevant in support of achieving the current goals and to address major immunization challenges?</td>
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<tr>
<td>10.30</td>
<td>Coffee/tea break</td>
<td>Break</td>
<td>30 min</td>
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<tr>
<td>11.00</td>
<td>Review and discussion cont’d, 1hr 30 min.</td>
<td></td>
<td>1hr 30 min.</td>
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<tr>
<td>12.30</td>
<td>Lunch</td>
<td>Break</td>
<td>1hr 15 min.</td>
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### 13.45 Value of Statistical Life (VSL) – Session 2

Use of VSL for Cost-Benefit Analysis (CBA) of vaccines
- Use of VSL for Decade of Vaccine (DoV), S.Ozawa, 10 min.
- Principles, description, use and pros/cons VSL methodology, R. Laxminarayan, 20 min.¹
- WHO’s perspective on the use VSL for CBA, D. Evans, 10 min.

IVIR review, J. Edmunds, D. Bloom², 15 min. each

Discussion: 15 min.

**FOR DECISION**

**Outcome:**
IVIR recommendation to SAGE on methodological issues and policy consequences on the use of VSL for DOV

**Questions:**
- Does IVIR consider that WHO should use of VSL in priority setting in health, in particular decision making in vaccines? Is this a robust/appropriate method?
- What are the advantages and disadvantages of VSL compared to other CBA and CEA outcome measures being used to evaluate vaccines and immunization strategies?

<table>
<thead>
<tr>
<th>15.00</th>
<th>Coffee/tea break</th>
<th>Break</th>
<th>30 min.</th>
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<tbody>
<tr>
<td>15.30</td>
<td>Review and discussion cont’d, 1hr 30 min.</td>
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<td>1hr 30 min</td>
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<tr>
<td>17.00</td>
<td>Closed IVIR administrative session</td>
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**WEDNESDAY, 26 SEPTEMBER 2012**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Purpose of session, target outcomes and questions for IVIR</th>
<th>Time allocation</th>
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</thead>
<tbody>
<tr>
<td>8.30</td>
<td>Yellow Fever burden of disease (BoD) – Session 3</td>
<td><strong>FOR INFORMATION</strong></td>
<td>30 min.</td>
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<td></td>
<td>Introduction, , N.Ferguson, T. Garske¹, M. Van Kerkhove, 10 min.</td>
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<td></td>
<td>Discussion: 20 min.</td>
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<tr>
<td>9.00</td>
<td>Broader economic impact of vaccines (BEIV) – Session 4</td>
<td><strong>FOR DECISION</strong></td>
<td>1hr 15 min.</td>
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<td></td>
<td>WHO BEIV framework and ongoing studies, M.Jit, 10 min.</td>
<td>Outcomes: IVIR to provide recommendations on the proposed framework and</td>
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</table>

¹ By telephone
² Written notes only
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Outcomes</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.15</td>
<td>Coffee/tea break</td>
<td></td>
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<tr>
<td>10.45</td>
<td><strong>Measles investment case for eradication – Session 5</strong></td>
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<td></td>
<td>Short introduction, A. Dabbagh, 5 min.</td>
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<td></td>
<td>Measles investment case: methods, assumptions and preliminary results, K.</td>
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<td></td>
<td>Thompson, 10 min.</td>
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<td></td>
<td>IVIR review: Z. Bhutta⁴, 10 min.</td>
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<td></td>
<td>Discussion: 45 min.</td>
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<tr>
<td>12.00</td>
<td><strong>Costing of HPV vaccines – Session 6</strong></td>
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<td></td>
<td>Introduction of the WHO cervical cancer planning and costing (C4P) tool and country applications, A. Levin, 10 min.</td>
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<td></td>
<td>IVIR review: E. Sinanovic, F. De la Hoz-Restrepo, 10 min. each.</td>
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⁴ Written notes only
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<tr>
<th>Time</th>
<th>Event</th>
<th>Duration</th>
<th>Notes</th>
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<tbody>
<tr>
<td>12.30</td>
<td>Lunch</td>
<td></td>
<td>Break 1hr 15 min.</td>
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<tr>
<td>13.45</td>
<td><strong>Costing of HPV vaccines – Session 6 cont’d</strong></td>
<td></td>
<td>FOR DISCUSSION AND DECISION 45 min.</td>
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<td></td>
<td>Discussion: 45 min.</td>
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<tr>
<td>14.30</td>
<td><strong>Proposed dynamic method for static models – Session 7</strong></td>
<td></td>
<td>FOR DISCUSSION AND DECISION 1hr 15 min.</td>
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<tr>
<td></td>
<td>Introduction, M. Johri and M. Jit, 15 min.</td>
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<td></td>
<td>IVIR review: D. Burke, B. Grenfell, 10 min. each.</td>
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<td></td>
<td>Discussion: 40 min.</td>
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<tr>
<td>15.45</td>
<td><strong>Coffee/tea break</strong></td>
<td></td>
<td>Break 30 min.</td>
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<tr>
<td>16.15</td>
<td><strong>Varicella/Zoster (VZ) burden of disease estimation – Session 8</strong></td>
<td></td>
<td>FOR DISCUSSION AND DECISION 1hr 15 min.</td>
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<td></td>
<td>Introduction, J. Seward, M. Brisson, each 10 min.</td>
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<tr>
<td></td>
<td>IVIR review. P. McIntyre, R. Feilden, 10 min. each</td>
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<td></td>
<td>Discussion: 35 min.</td>
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<tr>
<td>17.30</td>
<td><strong>Wrap up of the meeting</strong></td>
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<tr>
<td>17.45</td>
<td><strong>Closure</strong></td>
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Annex B: List of Participants

Initiative for Vaccine Research
Immunization and Vaccines related Implementation Research
Advisory Committee (IVIR-AC)
Salle D, WHO HQ, Geneva, Switzerland

25-26 September 2012

LIST OF PARTICIPANTS

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