Report on the WHO Quantitative Immunization and Vaccines Related Research (QUIVER)

Advisory Committee Meeting
5-7 October 2010
Geneva, Switzerland
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Abbreviations and acronyms

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BMGF</td>
<td>Bill and Melinda Gates Foundation</td>
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<tr>
<td>CEA</td>
<td>cost-effectiveness analysis</td>
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<td>CFR</td>
<td>case-fatality rate</td>
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<td>CHERG</td>
<td>Child Health Epidemiology Reference Group</td>
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<td>EPI</td>
<td>Expanded Programme on Immunisation</td>
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<td>HIS</td>
<td>Health Statistics and Informatics (WHO)</td>
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<td>HPV</td>
<td>Human Papillomavirus</td>
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<td>IHME</td>
<td>Institute of Health Metrics and Evaluation</td>
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<td>IARC</td>
<td>International Agency for Research on Cancer</td>
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<td>IVB</td>
<td>Immunization, Vaccines and Biologicals (WHO)</td>
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<td>IVR</td>
<td>Initiative for Vaccine Research (IVR)</td>
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<td>JHSPH</td>
<td>John Hopkins School of Public Health</td>
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<td>JTEG</td>
<td>Joint Technical Expert Group</td>
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<td>LSHTM</td>
<td>London School of Hygiene and Tropical Medicine</td>
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<tr>
<td>PCV</td>
<td>pneumococcal conjugate vaccine</td>
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<td>PCV7</td>
<td>7-valent pneumococcal conjugate vaccine</td>
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<td>SAGE</td>
<td>Strategic Advisory Group of Experts of Immunization (WHO)</td>
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<td>SIA</td>
<td>Special Immunisation Activity</td>
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<td>QUIVER</td>
<td>Quantitative Immunization and Vaccines Related Research</td>
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<td>SAGE</td>
<td>Strategic Advisory Group of Experts on Immunization</td>
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<td>UNDP</td>
<td>United Nations Development Programme</td>
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<td>UNFPA</td>
<td>United Nations Food</td>
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<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
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<td>VMI</td>
<td>Vaccine Modelling Initiative</td>
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<td>WHA</td>
<td>World Health Assembly</td>
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Executive Summary

The fourth annual meeting of the WHO Quantitative Immunization and Vaccine-Related Research (QUIVER) advisory committee was held in October 2010 in Geneva. The 12 members of the advisory committee provide advice to WHO on estimates of the burden of vaccine-preventable diseases, mathematical modeling related to vaccines and immunization programmes, estimates of the impact of vaccines, economic evaluations of vaccines and immunization programmes, and other quantitative methods of generating information relevant to policy decisions about the introduction of vaccines. The demands on QUIVER have been growing as a result of the increasing emphasis being placed on evidence-based policy-making.

Several groups within WHO (for example, the departments of Health Statistics and Informatics (HIS), and Immunization, Vaccines and Biologicals (IVB)) and outside WHO (for example, the Institute for Health Metrics and Evaluation (IHME)) have methods for estimating worldwide cause-specific childhood mortality. Each method has its strengths and weaknesses, but all focus on a single cause of death despite the fact that many people die from multiple interacting factors. QUIVER recommends that methods for estimating childhood mortality reflect the multi-cause nature of many deaths and the uncertainty of point estimates. QUIVER recommends that the activities on estimation of childhood mortality carried out by the WHO Child Health Epidemiology Reference Group (CHERG) and IVB be coordinated, particularly in terms of harmonizing total deaths with deaths attributed to a specific condition when there are multiple causes of death. QUIVER recommends that an independent group review the methods used by entities within and outside WHO to estimate child mortality, and clarify the uncertainties around point estimates, so that general audiences understand why estimates of child mortality may differ.

A natural-history model of pertussis is being developed by the Ontario Agency for Health Protection and Promotion in Canada in collaboration with WHO to estimate the burden of disease and the impact of vaccination. Owing to lack of data, parameters in the model will be determined after consultation with experts. QUIVER endorses this method of modelling, although it recommends that work be conducted to collect these data directly instead of relying on expert opinion only.

A model to estimate the burden of measles deaths that incorporates data on disease dynamics has been developed by Pennsylvania State University, United States, and endorsed by QUIVER.
A systematic review and modelling exercise being conducted by the University of Bern, Switzerland, to inform national vaccination schedules has been endorsed by QUIVER with caveats. QUIVER endorsed the overall approach of the systematic review. The modelling exercise focuses on invasive pneumococcal disease, and QUIVER recommended incorporating end-points for natural immunity and noninvasive disease into the model.

The Joint Technical Expert Group (JTEG) on Malaria Vaccines Entering Pivotal Phase 3 Trials should draft joint policy recommendations with QUIVER to present to the WHO Strategic Advisory Group of Experts on Immunization (SAGE) using input from modelling studies when interim phase 2 field efficacy trial results become available in 2012. The literature review of malaria transmission models and the cost–effectiveness analysis presented to QUIVER provided a useful overview of existing work. QUIVER felt that a comparison exercise of malaria vaccine cost-effectiveness tools is premature given the current status of malaria modelling and economic tools. QUIVER recommended that for the next step IVR should work with the JTEG to evaluate existing models of malaria transmission.

A study on the impact of measles eradication on healthcare systems by the London School of Hygiene and Tropical Medicine (LSHTM) and two cost–effectiveness analyses of measles eradication by the Johns Hopkins School of Public Health (JHSPH) and independent consultants were presented. These studies were carried out in response to a request from the World Health Assembly (WHA). QUIVER endorsed the 3 studies, but suggested that further work will be needed to evaluate strategies for measles endgame.

QUIVER was updated on: continuing work on estimates of the burden of rotavirus disease; comparisons of various tools for assessing the cost-effectiveness of human papillomavirus (HPV) vaccines; modelling of supply-chain logistics; dengue vaccine modelling; social contact surveys in South-East Asia; and work being undertaken by the Vaccine Modeling Initiative (VMI) on measles and rubella modelling.

Due to the complexity of modelling the impact of vaccines and their cost effectiveness, and the important policy recommendations that modelling supports, QUIVER has been requesting that different modelling groups use common data sets, model parameters and assumptions. Experiences in modelling measles eradication, and the impact of pneumococcal vaccine, rotavirus vaccine and HPV vaccine, have shown that comparisons of various vaccines provide more insight into disease dynamics and emphasize the importance of not relying on a single model or set of assumptions for decision-making.

Working groups were recommended to (i) work with SAGE to collect data on pertussis, (ii) develop an eradication strategy for measles, (iii) advise WHO on methods to be used to update estimates of rotavirus mortality, (iv) work with the JTEG to develop guidance for modelling the economic aspects of malaria vaccination, and (v) liaise with WHO on dengue modelling.

QUIVER proposed that WHO should examine the broader economic impacts of immunization beyond cost–utility analyses, such as the effects of improved health on economic growth – for example, by assessing the impact of vaccines on education, productivity, savings and investments.
1. Introduction and Charge to the Committee

*Introduction: J. Hombach*

Attendees were welcomed to the fourth QUIVER meeting. They were reminded about the role of SAGE, which was to make key recommendations about vaccination policy. SAGE is then supported by input from a number of expert committees, including QUIVER, whose role is to provide input with regards to burden estimates, mathematical modelling, estimates of the impact of vaccine interventions, economic evaluation and other quantitative methods. The demands on QUIVER have been growing as a result of increasing emphasis on evidence-based policy making. Another relevant expert committee providing input to SAGE is CHERG. CHERG has provided some observers to the QUIVER meeting due to the closely related interests of both groups.

QUIVER has an agenda to address specific WHO policy questions such as measles elimination, as well as work that the WHO is developing as a result of its own initiatives (listed under “For information” on the agenda for Day 2). All sessions are open except for a closed session on Thursday morning for advisory committee members.
2. WHO-CHERG estimates of child causes of death - Introduction

Introduction: T. Burton

One of the uses of models is to provide estimates where empirical data are missing. EPI has a track record of collecting data on vaccine coverage and impact, with annual data going back to 1974. Surveillance is routinely recommended, but this is often incomplete and non-standardised. When good surveillance data are unavailable or of uncertain quality, models can be used to estimate the number of cases and deaths due to vaccine-preventable diseases. A model-based estimate of cases and deaths before and after vaccination for several vaccine-preventable diseases was made as early as 1987. Since then the quality of statistical methods and data have significantly improved, so the quality of estimates can also be enhanced.

2.1 CHERG model

Presenter: R. Black

CHERG was introduced as an expert committee established by WHO to serve as an external reference group for both WHO and UNICEF. Its responsibilities include the estimation of child and maternal mortality, as well as the effects of interventions on mortality. Child mortality estimation is subdivided into estimation for neonatal deaths (1-28 days) and for older children (1-59 months). The estimation incorporates vital registration data where available, and where it is not, uses a multi-cause logistic regression model with data from several sites, adjusted by country. Deaths due to malaria, pertussis, measles, tetanus, meningitis and AIDS obtained from external estimates or separate models rather than from multi-cause model. For China and India, nationally representative studies are utilised.

Discussion points

- Deaths can be due to more than one cause (for instance, diarrhoea and malnutrition). The model is based on a single cause of death, based on the ICD-10 code of the disease that started the chain of events leading to death. Co-morbidities are being considered as a separate activity by CHERG. It is possible to estimate the proportion of deaths with risk factors (such as malnutrition) overlaid across other causes of death. However, severe malnutrition (such as kwashiorkor) would be considered a cause of death on its own.

- In principle, updates are planned as a long term effort, although whether or not it will be published on a national basis will depend on funding. Currently, the Gates Foundation funds the work, but at the end of a four year period, the intent is that WHO will pick up work.
It was pointed out that as 2015 approaches, pressure to reduce mortality may increase as may the gap between officially reported and actual mortality. However, critical appraisal of sources of data is not part of the mandate of CHERG.

Large parts of Central and West Africa (including Nigeria, Angola and Congo) appear to be missing from the data sites. For the most part, CHERG does not have the resources to conduct primary studies and has to rely on systematic reviews and contacts to incorporate into the model.

QUIVER may be asked to review the CHERG child mortality estimates, as well as to bring academic input to the table. QUIVER would focus on evaluating the methods rather than endorsing the final numbers.

QUIVER would also seek to encourage groups to focus on uncertainty ranges around point estimates, as well as to develop methods to estimate contributions to death. Use of Venn diagrams to show interactions between causes of death was suggested.

CHERG is keen to collaborate with QUIVER.

The work on pertussis is not something CHERG can take on as a major project since it’s objective is the global burden of disease in general.

CHERG could help QUIVER on the issue of improving the use of case fatality ratios for measles.

CHERG is working on methods to propagate uncertainty in mortality estimates.

CHERG proposed the use of counterfactuals to estimate the contribution of comorbidities to mortality, although it was also pointed out that this would underestimate conditions for which there are no effective preventive interventions.

QUIVER suggested that there should be continued development on surveillance sites and approaches that will provide better data on the occurrence and severity of disease.

2.2 WHO process for preparing consistent child causes of death estimates

Presenter: C. Mathers

WHO obtains cause-specific child mortality estimates from several sources. Data are collected where vital registration systems exist, but these data are rare and often incomplete, biased or poorly coded. Additionally, programmes such as IARC and CHERG produce estimates. All available data are pooled together in the World Health Statistics so as to be consistent with overall mortality “envelopes” for neonatal and under 5 years deaths, which is estimated from vital registration data and birth histories. The distribution of deaths by cause is estimated using a multi-cause regression model, with each death attributed to a single cause. An interagency expert group advises on the methodology for data collection and analysis. There are some difficulties since several agencies have different models (eg. WHO, UNICEF, UNFP) which are not always consistent.
Discussion points

- Attribution of deaths to a single cause may not be realistic since deaths can often be due to multiple causes. A partial solution is to use risk factor analyses to estimate the attributable mortality due to underlying causes such as hepatitis or malnutrition.

- The regression model produces unlikely results when it is fitted to several inconsistent data sets, but it was pointed out that this was better than fitting to no data or a single incorrect data set.

- QUIVER was pleased to see progress in harmonising different approaches that take into account the statistical complexities of mortality estimation.

2.3 Summary points and recommendations

- Although there are different approaches to estimating childhood mortality by cause, there is progress on harmonisation between different approaches, and in taking account of the statistical complexities of the estimation.

- QUIVER will coordinate activities with CHERG on childhood mortality estimates, particularly with respect to harmonising overall deaths with deaths attributed to particular conditions (when there are multiple causes of death).

- QUIVER urged the investigation of the availability of funding to collect additional data on child mortality particularly in regions which are currently underrepresented in the CHERG child mortality estimates.

- QUIVER recommends that a technical advisory group review the methods used to estimate the child mortality estimates, and to explain the uncertainties around point estimates in ways that are comprehensible.

- QUIVER recommends that techniques be developed to present the contributions of different conditions to death which are attributed to single causes, and the potential role of interventions in preventing such deaths.
3. Burden of pertussis model

Introduction: P. Strebel

Three pertussis models are being considered in order to generate estimates of cases and deaths due to pertussis, as well as cases and deaths averted through vaccination. The models will be used to monitor the impact of recent investments and to guide vaccine priorities, but not to evaluate alternative vaccine strategies. The first model is a static natural history model of pertussis developed by Natasha Crowcroft in order to inform IVB pertussis incidence estimates. A second model was developed by Mark Miller in response to a request for proposals from the WHO. Both these models were reviewed by QUIVER, which had some misgivings about the way some aspects of pertussis natural history were represented.

3.1 Pertussis model structure and expert elicitation

Presenter: T. Burton

A third model is now being developed based on the Crowcroft model. The model is static, with states for being susceptible, infected and partially/fully vaccine protected. The population is stratified by age and setting (high birth rate, low coverage and high coverage, low birth rate). The model contains many parameters for which there are little or no data on, particularly for developing countries. Hence the modellers propose to obtain parameter values using the Cooke method of expert elicitation. This includes seed questions in order to weight the accuracy of expert answers.

QUIVER review (QUIVER reviewers: M. Postma, J. Edmunds)

Both reviewers agreed that there were significant gaps in the data needed to parameterise a pertussis model, such as for data on protective immunity and transmissibility. While the ideal solution would be to design studies to fill those gaps, in the absence of such studies the alternative is to ask for expert opinions. The current pertussis model was felt to present a rational, systematic approach to eliciting such information from experts. However, once the process was complete, it may be useful to use the model to assess the most influential parameters which could be the target for collecting primary data.
Discussion points

- There were concerns over the dichotomy of countries into two groups (low birth rate, high coverage and high birth rate, low coverage). It was suggested that more categories may be useful. In particular, the case fatality ratio (CFR)\(^1\) for pertussis were felt to differ widely between countries. The NIH model in which the CFR was indexed to the overall childhood mortality rate was pointed to as one possible alternative. GDP per capita was also suggested as a possible proxy variable for CFR due to pertussis.

- Because the epidemiology of pertussis has been changing rapidly, the elicited parameters may not be relevant for long. Further complications may arise as a result of the introduction of acellular vaccines, hypersensitive diagnostic methods and an increasing role in some countries for adults in transmission.

- Ultimately, the issue may only be resolved by collecting real data.

- It may be useful to conduct the expert elicitation exercise on a disease area for which answers are known, as a means of validating the technique.

- Case-fatality ratios for developing countries are based on a single study (from Senegal). QUIVER discussed using a distribution of mortality values across countries (perhaps by indexing to relative infant mortality compared to Senegal’s) rather than a single number.

- While the method used may be appropriate in the current circumstances, QUIVER was concerned that it may set a precedent to collect data by expert elicitation rather than designing primary studies.

3.2 Summary points and recommendations

- QUIVER endorsed the new natural history model using expert elicitation to estimate the parameters, given the shortcomings in the data on pertussis. QUIVER suggests that efforts be made to try to validate this approach of parameterisation.

- QUIVER would encourage the funding of more primary studies to collect these data directly, using the model to understand what the most influential parameters are.

- QUIVER suggests that the modellers consider whether having only two scenarios for model parameters is appropriate, or whether the number of scenarios should be expanded.

\(^1\) It was pointed out that the term “death case ratio” was more accurate than “case fatality ratio” to describe the ratio of deaths due to a disease to the number of cases of the disease.
4. Estimating the burden of measles

Introduction

Presenter: P. Strebel

In May 2010, WHO established targets for measles vaccine coverage, incidence and mortality as milestone towards measles eradication. This created a requirement to report annually on these statistics, which WHO has been doing in annual publications estimating measles deaths by WHO region in people under and over 5 years old. However, QUIVER had concerns about the approach used to conduct this estimation, as it was thought that it may overestimate deaths by relying too much on coverage data, not incorporating herd immunity and using outdated CFR figures. It also fails to adequately capture the uncertainty in the estimates.

4.1 Measles model

Presenter: M. Ferrari

An alternative model was developed in order to address QUIVER’s concerns with the previous model. This model firstly estimates measles cases by country and year using surveillance data. The estimation uses the Kalman Filter method in order to make explicit projections about dynamic transitions over time as well as overall patterns in incidence. The cases are then stratified by age classes based on a model fitted to data stratified by national GDP and vaccine coverage. The results are applied to age-specific CFRs and then aggregated again to produce overall deaths. Uncertainty is estimated by bootstrap sampling from the distribution of incidence and age distribution estimates.

The results are fairly similar to those estimated using the previous method, since the biases in the previous method tended to offset each other (the previous method overestimated case, but the age distribution of cases tended then to underestimate deaths). The benefit of the new method is that it allowed for herd immunity as suggested by QUIVER. The statistical methods used also allowed more robust estimation of uncertainty bounds in both the incidence and age distributions of cases.

QUIVER review (QUIVER reviewers: A. Nelson, R. Laxminarayan by telephone)

The reviewers felt that the new method was elegant and allowed the integration of dynamic data in the way the previous method did not. However, there were a number of concerns:
• Biases in under-reporting may not necessarily be constant as assumed in the model. The investigator acknowledged the problems with this. A number of time varying reporting rates (such as linear or varied according to vaccine coverage) were tried but were found not to be consistent with data.

• Reporting figures for Bolivia appeared to be suspect. The investigator suggested that this was because Bolivia went through a transition from endemic to episodic dynamics. The model performs poorly in regions with episodic measles outbreaks.

• The uncertainty in CFR figures was not captured in the model. Lastly, it was suggested that using serological data may be a means of validating the model.

Discussion points

• The model uses data on the proportion of the population that is susceptible at the start of the time series (in 1980). There were concerns that the data on this figure were not robust. However, this is a necessary evil of the model. Projections are only made starting from 2000 so the hope is that the inaccuracies in the initial estimate are corrected by later data.

• Measles importations due to migration may also not be static over time; this may be particularly important close to elimination.

• The dynamic link between susceptibility and incidence is quasi-mechanistic. There were concerns that it may be inaccurate close to the herd immunity threshold.

• There were concerns over the use of mortality figures from WHO without considering the uncertainty around them.

4.2 Summary points and recommendations

• The overall model approach was endorsed by QUIVER as it addresses the issues raised by QUIVER last year.

• QUIVER highlighted some issues, although they may be difficult to immediately address given limitations in the data, including the dynamic nature of reporting biases, vaccine coverage and susceptibility to disease close to elimination.

• Given the dramatic changes in measles transmission we encourage incorporation of new data in the model. The model has the flexibility to incorporate data on disease dynamics as they become available.
5. Immunisation schedules

Introduction: A-M. Henao - Restrepo

In 2005, SAGE suggested that existing immunisation schedules may not be optimal considering recent advances in vaccination. Hence WHO sought to review evidence and analyse data that would be useful to policy makers.

5.1 Generic approach – systematic review

Presenter: N. Low

A systematic review of schedules for pneumococcal conjugate vaccines was conducted in order to establish a general protocol that could be applied to other systematic reviews of vaccine schedules. The review would encompass randomised, cohort and case-control studies. One difficulty was that the only studies which directly compared different schedules of the same pneumococcal conjugate vaccine within the same study were observational studies with serological endpoints. This raised issues of biases due to the observational nature of the studies, as well as the lack of reliable immunological correlates of protection. Some data suggested that 0.35ug/ml correlated with protection from invasive disease, but this was not universal across all serovars.

QUIVER review (QUIVER reviewers: F. Restrepo, A. Nelson; External reviewer: P. Garner)

This was felt to be an important initiative that could make decision making about vaccine schedules more evidence-based. Some suggestions to the review team included the following:

- The scope of the review was very large since there were many possible schedules and outcomes to look at. Each combination of these may require a different protocol.
- Also, it was unclear how the review would take into account emerging issues with the vaccines over time, since the field was rapidly changing. Engagement with policy and clinical experts would help to drive questions and interpretation of data.
- Much of the evidence about schedules may be in the grey literature, such as in deliberations of national advisory committees on vaccination.
- The correlation between immunological and clinical efficacy endpoints has only been measured for short time periods and could change over longer periods.
- The reasons for heterogeneity between studies needs to be analysed qualitatively as well as statistically.
• It may be useful to devise an optimal schedule based on biological principles, then to develop review questions that could examine that schedule.

In her response, the investigator agreed that the review question was very important, and indeed the scope of it involved more than a single literature review. With regards to immunogenicity outcomes, while these were problematic, once the licensure studies were completed all vaccine studies used immunogenicity outcomes.

Discussion points
• The final decision about vaccine schedules will need to depend on issues of feasibility, fit with existing schedules and cost-effectiveness, so the best schedule may not necessarily be the optimal one with respect to clinical efficacy. The review is part of a larger process, including economic modelling as well as investigation of issues of political feasibility and desirability. The value of the review is that it will present an optimal schedule from an efficacy standpoint, which will be a starting point for discussion potentially leading to change.
• Serological correlates of immunity are not perfect, especially for viral vaccines.
• The review will report intention to treat analyses, unless they are unavailable. It will follow the Cochrane principle, in updating the review when new evidence becomes available.
• There were concerns that the scope of the review may miss important evidence, since few randomised trials are conducted after vaccine licensure. For instance, ecological studies may be useful to compare countries with different schedules. The correlation between immunogenicity and clinical efficacy would be difficult to determine based on the review scope.
• It would be useful if the review did not simply repeat results from currently ongoing reviews of PCV.

5.2 Specific model of PCV schedules

Presenters: N. Gay ; A. Melegaro

The committee were reminded that modelling was severely limited by available data. However, the modellers were interested in whether the overall structure and main assumptions of the model made sense.

The overall aim of the study was to evaluate a number of potentially useful vaccination schedules, to estimate the incremental cost-effectiveness ratios of each (compared to alternative schedules) using dynamic models, and to explore the uncertainty associated with these estimates. In addition, the study aims to explore interactions between diseases as a result of vaccine co-administration, competing causes in mortality and some syndromes caused by more than one disease. Since high quality surveillance data are rare, the study would focus on regions with the best surveillance, such as the MRC study site in the Gambia. The vaccines to be evaluated would be diphtheria, tetanus, pertussis, Haemophilus influenza, hepatitis B, pneumococcal and rotavirus.
The first vaccine to be evaluated is PCV7 in Burkina Faso. Modelling the effect of this vaccine is complicated because pneumococcal disease has a range of outcomes, the vaccine induces indirect effects (such as herd immunity and serotype replacement), most infections do not lead to severe disease, there are multiple serotypes, multiple carriage is possible and competition between serotypes occur. Consequently, simplifying assumptions will be used to make progress on this. Three possible approaches to modelling PCV7 are to use a static model with a herd immunity adjustment, a compartmental dynamic model and an individual-based model. The compartmental dynamic model approach was chosen since there are limited data to parameterise an individual-based model or to approximate the herd immunity impact of vaccination in a static model. A model previously used to explore PCV7 impact in England and Wales was adapted to demographic, vaccine coverage and vaccine schedule assumptions for a low income country. Serotypes in the model are divided between those in the PCV7 vaccine and those which are not. Individuals infected by one group of serotypes have a lower risk of being infected by a different group of serotypes, with this risk determined by a competition parameter. Preliminary results exploring six different scenarios about vaccine schedules indicate that scenarios with the most doses (doses given at 6, 10 and 14 weeks) would be the most cost-effective. A catch-up campaign up to 24 months of age may also be cost-effective.

**QUIVER review (QUIVER reviewer: J. Koopman; External reviewer: K. Auranen)**

Reviewers agreed that the work was extremely interesting and that modelling a complex disease such as pneumococcal disease required simplifying assumptions. However, there were concerns about the particular assumptions used in the model, including the following:

- Uncertainty analysis needs to consider the impact of simplifying assumptions as well as of different choices of parameters.

- Natural immunity may be important especially if boosted by continual exposure to re-infection, since this may decrease after vaccination. Some strains are common between childhood invasive disease and late adulthood invasive disease. This suggests a natural history of serotype specific waning. If vaccination eliminates continual boosting for these strains, late adult disease could appear earlier and be more severe. There is also a possibility that serotype replacement may provide sufficient cross immunity for these strains. But this seems unlikely.

- The choice of competition parameter is crucial; it is not clear how this was determined. Studies have found that replacement in carriage by non-vaccine serotypes following PCV7 vaccination is almost complete; however this is not reflected in the model. The investigators suggested that this could be looked at when post-vaccination data on carriage from Burkina Faso were obtained.

- The aggregation into vaccine and non-vaccine types may produce different dynamics from having individual types.

- The age-distribution in carriage is averaged over all serotypes. This may affect the case-carrier ratio and post-vaccination predictions of carriage.
Discussion points

The modellers were congratulated for taking on a challenging disease to model; however, there were some further concerns from the rest of QUIVER:

- For policy purposes, countries are facing a decision between PCV10 and PCV13 rather than PCV7. The idea was that the model would be applied to data for these vaccines; however, there is currently no data on alternative schedules for them.
- The discussion may highlighted the underlying shortage of data in developing countries, necessitating models in such countries to be parameterised using data from developed countries.
- Accuracy is particularly important in this exercise because the differences in outcomes between different schedules are likely to be small; hence uncertainties are likely to be magnified in importance.
- There are likely to be important differences between developed and developing country models and cost because of the differing role of invasive diseases like pneumonia and septicemia and non-invasive diseases like otitis media and bronchitis. Very little is known about the non-invasive disease burdens in developing countries. These could be potentially much greater than in developed countries. Data are currently being collected in the Gambia in order to populate the model with such data.
- There was an active discussion about the appropriate time horizon for the analysis, given that both pneumococcal vaccines and disease epidemiology are likely to change dramatically over the next decade.
- There were concerns about the lack of immunity and of non-invasive disease endpoints in the overall modelling approach to PCV schedules.

QUIVER was reminded that they needed to be pragmatic given the lack of data on pneumococcal disease and the decisions that were being made on far less sophisticated models. QUIVER concluded that there was general support for the approach, but some concerns over the way the model represented specific aspects of pneumococcal epidemiology.

5.3 Summary points and recommendations

Immunisation schedules – systematic review

- The overall review philosophy was endorsed, but the scope of the review is very large, and consequently the questions that are being addressed need to be carefully defined.
- QUIVER suggests expanding the literature review to incorporate at least some of the grey literature and other types of studies.
- The review is a useful first step but results need to be graded in terms of quality, and considered in the context of wider programmatic and economic issues that are also important to vaccine implementation.
- In addition to reviews of schedules of individual vaccines, a further step will need to be considering optimising the schedule of multiple vaccines.
Immunisation schedules – mathematical model

- QUIVER recommends that the model incorporates pneumonia deaths as well as invasive pneumococcal disease, and that it incorporates the role of epidemic as well as non-epidemic strains, as well as of natural immunity.
- The model should focus on PCV10 and 13, rather than PCV7.
6. For information updates

6.1 Rotavirus burden estimates

*Presenter: T. Burton*

In 2005, rotavirus childhood mortality was estimated to be around 527,000 in 2004. The estimation was done by reviewing literature on country-specific childhood diarrhoeal deaths and estimating the proportion of deaths associated with rotavirus based on the number of hospitalised diarrhoea deaths in which rotavirus was identified. Data for countries for which data were available was then applied to other countries in the same region (defined by geography and child mortality). A new estimate for 2010 will now be made, based on data from 124 relevant studies published since 2000. Subsequently, estimates for 2004 will be revisited. The estimate will not take into account the effect of co-morbidity or immunisation.

**Discussion points**

- No genotype data will be synthesised.
- There are data in the grey literature that may be helpful in informing the estimates, which has so far been restricted to the published literature.
- In the Americas, most countries introduced rotavirus vaccination in 2007, so this would need to be factored in an estimate.
- Sentinel surveillance is often flawed as it does not pick up cholera outbreaks which are important in many countries.
- The age classes in the previous analysis were somewhat crude (all under 5 deaths were grouped together), which made it difficult to estimate mortality in pre-immunised children.
- Differences in the proportion of diarrhoeal deaths due to rotavirus in different regions in the world seem to have diminished since the last study.
- Thresholds for hospitalisation for diarrhoea differ between countries, so this may confound estimates.
- QUIVER will set up a working group on rotavirus to advise the childhood mortality estimation work.
- Several QUIVER members will participate in a working group established to appraise estimates of the number of deaths due to rotavirus.
6.2 HPV cost-effectiveness tool comparison

**Presenter: M. Postma**

A consultation on the cost-effectiveness of HPV introduction in low and middle income countries was held in Montreal in 2009, in order to develop guidance for policy makers on existing cost-effectiveness tools. Participants included modellers, HPV experts as well as representatives from WHO and industry. Modellers were given a standardised data set in order to compare model results using the same data. None of the models were able to perfectly reproduce the standardised data set, although most predicted large decreases in vaccine-type disease. The most influential factors in sensitivity analysis were rate of discounting, duration of protection and vaccine price. The exercise indicated that it may be more useful to provide a set of tools rather than recommend a single model, so that local policy makers can select models based on their local situation and data availability.

**Discussion points**

- This is the third such exercise following exercises for pneumococcal and rotavirus vaccines. QUIVER was comforted that there were people looking at the same data with different models to identify optimal strategies.
- Policy makers in low and middle income countries often do not find results in terms of cost per DALY useful. The threshold for cost-effectiveness used by the WHO (based on GDP per capita or three times GDP per capita) was also felt to be too high for useful discrimination. Budget optimisation analyses, as well as the break even price of vaccines, were felt to be more useful.
- Screening was not evaluated (except to assume a background rate of screening) since the exercise was focused on vaccination.
- Public-private partnerships were felt to be helpful so that assumptions behind models would be made transparent and explicit.
- The application of standardised data sets for different models such as for HPV vaccination is useful.
- The public-private partnership may be useful to encourage transparency about assumptions in economic models.
- Economic evaluations are useful; however there needs to be investigation into alternative ways (besides cost per DALY) of presenting outcomes that are useful to decision makers in low and middle-income countries.

6.3 Modelling supply chain logistics and impact on health outcomes

**Introduction: Patrick Lydon**

Several groups have been modelling supply and logistic chains for vaccines and other health care commodities. Models in existence include the Unified Health Model, the USAID-funded 2020 Supply Chain Model, HERMES from the Vaccine Modelling Initiative and WHO-PATH’s Optimize Supply Chain model.
6.3.1 The Unified Health Model

**Presenter: Karin Stenberg**

An interagency working group on developing tools to optimise health systems was established in 2008 in response to requests by several UN agencies (including WHO, UNICEF, World Bank, UNAIDS, UNFPA and UNDP) to harmonise different tools available for this. This resulted in an integrated tool that could respond to questions on the cost and mortality impacts of different packages, given existing health systems constraints. The intended audience is health care planners, ministries of health and donor organisations. A version of the model may be available for testing in early 2011.

**Discussion points**

- The model can be used at sub-national levels, although it is not suitable for detailed market analysis. It does not cover “last mile” transport from service centre to client.
- IHME is looking at models which take flows (such as attrition of equipment) into account. The Unified Health Model also looks at this.
- QUIVER agreed that this was a new area of modelling that could potentially address key issues that current models are unable to.
- QUIVER would like to be kept informed about the progress of the four available models, and in particular how the developer groups would relate to each other, and how their suitability could be appraised.

6.4 Workshop on dengue vaccine modelling

**Presenter: P. Namgyal**

WHO organised a workshop on dengue vaccine modelling in collaboration with Vaccine Modelling Initiative at Pittsburg University in August 2010. One impetus for this was a vaccine developed by Sanofi Pasteur entering phase III trials, with data expected by the end of 2011. Initially, the plan was to pose questions that modellers could explore answers for. However, this turned out to be too ambitious, so the workshop focused on discussing work that had already been done and reaching a consensus about the way to progress. An opinion paper is in preparation, and a follow-up meeting is planned in 2011.

The workshop clearly showed the benefit of a multi-disciplinary approach to dengue modelling, involving disease experts, clinicians and policy experts as well as modellers. A key concern for modellers was the lack of public availability of relevant data sets. Current models all rely on a single data set based in Thailand.

QUIVER agreed that it would be useful to encourage investigators with sero-epidemiological data on dengue in settings outside Thailand (as well as their funders) to make results publicly available. In some cases, samples still have not been tested and targeted investment to perform the testing may be useful. Data sets based in Cuba, Puerto Rico and Vietnam were also suggested as ones that could potentially be tapped; there may also be data from Latin America published in the Spanish literature. Key issues that needed to be explored by models informed with good data included the effect of enhancement (increase in the severity of subsequent dengue infections) and the effect that vaccination would have on this and the existence of waning immunity.
Co-existence of dengue with syndromically similar diseases such as typhoid and rubella may also complicated data interpretation.

**Discussion points**

- Current models of dengue vaccination are dependent on a single data set (the Thai data set). Other studies on dengue seroprevalence have been carried out, and QUIVER would like to encourage the investigators and their funders to make the data sets publicly available to improve models. More data collection activities are also needed.
- The diagnostic challenges in identifying dengue patients were acknowledged.

6.5 **Influenza social contacts and mixing patterns in South East Asia**

**Presenter: J. Edmunds**

A WHO-funded study of contact patterns relevant to the spread of close-contact diseases was presented. The study was carried out in Thailand, Vietnam and Indonesia, with the sample population chosen to achieve balance in terms of urban/rural mix, age, gender and day of the week. 10,189 respondents were orally interviewed using a standardised survey instruments. There were also links to similar surveys in Taiwan, Korea, southern China and Vietnam.

Future work may involve comparison with parallel outbreak data as well as use of technology such as cell phones or RFID chips. QUIVER agreed that this could potentially be very interesting, as would more detail about contacts with animals. The survey did ask about contact with live animals within a metre, but more information about the type of contact involved would be useful.

The survey allowed definition of different kinds of contacts by frequency, duration and physicality. However, it did not cover casual non-conversational contacts in public settings such as trains and shops. The investigator suggested that these kinds of contacts were actually less important in infection transmission; for instance, for the case of SARS most cases knew another case except for the initial few cases and those in one particular outbreak (Amoy Gardens).

**Discussion points**

- The study results were very interesting and useful.
- For further work, comparison with parallel outbreak data, investigation of changes to networks over time, and more information about animal contacts would be useful.
6.6 Measles and rubella modelling

Presenter: B. Grenfell

The Vaccine Modelling Initiative is based in the University of Pittsburg, with collaborations with Pennsylvania State University and Imperial College London. In November 2010, a measles and rubella meeting was held to bring together modellers and disease experts. The outcomes of the meeting will be shared with QUIVER, who may be asked to look over the analyses.

Discussion points

- The outcomes of the Princeton meeting will be shared with interested QUIVER members.
7. Malaria vaccine modelling

Introduction: V. Moorthy

In 2008, there were an estimated 243 million malaria cases resulting in 863,000 deaths. However, incidence has dropped in some countries due to control measures such as bednets, sprays and artemisinin. These need to be taken into consideration when evaluating vaccines. Currently, there is one malaria vaccine (RTS,S) produced by GSK undergoing phase III trials. A joint technical expert group on malaria will draft policy recommendations for SAGE.

7.1 Evaluating the cost-effectiveness of malaria vaccines: a review of modelling tools

Presenter: A. Ghani

A systematic review of epidemiological and economic models of malaria vaccination was presented. Only four publications were found relating to malaria vaccines, originating from the University of Florida, Mahidol-Lisbon group, Imperial-LSHTM group and Swiss Tropical Institute. The Swiss Tropical Institute model is the furthest developed. In addition, GSK is developing a model, and a consultancy called Intellectual Ventures is developing a malaria simulation. Results from different models are difficult to compare due to the different perspectives taken by the models.

Remaining uncertainties with the models include:

- Poorly identified correlates of protection.
- Different stages for naturally-acquired immunity that could be targets for vaccination, but would have different effects on transmission.
- Heterogeneity in malaria epidemiology depending on vector ecology, climate, housing, availability of treatment and existence of other interventions (such as bednets and aerosol spraying).
- Long-term protection from vaccines (individuals vaccinated with RTS,S could still be infected, and duration of protection is unknown).
QUIVER review (QUIVER reviewers: Z. Bhutta, S. Supakankunti)

- There needs to be a balance between simplification and realism. Existing models sometimes ignore uncertainties in malaria biology and epidemiology that may affect the effect of vaccination (such as the issue of drug resistance).
- It would be useful to look at the effect of combined interventions (such as vaccination and bednets), movement of people and vectors, as well as vaccination of pregnant women.
- Heterogeneity in existing studies could be examined (such as their setting, model structure, study year, transmission intensity and cost).
- When inflating results of individual studies for comparative purposes, it may be better to use local inflation rates rather than US inflation rates.

Discussion points

- A vaccine with short duration (such as RTS,S) delivered under an EPI programme may have little impact on transmission since the main transmitters are school children and adults. It may be useful to look at alternative distribution pathways outside the EPI programme such as more targeted programmes. However, the current trials only consider young children partly because the current reductions in malaria transmission as a result of other interventions were not obvious when the trials began. Also, in sub-Saharan Africa, most of the burden is still in children under 5 years old.
- Interaction between vaccine-induced and natural immunity is important, but studies to collect such data are difficult to conduct.
- A tool comparison exercise may be premature since there are few existing models to compare, and still many uncertainties relating to malaria biology and epidemiology.
- However, WHO will need to have guidance about existing tools when approached by policy makers. The joint technical expert group on malaria is the expert committee bringing together malaria and immunisation experts, but not experts in modelling. QUIVER proposed setting up a working group to collaborate with the group to provide guidance on existing models.
- Modelling can also help to identify the most important knowledge gaps to fill. In the Swiss Tropical Institute model, key parameters are vaccine cost, vaccine duration and how transmission varies across carries.

7.2 Summary points and recommendations

Review of malaria vaccine models

- The literature review was a useful overview of existing work.
- QUIVER felt that a tool comparison exercise was premature given the lack of knowledge about key features of malaria natural history and epidemiology.
- There were concerns about the uncertainties in current models; however, at the same time there is a pressing need to provide guidance to policy makers as the first malaria vaccine approaches licensure.
- QUIVER will set up a malaria working group to work with JTEG in order to provide this guidance.
8. Update on the feasibility of measles eradication

Introduction: Alya Dabbagh

In 2009, QUIVER reviewed several studies on the feasibility of measles eradication. The aspects of measles eradication that the studies considered were the following: biological feasibility, programmatic feasibility, vaccine market analysis, impact on immunization and health systems, economic analysis, risk of reintroduction, stakeholder analysis and comparison with other eradication programmes.

The studies were completed and reviewed in July 2010. The recommendations will be considered by SAGE, and a decision about global goals made at the World Health Assembly. An ad-hoc advisory group recommended that measles eradication should proceed, but should be carried out in context of strengthening routine immunization programmes.

8.1 LSHTM study on impact of immunization and health systems

Presenter: P. Hanvoravongchai

A study was conducted by investigators from the London School of Hygiene and Tropical Medicine with collaborators in six countries (Cameroon, Tajikistan, Bangladesh, Vietnam, Ethiopia, Brazil), representing a range of regions, income levels, measles and vaccine coverage levels. They looked at the impact that accelerated measles elimination activities would have on routine immunisation services and health systems, using document reviews, secondary data collection, key informant interviews, staff profiling surveys.

The key findings of the study were that the degree of integration between measles activities, overall EPI programmes and health systems varied widely between the six countries, as did the impact that measles activities would have on wider immunisation and health care systems. In particular, negative impact appeared to be more likely to occur in resource poor countries which had weaker health systems, less integration, and more reliance on ongoing SIAs. The study authors recommended that efforts be made to prevent these negative impacts by proposing specific guidelines, modifying toolkits for country-level impact assessments, strengthening routine immunisation systems, exploring innovative approaches and contributing to removing health systems bottlenecks.
8.2 Cost-effectiveness of measles elimination (model 1)

**Presenter: D. Bishai (by telephone)**

The presenter described a cost-effectiveness analysis of four strategies concerning measles vaccination (continuing with present levels of immunisation, achieving 95% reduction in measles mortality by 2015, achieving 98% reduction in measles mortality by 2020 and eradication of measles by 2020). This used a discrete time SIR model with population growth, importations, and declines in measles mortality in step with all-cause mortality. Countries in the Americas that have already eliminated measles were assumed to have lower costs after measles eradication, as they were assumed to be able to increase intervals between SIAs.

A key finding was that in the six countries examined, measles eradication was found to be cost saving in Brazil and Colombia, and to be below a threshold of GDP per capita per DALY gained in Bangladesh, Ethiopia and Uganda. However, measles eradication was found to be above that threshold in Tajikistan. At a global level, measles eradication was found to be below the threshold across all income levels, and cost saving in some cases. However, it was difficult to distinguish between cost-effectiveness of reducing mortality and eradication, since the uncertainty intervals overlapped in these scenarios. Incorporating the benefit of rubella reduction as a result of immunisation would increase societal savings in the order of 50-100% of the benefits of the measles programme across all strategies. Key uncertainties remained, particularly the cost of reaching hard-to-reach populations, both in places with weak health systems and in countries with ideologically opposed groups.

8.3 Cost-effectiveness of measles elimination (model 2)

**Presenters: A. Levin (by telephone), C. Burgess (by telephone)**

A second model of measles eradication was presented. This was built on an SEIR model. It estimated the cost of different measles immunisation strategies by interviewing programme managers about the resources needed to increase coverage and improve surveillance. After elimination, costs were expected to decline due to the reduction in SIAs. Epidemiological results were validated using WHO mortality estimates. To extrapolate from the six countries examined to the whole world, a global contact matrix was used to represent the entire world as a single country with 180 districts.

Achieving 95% reduction in mortality requires a substantial increase in coverage. Eradicating measles by 2020 is cost saving in countries that have already eliminated measles, and cost-effective in other countries except Tajikistan. It is estimated to be more cost-effective than 95% or 98% mortality reductions. On a global level, eradicating measles is cost-effective across all income levels, and cost saving in countries that have eliminated measles. The level of case importation greatly affects measles transmission. Also, campaigns such as SIAs and outbreak responses are more effective than increasing routine vaccination over small time period at rapidly decreasing mortality. Key drivers are the cost of increasing routine and campaign coverage, and the impact of routine and campaign measles vaccination on morbidity and mortality, and the role of case importation.
QUIVER reviews (QUIVER reviewers: R. Laxminarayan by telephone, B. Grenfell)

The reviewers commended both modelling teams for a substantial piece of work that addressed many issues raised by QUIVER. They were comfortable with the overall analysis but raised a number of queries about aspects of the model:

- The models assumed that populations within each country were homogeneous. However, local heterogeneities are likely to be increasingly important as the point of eradication draws closer. This would require a different set of models to explore, as well as data on the subgroups who were refusing vaccination and their mixing patterns.

- The game theoretic aspects of obtaining coordination from different countries could be important, although it was beyond the mandate of the modelling teams.

- Importation of measles cases through migration was assumed to decrease linearly to the point of elimination. It is possible that realistic relaxation of this assumption to correspond to predicted transmission dynamics from micro-simulation might significantly change cost-benefit calculations.

- The benefits in terms of reduction in rubella incidence were not modelled in a way that captured local heterogeneities and their effect on the reproduction number of rubella.

The modelling groups supported the concerns about local heterogeneities, migration and the need for collecting primary data on hard-to-reach groups, suggesting that these issues be addressed in future work.

Discussion points

- Of the six countries examined, Tajikistan had the least cost-effective profile for measles elimination in both models. One of the modelling groups was not comfortable with the Tajikistan data as the cost data were poor and the coverage levels may have been elevated.

- Tajikistan also demonstrates that eradication becomes less cost-effective as countries get closer to the goal of elimination. Decision makers (at the national, subnational and individual levels) act according to what others are doing, so a game theoretic perspective may be needed to understand their behaviour. However, the modellers were not asked to consider these aspects.

- QUIVER previously discouraged the modellers from extrapolating results from the six countries to the entire world. The models have partly circumvented this by presenting results stratified by income level and current status of measles elimination.

- Measles eradication needs to be conducted in the context of strengthening routine immunisation programmes and the rest of the health system in general. Interviews with people in the six countries studied suggested that this may be possible.

- QUIVER concluded that this was good work that satisfied its remit but also raised further questions that needed to be addressed.
• There were serious caveats about the method used for costing and the rubella sub-analysis.
• QUIVER was concerned that the cost-benefit profile of measles eradication appeared to be worst in the poorest countries with the least developed health systems.

8.4 Summary points and discussions

• QUIVER endorsed the two models and the LSHTM study as huge pieces of work, particularly given the timelines and resources available to address issues raised at the World Health Assembly.
• While both models gave similar results about the favourable cost-effectiveness of measles eradication, QUIVER had some caveats about the costing method and the addition of rubella.
• As eradication approaches, models that capture heterogeneity, behavioural response and contact patterns may be needed.
• As these models do not address the end game QUIVER members volunteer to work with programme staff in order to develop models to address these issues.
9. Other business

9.1 Working groups

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<td>Pertussis</td>
<td>J. Koopman, M. Postma</td>
<td>Work with SAGE to encourage data collection</td>
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<tr>
<td>Measles</td>
<td>B. Grenfell, J. Edmunds, R. Laxminarayan</td>
<td>Work with programme staff to address measles edingfame</td>
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<tr>
<td>Rotavirus</td>
<td>A. Nelson, Z. Bhutta, J. Edmunds</td>
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<td>M. Postma, Jim Koopman</td>
<td>Work with JTEG to develop guidelines on use of cost-effectiveness models</td>
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<tr>
<td>Dengue</td>
<td>F. Restrepo, Derek Cummings</td>
<td>Liaise with WHO to advise on dengue modelling</td>
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9.2 Broader economic impact of vaccines and immunization

Results of economic evaluations used in high countries such as the incremental cost per DALY of interventions are not very useful for policy makers in low and middle countries (particularly those who have to fund vaccine introduction themselves). WHO is working with David Bloom to develop innovative measures of the broader economic impact of health. There is also a need to consider approaches such as budget impact assessment and return on investment. Perspectives could range from the individual to society. WHO will share results from this work with QUIVER for their critical input and discussion.

QUIVER also had concerns about the WHO threshold for cost-effectiveness (cost per DALY falling under GDP per capita), which was not helpful for decision-making since almost all interventions tend to fall under the threshold. The use of other metrics such as league tables was suggested. Also, QUIVER was reminded that the threshold should only be used as a league table, to be used at supranational level and at a national level only if no other guidelines were available.

9.3 Mortality estimation

QUIVER requested the Secretariat to keep the committee informed of developments with regards to mortality estimation by CHERG and other groups.
9.4 QUIVER terms of reference

There are more people wanting to consult QUIVER than can be accommodated within the current meeting time. QUIVER consultees make contributions towards travel expenses for the committee. It was suggested that QUIVER meetings be increased to biannual. However, this may take place as a satellite meeting following a different meeting, in order to save funds.

QUIVER also regularly needs new members in the committee as members as rotated every four years. S. Supakankunti will be stepping down after the present meeting. Her contribution was appreciated by the remaining members. The committee consists of a balance of epidemiological modellers, economists and consumers of models.

QUIVER will publish a summary of discussions during this meeting in the Weekly Epidemiological Record. Other groups doing studies in which QUIVER made substantive comments will be encouraged to acknowledge QUIVER in their publications.

QUIVER members were asked to submit suggestions for a different name for the committee to the Chair within the next two weeks.
### 10. Meeting agenda

**WHO Quantitative Immunization and Vaccines Related Research (QUIVER) Advisory Committee Meeting**  
5-7 October 2010  
Salle B, Geneva, Switzerland

**Chair:** A. Hinman  
**Overall Meeting Rapporteur:** M. Jit

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<td>• Adoption of the agenda</td>
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<td><strong>WHO-CHERG estimates of child causes of death</strong></td>
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<td>• WHO process for preparing consistent child causes of death estimates (15’)</td>
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<td>A. Henao-Restrepo&lt;br&gt;N. Low/ P. Scott&lt;br&gt;F de la Hoz/A. Nelson&lt;br&gt;P. Garner</td>
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<td>Pneumococcal transmission model for schedules project</td>
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<td>A. Henao Restrepo&lt;br&gt;A. Melegaro/N. Gay&lt;br&gt;B.F. Baryarama/J. Koopman&lt;br&gt;K. Auranen</td>
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### Wednesday, 6 October 2010

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<td><strong>Rapporteur:</strong> M. Jit&lt;br&gt;<strong>08:30-09:00</strong>&lt;br&gt;- Rotavirus burden estimates – update on new estimates&lt;br&gt;<strong>09:00-09:15</strong> HPV Cost-effectiveness tool comparison – results and follow up&lt;br&gt;<strong>09:30-10.00</strong> Modeling supply chain logistics and impact on health outcomes&lt;br&gt;<strong>10.30-11.00</strong> Coffee break</td>
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<td>10.30-11.00</td>
<td>Influenza social contacts and mixing patterns in South East Asia – results&lt;br&gt;- Introduction (10’)&lt;br&gt;- Discussion (20’)&lt;br&gt;<strong>10.30-11.00</strong> Coffee break</td>
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12:00-13:30 **Lunch break**

**Vaccine modeling (continued)**

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<td>• Follow up (10’)</td>
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15.30-16.00 **Coffee break**

**Measles Eradication**

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<th>16.00-18.00 Outcome July 2010 Final meeting in Washington DC</th>
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18.00 **Adjourn**

**Thursday, 7 October 2010**

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<th>Closed session</th>
<th>Rapporteur: R. Hutubessy</th>
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10.30-11.00 **Coffee break**

11.00-13.00 Future directions QUIVER | A. Hinman |

13:00 **Closure**

* Attend by teleconference
11. List of participants

Initiative for Vaccine Research (IVR)
Quantitative Immunization and Vaccines Related Research
Advisory Committee (QUIVER)
5-7 October 2010
WHO HQ (Room B), Geneva, Switzerland

Advisory Committee Members

Dr Fulgentius Baryrama, CDC-Uganda, Uganda Vaccine Research Institute, Entebbe, Uganda

Professor Zulfiqar Ahmed Bhutta, Head Maternal and Child Health Division, The Aga Khan University, Karachi, Pakistan

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Dr Pem Namgyal, Scientist, Initiative for Vaccine Research, Implementation Research, World Health Organization, 1211 Geneva 27, Switzerland

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Dr Karin Stenberg, Costs, Effectiveness, Expenditure and Priority Setting, World Health Organization, Switzerland

Dr Peter Strebel, Medical Officer, Expanded Programme on Immunization, World Health Organization, 1211 Geneva 27, Switzerland
The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization, Vaccines and Biologicals (IVB).

IVB’s mission is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. The Department covers a range of activities including research and development, standard-setting, vaccine regulation and quality, vaccine supply and immunization financing, and immunization system strengthening.

These activities are carried out by three technical units: the Initiative for Vaccine Research; the Quality, Safety and Standards team; and the Expanded Programme on Immunization.

The Initiative for Vaccine Research guides, facilitates and provides a vision for worldwide vaccine and immunization technology research and development efforts. It focuses on current and emerging diseases of global public health importance, including pandemic influenza. Its main activities cover: i) research and development of key candidate vaccines; ii) implementation research to promote evidence-based decision-making on the early introduction of new vaccines; and iii) promotion of the development, evaluation and future availability of HIV, tuberculosis and malaria vaccines.

The Quality, Safety and Standards team focuses on supporting the use of vaccines, other biological products and immunization-related equipment that meet current international norms and standards of quality and safety. Activities cover: i) setting norms and standards and establishing reference preparation materials; ii) ensuring the use of quality vaccines and immunization equipment through prequalification activities and strengthening national regulatory authorities; and iii) monitoring, assessing and responding to immunization safety issues of global concern.

The Expanded Programme on Immunization focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: i) immunization systems strengthening, including expansion of immunization services beyond the infant age group; ii) accelerated control of measles and maternal and neonatal tetanus; iii) introduction of new and underutilized vaccines; iv) vaccine supply and immunization financing; and v) disease surveillance and immunization coverage monitoring for tracking global progress.

The Director’s Office directs the work of these units through oversight of immunization programme policy, planning, coordination and management. It also mobilizes resources and carries out communication, advocacy and media-related work.