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

Advisory Committee Meeting
Geneva, 13-15 October 2009
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## Abbreviations and Acronyms

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>anti-HBc</td>
<td>antibody to hepatitis B core antigen</td>
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<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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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CRS</td>
<td>congenital rubella syndrome</td>
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<tr>
<td>cVDPV</td>
<td>circulating vaccine-derived polio virus</td>
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<tr>
<td>DALY</td>
<td>disability adjusted life year</td>
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<tr>
<td>DTP</td>
<td>diphtheria-tetanus-pertussis vaccine</td>
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<tr>
<td>EPI</td>
<td>Expanded Programme on Immunization</td>
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<tr>
<td>FOI</td>
<td>force of infection</td>
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<tr>
<td>GAVI</td>
<td>The Global Alliance for Vaccines and Immunization</td>
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<td>GBD</td>
<td>global burden of disease</td>
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<tr>
<td>GDP</td>
<td>gross domestic product</td>
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<td>GEM</td>
<td>global epidemic model</td>
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<td>GNI</td>
<td>gross national income</td>
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<td>GSK</td>
<td>GlaxoSmithKline</td>
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<tr>
<td>HAV</td>
<td>hepatitis A Virus</td>
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<tr>
<td>HBV</td>
<td>hepatitis B Virus</td>
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<tr>
<td>HEV</td>
<td>hepatitis E Virus</td>
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<tr>
<td>IBM</td>
<td>individual based model</td>
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<tr>
<td>ICER</td>
<td>incremental cost-effectiveness ratio</td>
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<tr>
<td>ILI</td>
<td>influenza-like illness</td>
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<tr>
<td>IPV</td>
<td>inactivated poliovirus vaccine</td>
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<tr>
<td>iVDPV</td>
<td>immunodeficiency-associated vaccine-derived polio virus</td>
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<tr>
<td>IVB</td>
<td>Immunization, Vaccines and Biologicals (WHO)</td>
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<tr>
<td>IVR</td>
<td>Initiative for Vaccine Research (WHO)</td>
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<tr>
<td>KRR</td>
<td>knowledge reasoning and representation system</td>
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1. Introduction and charge to the committee

The third meeting of the QUIVER advisory committee was introduced. Briefly, QUIVER — a technical committee directly advising the Strategic Advisory Group of Experts (SAGE) provides expert advice in quantitative immunization and vaccine related research to the World Health Organization (WHO). More specifically, the terms of reference (TORs) for the committee are to advise the Initiative for Vaccine Research (IVR) and the Department of Immunization, Vaccines and Biologicals (IVB) regarding: quantitative research on the estimation of burden of vaccine-preventable diseases; modelling the impact of vaccine interventions; economic evaluation of vaccine interventions, and other analytical components of operational and implementation research (e.g. establishing contact and behavioural patterns in developing countries). Currently, the advisory committee consists of 12 advisory committee members with a range of applicable skills.
2. Coverage estimates at WHO-UNICEF

An introduction to the WHO/UNICEF estimates for national immunization coverage (WUENIC) was given. In brief, the objective of the tool is to estimate immunization coverage in a transparent, consistent and replicable way, with an optimal use of the data in a non-manual process.

In order to make the coverage estimates more transparent and replicable, the data, decisions and rules are summarized in computational logic representing a formal knowledge reasoning and representation system (KRR). All rules are written in natural languages, symbolic notation and instantiated in computer language (e.g. Prolog, SQL, Clips). The coverage estimates produced are based on the data, decisions and rules represented in the KRR. The data, rules and decisions are clearly documented. The rules may be challenged, and serve as a device for structuring the discussion.

The advantages and disadvantages in the process of using administrative data versus survey data were pointed out. The usefulness of defining an absolute difference of 10% between the reported administrative coverage-estimates and survey coverage-estimates as a cut-off limit for using only survey estimates was also discussed.

2.1 Immunization system monitoring

Presenter: R. Steinglass, JSI Research and Training Institute, Boston, USA

The presenter had a positive impression of WUENIC. He stressed the importance of the coverage estimates as they serve as a trigger for Global Alliance for Vaccines and Immunization (GAVI) payments, inform investment decisions, determine the timing of follow-up campaigns and inform models.

The presenter identified the challenge of resolving conflicts in data, as there are multiple data sources which are context-specific, with varying or unknown completeness. It was pointed out that the WUENIC process still needs to be validated. This will be difficult as there are no gold standards to use as a comparison. A suggestion was made to expand consultation with national programmes to improve estimates and to invest in capacity-building for active monitoring at all levels.

Some brief comments were made; coverage estimates might go down as data quality improves, and this might not be well accepted by authorities and other groups.
2.2  Formal knowledge reasoning and representation systems

Presenter: L.M. Pereira, Universidade Nova Lisboa, Lisbon, Portugal

An external expert gave his comments on computational aspects of the documentation and software.

The overall assessment was positive, with the design and implementation options considered to be good. The logic application that was chosen (Prolog) was the most appropriate one in terms of the language used. It is easy to extend and manipulate, and is well known. It is also easy to express and read and it is repeatable. The illustration with real examples provided the presenter with the evidence that the tool functions appropriately.

The advantages of the initial platform are that it has the capability of drawing upon ongoing research and is designed to deal with fuzziness. It provides explanatory capacities and has a user-friendly platform. The need for resources to realize this system was highlighted.

2.3  Outcome WHO-UNICEF immunization coverage estimates review meeting

Presenter: B. Grenfell, Pennsylvania State University, USA

A QUIVER member reviewed WUENIC, and was positive about the rule-based structure, particularly as it is replicable, consistent, transparent and flexible.

Another positive point highlighted was the significant broader potential. In brief, this includes using the framework to identify key data gaps, to refine statistical methods for extrapolation and to codify logical structure of work-group evaluations.

The appropriateness of the 10% difference rule between administrative and survey data was questioned. The difficulty of measuring uncertainty was pointed out. Suggestions were made to address the uncertainty by: analysis of survey microdata; comparison with existing/new biomarker measures of vaccine-derived and natural immunity, or cross-calibration with epidemiological modelling.

2.4  General discussion

The importance of validation of the model was discussed. It was suggested that validation of the model could be conducted using countries where there is good data available (e.g. seroprevalence data).

There was much discussion about the quality of the data used. The importance of clear documentation of what type of data is used in the estimates was highlighted. Currently, there are no quality scores for data captured within the system.
For administrative data, the need for a uniform guidance on these data was highlighted. The importance of checking whether the data is correct within each country was also discussed. Examples of methods which could be used include cross-tabulation with other health-system information (functionality and access), and involving national technical advisory groups in the process.

For survey data there are minimum criteria to be included (e.g. national coverage and sample size). Surveys are thought to be better because both the numerator and denominator are known. Survey quality could become apparent when looking at multiple surveys; therefore the value of the more frequent future multiple indicator cluster survey (MICS) 2–3 yearly surveys was discussed. It was further recognized that the role of the private sector cannot be ignored.

Some other brief comments were made including the difficulty of dealing with uncertainty and an explanation of how the rules can be validated or revised. For example, if the coverage estimates are questionable, the rules can be accepted or revised, or an exception can be made, so long as the decision-making process remains transparent.

2.5 Recommendations

- The approach was considered to be appropriate but estimates for within-country variations were also highlighted as highly desirable. Some very detailed refinements would be needed.
- Methods of dealing with uncertainty should be examined more fully. For example, the current method could be maintained (using an absolute 10% difference in survey and administrative data as a cut-off for using survey data only) or confidence intervals from the surveys could be used. Alternatively, a combination of these two methods could be used. A combination method was preferred, but this method was not clearly defined.
- While it was understood that there is no real gold standard of coverage estimates, and the inclusion of survey results in the estimation process represents some internal validation, other validation of the tool should be sought. In particular, the use of data from serosurveys was encouraged.
- QUIVER was unable to make concrete recommendations on how to deal with uncertainty in the estimates, and thus recommended further research.
3. Measles eradication

3.1 Introduction and outcome of June 2009 working-group meeting


This session was designed to examine both the feasibility and economic considerations of measles eradication.

Specific questions included:

1) Is measles eradication feasible and appropriate when considering factors such as biological feasibility, impact on health systems, economic analyses, vaccine market analyses, programmatic feasibility, risk analysis for post-measles era, global context and political feasibility?

2) What should the next global goal be, and should this be eradication or an intermediate goal? What should be the target date for this goal?

The task given to modellers was outlined. Briefly, this includes the use of dynamic models for both measles and rubella to address short-term (20 years) and long-term (50 years) costs and benefits (both independently and relative to intermediate goals), to identify sources of uncertainty for sensitivity analyses, and to carry out economic analyses from both societal and health-systems perspectives. Specific objectives of the economic analysis include estimating the costs of measles eradication and investigating the cost-effectiveness of eradication, both on a global scale, and for six selected countries. Several specified vaccine-delivery options should be investigated in the pre- and post-eradication periods.

QUIVER was asked to assess whether the models are appropriate to address the questions, how they can be improved, whether costing methods are appropriate, and how best to extrapolate from six countries to a global estimate.
3.2 **Dynamic measles Model 1**

*Presenter: D. Bishai, Johns Hopkins School of Public Health, Baltimore, USA*

The first model presented is a dynamic, age-stratified, compartmental model (SVIR), where V represents vaccinated. Heterogeneity in vaccine coverage is included (modelled as two compartments with either 20% or 80% coverage, and named “A” and “M” respectively) as well as a dynamic case-fatality rate which improves with improvements in under-five mortality. Five age groups are modelled (0–11 months, 12m–5 years, 6–15y, 16–49y, ≥ 50y) with population changes tracked in the model. Fertility rates are taken from UN data and the population is all female, with results doubled to estimate the total population. A two-week time step is used in the model. Seasonal forcing will also be added. A who-acquires-infection-from-whom (WAIFW) contact matrix will be used to describe contact patterns between age groups and high and low coverage areas (see the presentation for a full graphical representation of the mixing matrix). The mixing matrices will be calibrated to age-specific attack rates (pre-vaccination era) and outbreak data (post-vaccine era).

The model will be run from 2010 and will linearly ramp up the coverage of first and second doses of measles-containing vaccine (MCV1 and MCV2) to reach target coverages in a target year. MCV2 will start when MCV1 reaches 80% coverage for three consecutive years. Supplementary immunization activities (SIAs) will be run at set intervals (2–5 years). Values for MCV1 and MCV2 coverage as well as the frequency of SIAs will be trialled until elimination is achieved in the target year (2015, 2020 or 2025). The presenter asked QUIVER for guidance on how to model post-eradication threats.

The rubella model will contain a different force of infection (FOI) and a different recovery parameter but will use the same WAIFW matrix. The conditional probability (conditional on incident rubella while pregnant) of congenital rubella syndrome (CRS) will remain constant over time.

**Group discussion:**

Post-eradication scenarios for analysis were discussed. It was clarified that the SAGE sub-group wishes to know the cost of sustaining immunity after eradication using a variety of vaccination scenarios. The sub-group also considers the cost-effectiveness not only of eradication but also of alternative global goals to be important.

There was discussion about whether countries will want to pursue global goals, particularly if no scaling back of vaccination activities after eradication is envisaged.

The linearity of under-five mortality and measles deaths was questioned, and it was suggested that there may be a threshold beyond which the relationship is non-linear. Some concern was raised about how vaccine efficacy was modelled — the model should be constructed so that a vaccinated individual becomes either immune or not.
3.3 Dynamic measles Model 2

Presenter: C. Burgess, MathEcology, LLC, Phoenix, USA

A deterministic, age-structured compartmental susceptible (S), exposed (E), infectious (I), and recovered (R) model (SEIR) model was described. Vaccination will be simulated by a direct flow from S to R compartments. A WAIFW matrix will be used to define age-assortive mixing patterns and will be fitted to data on the percentage of individuals infected by each age as estimated from the six countries data, published or unpublished literature, or expert consensus. Seasonality will be added using an annual sinusoidal variation in transmission rate, and disease will be imported as a stochastic process. MCV1 will be included at 9 or 12 months for each country. This will switch from 9 to 12 months when incidence is less than three per million. MCV2 at 15 to 18 months will be added when MCV1 coverage is \( \leq 80\% \) for three consecutive years. Ramp-up rates will be dependent on current coverage and target dates. SIAs will occur at intervals which are calculated according to MCV1 coverage levels and target dates, and will stop after eradication. The simulations will be run from 2000. Vaccination strategies will continue unchanged during the certification period, with coverage level frozen after eradication.

Two methods were suggested for global extrapolation: one involves summing populations from all countries with similarities to the six case-study countries, and runs each scenario in grouped data; the other uses parameters taken from the six countries but runs the scenarios by country. Sensitivity analyses will be performed on SIAs, the contact matrix, case importation and other factors. Ramp-up rates will be determined using similar methods to that in Model 1.

The rubella model has the same structure as the measles model with rubella and CRS-specific parameter values. CRS is modelled as a proportion of rubella cases in child-bearing ages.

Group discussion:

The assumptions of homogeneity of mixing and vaccine coverage caused some concern in discussions and it was suggested that departure from these assumptions should be investigated.

3.4 Review and discussion of dynamic measles models

It was not clearly understood when eradication could be deemed to have occurred in deterministic compartmental models such as these. The presenters responded by saying that eradication was considered to have occurred once the number infected fell below one individual. There was also concern that stochasticity at low levels of infection could not be taken into account in deterministic models. There was some discussion around whether parameters should be standardized to allow comparisons of the two models. There was also discussion about the importance of underreporting of measles, and whether the level of underreporting varies with incidence. It was thought that validation of both models with historical data would be advantageous.
3.5 Recommendations

There was general agreement that heterogeneity in vaccine coverage should be more comprehensively included in both models. There was some discussion about whether parameters should be standardized across models as this would make comparisons between the models easier, but it might also make investigation of the effects of parameters more restricted.

The key recommendations for epidemiological models were:

- Insufficient data as well as model limitations (e.g. lack of spatial components, inadequate heterogeneity and stochastic effects) should be stressed, and that the models are not adequate for modelling eradication but are useful in making preliminary assessment for the cost and cost-effectiveness of interruption of local transmission. Both groups should indicate what data and technical developments would be needed for a more accurate and comprehensive analysis of scenarios near the measles ‘end game’ (e.g. in-country and transnational spatial stochastic models with realistic subpopulation heterogeneity will need to be analyzed to more accurately assess eradication costs).

- Heterogeneity in vaccine coverage needs to be included more comprehensively in both models.

- Both groups should ensure as much as possible that the model input parameters, scenarios and assumptions are the same.

- Both models should provide more details (comprehensive table/list) on model parameterization assumptions and inputs.

- Both models should be validated as much as possible against historical measles incidence data.

- Models should take into account dependence of 2nd MCV dose on 1st dose and the impact of this on population immunity.

- There is no need to include in the model the risk of introduction after eradication is achieved. That risk needs to be assessed in subsequent models like those suggested above, but not as part of these initial modelling efforts.

- Waning immunity is not considered significant and need not be included in the models.

- Both groups should re-submit the updated methods to the QUIVER measles ad hoc advisory committee, taking into consideration these recommendations for final input.

- Rubella and CRS need to be modelled more comprehensively.
3.6 Economic Evaluation 1

**Presenter: D. Bishai, Johns Hopkins School of Public Health, Baltimore, USA**

An economic evaluation based on the first dynamic measles model was presented. All scenarios will be compared to a “do nothing” scenario in this evaluation. Incremental cost-effectiveness ratios (ICERs) will be calculated for each country (using extrapolation from the case-study countries — see below) and globally. It was noted that there are few data available on the marginal costs associated with increasing vaccine coverage to eradication levels. Three costing options were presented. One estimates total costs based on known sub-costs (e.g. staff), and assumes that it is known how these costs translate into increased coverage. The other looks at district or country variation in costs, versus the coverage achieved. Both of these approaches were considered to have substantial drawbacks. The final option was to make some assumptions about how cost would rise with coverage. Some evidence was presented to show that costs of SIAs/child vaccinated does not vary with the level of routine vaccination coverage.

Extrapolations were made based on ratios of gross domestic product (GDP) per capita, from the six countries to other countries in the region, but some exceptions were made (see presentation for details).

**Group discussion:**

Discussion focussed on the lack of data on the marginal costs of increasing vaccine coverage, and emphasized that it is pivotal for any analysis of cost-effectiveness of measles eradication.

Extrapolation from the six case countries to a global estimate was considered to be problematic. It was suggested that these countries might be better used to give a range of possible costs.

3.7 Economic Evaluation 2

**Presenter: A. Levin, Bethesda, USA**

In this analysis, based on the second of the dynamic measles models, the cost and cost-effectiveness of measles eradication and other scenarios was compared to the current global goal of 90% reduction in measles mortality (see presentation for a full description of the scenarios examined). It was once again highlighted that cost per dose will increase with coverage. Cost data for this analysis have been collected from a variety of sources but the assumption still needs to be made that these marginal costs will occur. Health- system costs include routine measles vaccinations and SIAs, and societal costs include consumer costs and opportunity costs of health workers and other resources. A discount rate of 3% was used and it was assumed that real unit costs remain the same over time. Measures of effectiveness are: measles or rubella and CRS cases averted; deaths averted and disability adjusted life years (DALYs) averted. ICERs will be calculated and sensitivity analyses will be performed on the discount rate and the assumption of increasing costs with higher coverage. Extrapolation to other countries will be made based on various parameters, including GDP per capita and MCV1 coverage.
3.8 Review and discussion of economic evaluations

Two QUIVER members reviewed the models, and this was followed by a general discussion of all the measles eradication-related presentations.

The first reviewer highlighted the similarities in the work done by the two groups and emphasized, once again, that heterogeneity in vaccine coverage is extremely important for such an analysis. It was noted that this is partially incorporated in the first of the models. It was also highlighted that little detail was given on how models would be parameterized, including age-specific infection rates and WAIFW matrices.

The first reviewer also emphasized that these models should be validated with existing data, but that a priori criteria for assessment of goodness of fit will be needed. Other issues were that rubella modelling appeared be an afterthought, that the WAIFW matrices will be critical for rubella and that the time frame for rubella analyses was too short. In terms of the economic models, it was stated that having data on the cost of expanding coverage was very important, and it was suggested that signals on this might be detected in data already in existence. The potential effect on results of the choice of comparator was also raised. Extrapolation to global estimates from the six countries’ data was not considered to be appropriate. In summary, the epidemiological models are acceptable, other than the requirement for inclusion of heterogeneity and better informed WAIFW matrices. The economic models are more problematic as little data is available on the cost of scaling up coverage.

The second reviewer reiterated some of the comments made by the first including the problem of heterogeneity in vaccine coverage. Additionally, it was suggested that, as much as possible, the same parameters should be used in both models to allow a comparison between the two.

The discussion addressed several other issues, including that the interaction of the first and second doses of MCV (i.e. whether unvaccinated children are reached by the second dose, or whether the same children are again vaccinated) needs to be carefully modelled. Data on this interaction are available in the literature.

It was concluded that the models are generally acceptable, but need the inclusion or improvement of heterogeneity of vaccination coverage. Also, assumptions would need to be made about the marginal costs associated with increasing coverage levels. Extrapolation to global values will be difficult.
3.9 Recommendations

- A major discussion item was the potential extrapolation from the six case-studies to global estimates. This was considered to be unlikely to produce accurate estimates but might give an indication of potential ranges. The proposed country stratification according to country gross national income (GNI) was considered ill-founded.

- There was also concern that the data on the marginal costs of scaling up measles immunization were weak overall. Cost estimates might also be investigated using other approaches (e.g. using approximate doses of vaccine required along with costs that are known and then multiplying by an approximated factor), but there was some concern that the factor could not be estimated without more data. It was agreed that cost-effectiveness should be calculated at country level for the six case countries, and global costings (not cost-effectiveness) should be calculated using budgetary envelopes.

- The post-eradication strategies might need to be more carefully considered. For example, if measles is eradicated, the mumps and rubella components of measles, mumps and rubella vaccine (MMR) will still be needed, meaning that MMR cannot be discontinued where it is being used. The time frame considered in cost-effectiveness models may also be too short.

- The key recommendations for economic models were:
  - more data on the marginal cost of expanding measles coverage are needed;
  - the extrapolation of cost-effectiveness data from the six countries to a global estimate is discouraged, and a budget envelope should be made to provide an estimate of the global costs, until a more refined process has been developed;
  - a more detailed discussion should be held at the measles working group to discuss with modellers the issue of cost-effectiveness. Work should be continued, with some modifications, to give a global estimated cost, with cost-effectiveness at country level for the six countries. It was decided that John Edmunds would join the measles working group.
3.10 Impact of measles eradication on health systems

Presenter: V. Cruz, London School of Hygiene and Tropical Medicine, United Kingdom

A presentation was made on a toolkit for assessing the impact of measles eradication activities on routine immunization services and health systems at a country level. This will primarily be a qualitative study focusing on understanding the impact of measles elimination activities, rather than measuring their impact. The objectives of this work include developing a methodology, conducting studies in six diverse countries, and developing recommendations on how measles eradication activities can be used to strengthen routine immunization services and health systems while minimizing any negative impact. The studies will be conducted in Cameroon, Bangladesh, Brazil, Ethiopia, Tajikistan and Viet Nam. They aim to describe the health systems, immunization and measles control in the countries on many levels (e.g. governance, finance and human resources), and assess the integration and impacts of measles-elimination activities (e.g. SIAs, strengthening routine first dose) on health systems and immunization within the countries (see presentation for a detailed list of research questions). Key informants will be identified at national and sub-national levels (including “frontline” staff). Quantitative data analyses will include trend analyses before, during, and after campaigns of budgets for health, immunization and measles activities, as well as health-service utilization rates and time allocation of staff for immunization activities.

3.11 Review and discussion

A QUIVER member made an assessment of the toolkit, and this was followed by a general discussion.

The reviewer identified strengths of the proposed work; all aspects of health systems which could be affected will be addressed, and the framework seems appropriate and will be easy to adapt as needed. However, weaknesses are that it is mainly static, and doesn’t take into account opportunity costs, longer-term impacts or sustainability. More quantitative assessment could be undertaken, and financing aspects could be looked at in more depth. In summary, the framework is good but should be adapted to take a more dynamic view.

In general discussion it was suggested that Pan American Health Organization (PAHO) region countries and PAHO could be examined to assess why they were so successful in measles elimination. It was also said that the PAHO region’s situation could not be directly extrapolated to other parts of the world. Information is needed for other regions. It was also suggested that some method of assessing quality of interviews could be undertaken with validated tests, and that the measles eradication cost-effectiveness modellers might also be able to list information which will be useful for them, which can be collected in these studies.
3.12 Recommendations

The recommendations of the session reviewer were accepted. These are given below:

- The toolkit needs to adapt the framework so as to have a more dynamic view of health systems taking into account how the different actors within the health system respond.

- Potential sources of finance for the measles-control activities should be identified. If the government is the main source, the study should look at whether there is fiscal space for increasing spending, or whether the funding will have to be reallocated from other parts of the health system.

- Analysis of impacts on human resources in the health sector should look at opportunities for productivity improvements. If existing levels of productivity are low, the additional measles-control activities could be undertaken with minimal impacts on the health sector. Also, they need to look at private and public sector human resources together.

- The analysis of planning and management should include analysis of the planning processes within government (budget planning, allocation, execution, etc.) and the extent to which these are aligned with donor plans and budgets. Both of these have implications for how efficiently resources are allocated to and within the health sector.

- The analysis needs to take into account numerous other reforms that are taking place, as these will have implications for how the health system would respond in future.
4. Burden of vaccine-preventable disease session

4.1 Estimation of country-specific measles case and death burden

A brief introduction to measles burden estimation tools was provided. These tools are considered to have two functions: as an aid to programme planning/monitoring, and to estimate disease burdens. At the 2008 QUIVER meeting the measles strategic planning (MSP) tool was evaluated and its limitations outlined. The main limitations were that neither dynamics nor herd immunity were captured in the model. A new model has now been developed and is to be assessed for resolution of the major limitations. Additionally, given the limitations of the data, adequacy should be assessed for interim monitoring of progress towards measles goals.

Presenter: M. Ferrari, Pennsylvania State University, USA

The previous recommendations from QUIVER for a measles burden model were to: incorporate surveillance data; to explore dynamic and semi-dynamic models; to incorporate herd immunity, and to have an objective distinction between the “method 1” and “method 2” countries (i.e. countries with more or less reliable data).

The goal of this model is to estimate true incidence of measles and measles mortality. True incidence will be estimated from demographic and surveillance data using a state-space model, and mortality will be estimated using the fraction of true measles incidence which result in death.

The state-space model consists of two components: a state sub-model, and an observation sub-model. The state sub-model describes the progression of the states (true cases) from time point to time point (see the presentation for a detailed explanation of the equations used in the state sub-model). In brief, susceptible (S), infectious (I), and recovered (R) model (SIR) dynamics and herd immunity were mimicked by adding a term which means the transmission rate increases with the proportion of the population susceptible. There is an influx to the susceptibles of unvaccinated births (births minus the proportion rendered immune by either MCV1 or MCV2). SIAs reduce the size of the whole susceptible population and not only those in the birth cohort. In its current form, the second dose does not provide a first-dose opportunity, but this can be changed. The observation sub-model links the state model to the observed data by a factor currently (fitted from surveillance data) which represents the fraction of cases reported. The model has been tested against simulated data and appears to work satisfactorily at high incidence, but tends to be biased at low levels of incidence.
Mortality is calculated using age and country specific case-fatality rates (CFRs). However, as data is not reported by age, the age distribution of cases is estimated by combining age-specific probability of not being vaccinated (calculated from vaccination reporting) and age-specific probability of not being infected (calculated from estimated transmission rates). This method is applied to upper and lower confidence intervals of incidence estimate, to obtain confidence limits on mortality.

Limitations of the approach include that age structures are imposed after the dynamics and that mortality estimates are limited by assumptions about CFRs. Its benefits are that estimates are based on country surveillance and that a formal statistical method is used.

4.2 Review and discussion

A QUIVER member assessed the state-space model, and this was followed by a general discussion. The reviewer’s comments included: that comments from QUIVER 2008 had been incorporated; that results appear similar to the previous simple approach; that it was not clear if the quality of surveillance data had been assessed, and that the biases at low transmission levels could be problematic. It was suggested that the recent literature should be reviewed for case-fatality rate (CFR) data.

In group discussion, it was again reiterated that field CFR data is required, and there was some discussion about the potential variation of CFR (with time and location). The presenter also confirmed that, in the current model, only those having received MCV1 can receive MCV2, but that vaccinations in SIAs are independently distributed. It was also clarified that the observation model could be made more complex to incorporate, for example, that as coverage goes up, so does reporting efficiency. It was noted that to have a full dynamic model, at a minimum quarterly data from all countries would be required to capture seasonality. Serological data could also help in this respect. It was suggested that mortality data could also be fitted to the model, and was further suggested that, when the current model becomes biased, two sets of parameters could be used using different sets for low transmission.

The need for validation of the model using data from countries with good quality data was stated, and this was accepted by the presenter.

It was concluded that this model has addressed the issues raised by QUIVER in 2008, although it still has some limitations.
4.3 Recommendations

The recommendations from the session reviewers were accepted. These were that the state-space model represents an improvement over the current method being used by WHO to estimate global burden of measles. The following refinements to the state-space model should be explored:

- to vary the reporting fraction over time (e.g. correlating it with MCV1 coverage);
- to account for competing causes of death;
- to validate models against seroprevalence data in selected countries;
- to explore further country evidence of a secular trend in measles CFRs (e.g. in Brazil).

4.4 Update on NIH pertussis model and feedback from pertussis SAGE working group

A brief introduction was made in which the outcomes of discussions at the 2008 QUIVER meeting were summarized. The modelling approach in 2008 was thought to be reasonable given the limited data available, but it was felt that more consideration should be given to force of infection (FOI), CFR and duration of immunity. A new SAGE pertussis sub-group has been formed to consider model parameters. A meeting of this sub-group was held on 2–3 September 2009. A question to QUIVER was highlighted: i.e. given the nature of the model and the quality of input data, what method should be used to calculate uncertainty?

Presenter: M. Miller, National Institute of Health, Bethesda, USA

The previous model and 2008 QUIVER recommendations were summarized, once again highlighting that the model was not dynamic and contained age-specific forces of infection in two transmission settings (<70% DTP3 coverage and ≥70% DTP3 coverage). QUIVER recommended in 2008 that further field research be done to inform parameters.

The goal of this project is to have a tool which can be updated annually to produce global estimates of the burden of pertussis cases and pertussis deaths based on country-specific estimations of cases and deaths for children under five years of age, and for those older children.

The model is a cohort model with birth cohorts from 1980–2050. It has specific FOI for all age groups (<1y, 1–4y, 5–9y, 10–19y), incorporating benefits from partial vaccination, and different time courses for the waning of immunity after vaccination, and for natural infection. Country-specific population immunity profiles are generated by following each cohort from 1980 to 2050, tracking those susceptible and immune from either vaccination or infection, and applying age-specific FOIs. Cases are aggregated by age and time period and CFRs are applied (see the presentation for details regarding parameters). In brief, vaccine coverage is based on WHO/UNICEF estimates, different vaccine efficacies applied for DTP2 and DTP3, waning immunity over 5–15 years post-vaccination, and over 15–25 years after natural infection. Forces of infection are derived from published studies.
In addition to the recommendations or modifications previously mentioned, the SAGE pertussis working group also recommended that the model should be validated and that more specific FOIs should be used, preferably country specific. The modelling group is attempting to address these issues.

The presenter asked what would be the best way to address uncertainty in models which will arise from sources such as the input data, extrapolation and model structure. Parameters highlighted for future research include CFR, probabilities of infection, vaccine efficacy and waning immunity.

**Group discussion:**

Extensive discussion followed on the appropriateness of the model, including the appropriateness of the FOI estimates which had been used. It was suggested that WAIFW matrices could greatly influence these tables and so some investigation of the uncertainty in the tables should be carried out. The duration of immunity was thought to be potentially too long, particularly with regard to protection from infectiousness rather than disease. The inclusion of only one range of CFRs described for those under one year of age was questioned. At a minimum, having neonatal and post-neonatal CFRs would be preferable, especially as a new meta-analysis has recently become available. There was considered to be uncertainty in both parameters and the model, which could be problematic, and it was suggested that if data is not reliable then at least the best theoretical principles should be used. There was a suggestion that a model similar to the state-space model presented for measles could be developed.

4.5 **Recommendations**

- There was some discussion on the exact structure of the model, which is a static model with some dynamic ideas. It was considered that a static model might be acceptable as a first step but that this model needs some improvement.
- More could be invested in making a dynamic model, and duration of protection should be critically reviewed.
- Specific QUIVER recommendation: two QUIVER members (James Koopman and Martin Postma) should hold more detailed meetings with modellers (in conjunction with SAGE pertussis working group members) to examine the model structure and parameters and to offer specific recommendations.
4.6 Update on tetanus model

A brief introduction was made. Neonatal tetanus models had been discussed at the previous two QUIVER meetings. In the first, the model presented was not satisfactory. In the second, a new potential method was presented and it was agreed that this model should be taken further. The initial results are presented here.

Presenter: S. Cousens, London School of Hygiene and Tropical Medicine, United Kingdom

The objective of this work is to estimate neonatal deaths due to tetanus for 102 high mortality countries (excluding China). The underlying principle of the model is that the proportion of children dying from neonatal tetanus depends on three factors (the proportion of children born without effective immunity, what happens to the child at delivery in terms of cord cutting, and what happens after delivery in terms of cord care), and that these three factors might be estimated directly or from proxies. The first might be approximated from immunization data, the second from national data on skilled attendance at delivery (although this does not capture factors outside “skilled” care), and the third, for which less data are available, could be estimated using female literacy as a proxy. See presentation for a summary of data used in analyses (obtained from systematic review).

A random effects logistic regression model was used with a number of covariates considered, including protection at birth (PAB) coverage, skilled attendance rate, female literacy, region, time period, study design and case definition. Values were imputed where missing or implausible.

A basic model was considered where the parameters included were PAB, skilled attendance and female literacy, with both PAB coverage and female literacy estimating more than 95% reduction in neonatal tetanus mortality, if coverage or literacy improves from zero to 100%. There was around a 75% reduction in neonatal tetanus mortality if skilled attendant coverage improves from zero to 100%. The estimates from this model for neonatal tetanus deaths showed a steep decline from 1990 to 2008, with lower estimates provided for 1990 than were estimated in the past by the Child Health Epidemiology Reference Group (CHERG). Including each of the other covariates, as listed above, did not improve fit, or produced implausible estimates. The basic model was therefore retained. Differences to CHERG estimates were examined and it was suggested that differences were due to CHERG estimates being elevated if all-cause child mortality is high, and artificially low if mortality is low.

It was proposed to use the estimates from the basic model described here, except where a recent national survey has been conducted and results lie outside the model uncertainty range. This raises the problem of how to explain the discrepancies between current estimates and those previously published.

Group discussion:

There was some discussion around proxies, especially female literacy and why such a large effect was observed. It was explained that “going to school” was used where possible so that it might capture more than purely being able to read and write.

Potential reasons for differences in estimates were thought to be both that better data is available and that China is not included in the current estimates.
4.7 Recommendations

It was agreed that this approach seems appropriate and that it can be stated that new (lower) estimates of mortality for the past are due to new data being available and that China is not included in this analysis. Methods to address the biases observed in the model need to be studied.
5. Post polio eradication modelling

*Presenter: B. Aylward, POL, World Health Organization, Switzerland*

A short introduction to post polio eradication modelling was given. Poliomyelitis eradication is defined as the elimination of the indigenous transmission of wild poliomyelitis viruses (WPV).

There are several potential causes of polio virus-related clinical disease after eradication.

The first is vaccine-associated paralytic poliomyelitis (VAPP), which is estimated to cause currently between 250 and 500 global cases per year. This risk could be removed by stopping the use of the oral vaccine. The second risk is the emergence of vaccine-derived polioviruses (VDPV) which can cause outbreaks. Two forms exist: cVDPV (circulating VDPD) and iVDPV, chronic VDPV excretion by individuals with primary immunodeficiency.

Due to the high costs of inactivated poliovirus vaccine (IPV), IPV post-eradication policy options for low-income countries will require particular attention.

Mathematical models play an important role in the SAGE working group decision making process on what advice to give to low-income countries. Objectives for modelling include determining the expected impact of various strategies of OPV or IPV use on cVDPV, and indentifying the best strategy to minimize risks.

The presenter asked that guidance be directed to the SAGE working group, and specifically asked if decisions on post-eradication vaccination policy could be based on current models, or if more work needed to be done before decisions are made.

5.1 Post-eradication polioviruses risk assessment model

*Presenter: K. Thompson, Kid Risk Inc, Newton, USA, and R. Tebbens, Delft University of Technology, The Netherlands*

The objective of this U.S. Centers for Disease Control and Prevention (CDC)-funded project was to develop a model to aid global policy-makers in understanding the economics and health outcomes of various risk-management options after successful eradication of wild poliovirus.
As part of the overall decision model, a deterministic dynamic transmission sub-model was developed which was used to estimate the size of future outbreaks as a function of several different potential post-eradication vaccination options. The scenarios examined were: no routine vaccination, OPV vaccination with supplemental immunization activities (SIAs), OPV vaccination without SIAs, and IPV vaccination. The model captures some of the differences that exist between countries with respect to their perceived and actual risks and benefits by stratifying countries according to the four World Bank Income levels, because the modeling team recognized that a single “global” policy analysis that averaged over income levels would not provide appropriate or relevant insights.

Several initial immunity compartments were constructed with different probabilities of infection, given exposure and durations of infectiousness. These included a fully susceptible compartment and three partially susceptible compartments: recent live virus infection (OPV, VDPV or WPV), historic live virus infection, and IPV-vaccinated only. The model was stratified by age. Homogeneous mixing in every (sub)population was assumed and secondary OPV spread included. The model was validated against past outbreaks.

Critical uncertain inputs included the average $R_0$ (assumed to depend on the country’s World Bank income level), outbreak population size (stochastic), the number of cases needed to trigger a response from authorities, and the time between detection and response.

To estimate cVDPV outbreak risk, a baseline risk of cVDPV outbreaks given routine OPV is first estimated based on historic events in low- and lower-middle income countries. Then, for risk of cVDPV outbreaks after synchronized OPV cessation, an exponential decay in newly-generated outbreaks is assumed. A key assumption is that overall population immunity does not change over the timescale in which these outbreaks may occur.

An extensive sensitivity analysis was performed. However, only variation within the model input space was considered. It was pointed out that testing of some assumptions (i.e. homogeneity, ability to control outbreaks/international spread, and probability of cVDPV emerging from OPV used for response) would require a different model.

The scenarios examined were: no routine vaccination; OPV vaccination with and without SIA, and IPV vaccination. Each of these was stratified by country income level.

Many publications from the project were presented. The main inferences of the papers are listed here (see the presentation for a detailed overview of their conclusions).
The first paper concluded that countries will look differently at choices of immunization, outbreak response plan and surveillance, so no one “global” strategy can be developed. Another paper showed that there will be risks of at least one outbreak in 20 years expected following OPV cessation with any one policy, thus highlighting the need for a global stockpile of vaccine and having both containment plans and surveillance in place. It was also shown that switching to IPV will reduce, but not eliminate, the risk of cVDPV emergence (amount of reduction depends on coverage, but even with coverage levels using IPV as high as current OPV rates, cVDPVs are highly likely to occur immediately after OPV cessation). Another paper showed that the burden of VAPP is highest in lower-income countries and that using no routine vaccination appears cost- and life saving when compared to OPV (with and without SIA). This highlights the need to work on options to make IPV more cost effective.

The modeling team briefly discussed its on-going research and noted that it had recently received funding from the WHO to develop an individual-based model (IBM) to explore outbreak response modelling at the level of individual local outbreaks, and evolution of OPV viruses.

5.2 Review and discussion

Two reviewers assessed the published work for the suitability of methods, approaches and basic assumptions.

Presenter: N. Gay, Consultant to IVR, WHO

The background to cVDPV emergence was presented. The mechanism of cVDPV emergence is understood qualitatively but not quantitatively. OPV viruses are less transmissible and less virulent than wild polio viruses, but mutations in OPV can lead to increased transmissibility and virulence, approaching those of wild virus after sufficient generations of transmission. Emergence of cVDPV requires conditions that permit chains of transmission of OPV, notably low population immunity (absence of wild virus circulation, low routine coverage and lack of recent vaccination campaigns), and a high basic reproduction number, $R_0$. When OPV is still in routine use there is continual introduction of OPV into the population; emergence of cVDPV requires that effective reproduction number $R_n$ for wild polio virus is greater than one and becomes likely as the $R_n$ for OPV approaches one. The critical population size required for emergence of cVDPVs is not known. OPV cessation presents a different scenario; there is no longer continuing introduction of OPV into the population, but susceptibles accumulate rapidly through new births. In this scenario, cVDPVs can emerge if chains of OPV transmission can persist until the susceptibility threshold is reached (OPV $R_n$>1). A decision regarding a final vaccination campaign immediately prior to OPV cessation depends on whether it is preferable initially to have high population immunity but a high prevalence of OPV, or lower population immunity with a lower prevalence of OPV. Use of IPV post OPV cessation would reduce the risk of cVDPV emergence, as IPV recipients have lower susceptibility, lower infectivity and a shorter infectious period than fully susceptible individuals.
The main comments from the reviewer are given below.

The impression of the overall risk-assessment model from the reviewer was positive. The work on cVDPVs formed part of the overall assessment, but was not the main focus. Currently, the calculation of the historic baseline cVDPV outbreak rates are stratified only by World Bank income level (four strata) and by whether or not a recent SIA has been conducted, and not by other potentially relevant factors, such as routine vaccination coverage (this is captured to some extend by income level stratification), sanitation level (this is captured by income group stratification), or vaccine immunogenicity. The reviewer considered that the risk in countries where all conditions favour cVDPV emergence may be considerably higher than the highest risk calculated. This would be important if the number of countries in which conditions favour emergence is increasing, because of changes in vaccination strategy or coverage, or a reduction in WPV circulation.

When estimating the risks of cVDPV emergence post OPV cessation, the rates of decline of OPV are assigned based on the assumption of coordinated OPV cessation rather than being informed by a transmission model that can dynamically account for, for example, the impact of population immunity. Furthermore, the assumption that there is no decline in population immunity after OPV cessation would lead to underestimates of the risks in the medium and long term that might actually occur. The model adjusts for changes in vaccination by altering the population immunity profile with time, such that relatively larger outbreaks occurs later in time following OPV cessation due to the increasing number of susceptibles.

A key point is that a dynamic, stochastic transmission model should be used to assess the probability of emergence of cVDPV in a range of scenarios (note that this work is in progress).

A dynamic model is currently used to calculate outbreak sizes. Suggestions were made that the model should include heterogeneity in vaccination coverage, and variation in the basic reproduction number (up to higher numbers than currently done). Currently, in the calculation of the outbreak sizes, key parameters for each cVDPV outbreak are sampled at random. However, some randomly-sampled parameter combinations would not sustain outbreaks and it was suggested that only plausible values for conditions that cause outbreaks should be used. Also, stochastic variation in detection threshold was suggested which would introduce more variability in outbreak size.

Lastly, it was questioned whether the parameter ranges examined in the sensitivity analyses cover the plausible range and whether monovalent OPV can be used to control post-cessation outbreaks without the risk of establishing cVDPV.
Similar remarks were made on the model. They included the fact that the emergence of cVDPV should be modelled dynamically, and that stochasticity, individual heterogeneity and broader ranges of the basic reproduction number should be included.

The main inferences identified by the reviewer as sensitive to model assumptions were: that OPV cessation must be coordinated worldwide; that pre-eradication immunization activities are costly but high risk targeted activities may be justified, and that acute flaccid paralysis surveillance costs per case saved vary from acceptable to huge.

Two robust inferences listed were; the conclusion that IPV manufacture in high-risk areas could be a significant risk, and cessation of OPV immunization at eradication is both cost- and life-saving in all income groups.

Additional assumptions that need inference robustness assessment were listed. In brief, these include: there are no immunity-waning effects on colonization, contagiousness and severity during outbreaks there is no direct interference between OPV and cVDPV; control of an outbreak in a population can be achieved before spread to other populations, and that there is a narrow range of the relative immunity from wild type, OPV and cVDPV. More biological and epidemiological data (for example immunity in the host) could be considered.

It was suggested that next-stage modelling should address the questions of how OPV cessation should be coordinated and how containment of cVDPV outbreaks can be assured. The new model should then include a stochastic individual-based model of cVDPV emergence, use integrated deterministic and stochastic simulations at larger population level, and model cVDPV outbreak control decisions involving, for instance, use of genetic sequences to determine cVDPV transmission dynamics.

**Group discussion:**

The modellers responded to the comments made by the reviewers. They confirmed that heterogeneity could be further addressed in the model. Surveillance has not been a priority so far in the model, but its importance is understood.

The model was then discussed by QUIVER members and meeting participants. The need for stochasticity was discussed. A gradual transition to full complex individual based models was suggested via meta-population models. The importance of including demographics and human movement in the model was also discussed.

There is a need for QUIVER to provide identification of the critical knowledge gaps and guidance on whether decisions can be based on the current model. Generally QUIVER was positive about the model. It was suggested that an advisory committee to guide the modelling.

Given the major policy implications it was noted that it might not be prudent to base decisions on one model only, and that it might be advisable therefore for WHO to consider results from an independent modeling effort.
The incentive in many countries to stop vaccination after eradication was discussed. Understanding these incentives will be critical for the design of policies which are likely to be adopted by countries. A more formal game theory model was also suggested.

There was a brief discussion on the economic section of the model. It was questioned whether secondary immunization benefits, heterogeneity in costs and long-term complications, were incorporated in the economic model. It was suggested that it is not ideal that the model determines the best strategy instead of feeding the model with a particular scenario. The assumptions underlying surveillance costs and the financing for a global stockpile of vaccine (as a strategy for containing cVDPV circulation) were not presented or discussed. It was also suggested that an optimization modelling approach might be useful, in addition to the scenario approach, and that there was a need to consider a total switch to IPV to eliminate the risk of cVDPV.

Discussion followed the suggestion that more emphasis is needed on environmental surveillance in both pre- and post-eradication eras (i.e. that characterization of viruses and phylogenetic analyses should be undertaken in order to understand the development of cVDPV).

5.3 Recommendations

There was general agreement that the work presented on modelling the risks of post-eradication polio outbreaks, the impact of vaccine interventions and the associated costs, represents an impressive and comprehensive analysis. QUIVER considered the modelling approach to be appropriate. The review conducted by QUIVER primarily addressed the approach to estimate the risks of polio outbreaks, with particular attention to cVDPV risks.

Overall recommendations:

- Without prejudice to the work presented and given the important policy implications arising from it, an independent modelling approach by a separate group was considered desirable to make a comparative assessment.
- Modelling efforts to guide the post-eradication decision-making need to be coordinated with the modelling efforts of the final stages of eradication. More cooperation between post- and pre-eradication modellers is suggested.
- More modelling on end-stages of polio eradication is desirable, especially in difficult areas where polio transmission currently persists, such as Uttar Pradesh (UP) in India. There is a need to understand why eradication is so difficult, both for its own benefit and for important input for post-eradication modelling.

Model-specific recommendations:

- The highest priority in assessing the risks of emergence of cVDPVs is to incorporate a dynamic model of the emergence of cVDPV. QUIVER noted that this work is already in progress.
- The data that characterize meta-population contact patterns in high-risk areas and the extent to which extremely high transmission areas are connected should be pursued, in coordination with the eradication programme, and incorporated in the post-eradication cVDPV models.
- A meta-population structure should be incorporated, or an individual based model developed. The current model inadequately captures individual variability and stochasticity, and inadequate assumptions about spread of cVDPV at a local level.
- Theoretical immune-effect models simulating the dynamics of within-host PV infection could be used to better establish appropriate ranges of the immunity parameters. Also, the initial immune-level ranges explored need to be better established using transmission models capturing the dynamics of eradication.
- In the model, a total switch to IPV should be included.
- A model specific for UP, India, was recommended to capture the specific epidemiology of that region.
6. Information session

6.1 Introduction of hepatitis A, B and E models

Presenter: S. Wiersma, World Health Organization, Geneva, Switzerland

The objective of the study was to estimate the global disease burden of hepatitis A, B and E.

A static natural-history model has been developed and a systematic review is being conducted to estimate parameters for the model. The hepatitis A virus (HAV) and hepatitis E virus (HEV) model are based on previous published models and are built in Microsoft Excel® with visual basic. HEV is a simpler form of the HAV model. The model inputs include region-specific incidence, country-specific population and mortality and disease-specific probabilities of mortality and morbidity. Output tables include number of infections and days of symptomatic illness, by severity and mortality. The HBV model used the model published by Goldstein et al, IJE, 20051. The model inputs for this model are: country-specific inputs about population of birth cohort; prevalence of hepatitis B and E surface antigen of women of childbearing age; prevalence of antibody to the hepatitis B core antigen (anti-HBc) at five years of age; prevalence of anti-HBc at 30 years and older, and vaccine coverage and hepatitis B vaccine efficacy. Model outputs are the current burden and future burden with, and without, immunization.

For the HEV model, expert opinion was requested on the symptomatic disease duration, and whether there is a need to stratify parameters to capture genotypic differences which vary by region.

For the HBV model, expert opinion was requested on soundness of approach, whether there is a need to set rules for data consolidation at country level, whether there is a need to take into account treatment for chronic HBV infection, and whether there is a need for country estimates prior to global burden of disease (GBD) regional estimates.

Group discussion:
Some comments were made on the importance of chronic HBV infections in rich countries and whether the model captured transmission via unsafe drug injection. It was explained that all modes of transmission are included as age-specific risks for infection for the cohort.

There was discussion about the appropriateness of the HAV model. Since the age pattern of HAV is not stable, a dynamic approach might be more realistic. The current model was therefore considered to be acceptable for estimating burden for a short timescale but not for predicting the burden for a long timescale. Discussion centred on, as an alternative for a dynamic model, that different models could be made for different global epidemiological zones. It was agreed that John Edmunds would be invited to participate in the expert group giving guidance to the project.

6.2 Influenza social contacts and mixing patterns in South-east Asia

Presenter: J. Edmunds, London School of Hygiene and Tropical Medicine, United Kingdom

The objective of the social mixing for influenza-like-illness (SMILI) project is to collect country-specific estimates of contact patterns by age in three Asian countries: Indonesia, Thailand and Viet Nam.

A survey will be performed in between two and five provinces per country (Viet Nam: 2; Thailand: 4, Indonesia: 5) that are stratified by urban/rural areas, age, gender, and working day and weekend day.

There will be a standardized survey instrument for all countries. A face-to-face interview will be performed to obtain socio-economic variables, normal travel and contact patterns and information on contact with animals. There will be a second interview two days after the initial questionnaire, about contacts during the intervening day. Data about the age and sex of the contact and the frequency of the contact, as well as the duration and setting of the contact, distance from home of the contact, and if they had physical contact, will be recorded. In order to get an idea of clustering, two contacts will be randomly selected and asked if they know each other.

Group discussion:
Discussion centred on the fact that the contact data collected in the SMILI study do not directly link to infection. However, if there are serological profiles available, then an association can be made on ecological basis. The possibility of follow up of the participants has been discussed; however this would be very difficult.

Questions were asked about how to control for seasonality and holidays. Holidays are accounted for because the study will be conducted over a period of time. Seasonality will be more difficult to account for because of the relatively short study period.

The sample can be weighted if necessary, as socio-economic data is collected in the SMILI study which can be compared with the available census data.
6.3 New vaccines cost-effectiveness modelling for national policy-makers

Presenter: R. Hutubessy, IVR/IMR, World Health Organization, Geneva, Switzerland

Economic evaluations in the context of IVR were introduced, and the example of the process used for pneumococcal conjugate vaccine (PCV) was provided.

The WHO Vaccine Introduction Guidelines 2005 outline an evidence-based decision-making process which includes an evaluation of economic and financial issues. IVR's contribution to this is to support country-level cost-effectiveness analyses (CEAs), encourage sector-wide CEA studies in health, and standardize economic studies to improve comparability and transparency.

A PCV mathematical modelling and cost-effectiveness workshop was held with model developers, modelling experts, country-level stakeholders, and health-related organizations, in June 2009. The aim of the workshop was to provide an overview of existing literature on the cost-effectiveness of PCV (the results of a systematic review) and to critically review existing decision support tools. The systematic review showed, among other things, that the inclusion of herd immunity significantly affects results, and that vaccine cost, vaccine efficacy and disease incidence data also influence results. None of the analyses found described a validation process. Three decision support tools were reviewed: PneumoADIP® (New Jersey Medical School), TRIVAC® (PAHO/LSHTM), and SUPREMES® (GSK). The model attributes, assumptions, parameters and sensitivity analyses performed were summarized. Standardized data sets were used where possible to allow comparisons of model outputs. Main drivers of models were seen to be vaccine efficacy against pneumococcal pneumonia, vaccine coverage, serotype coverage, disease burden and vaccine price. The assessment of tools was thought to be useful, particularly to aid those involved in PCV adoption decisions, to learn about the models and the key assumptions inherent in them. Additionally, the exercise was useful to inform surveillance activities.

The overall objective of the exercise is to provide country-level decision makers with a menu of cost-effectiveness tools and their characteristics, rather than to recommend a single model. It was thought that this would be a worthwhile exercise to perform for other new vaccines.

Group discussion:

In group discussion this process was considered to be particularly useful for low- and middle-income countries, as it provides tools to perform country-specific analyses (where data and training is available), and allows more transparency and understanding of how the models work. It was highlighted that these tools are often most useful for policy makers to determine the vaccine cost at which it becomes cost effective, thus aiding price negotiations with suppliers. The importance of validated dynamic models was reiterated. The need for budget impact analysis at country level was mentioned, to put the cost-effectiveness results in perspective and to guide introduction decisions.

The selection criteria for the models which had been reviewed were thought to be unclear. A priori criteria for selection in future might be beneficial.
7. Meeting agenda

WHO Quantitative Immunization and Vaccines Related Research (QUIVER)
Advisory Committee Meeting
13–15 October 2009
Room 27, UN E-Building, Geneva, Switzerland

Chair: Alan Hinman
Overall Meeting Rapporteurs: Pippa Scott/Janneke Heijne

Tuesday, 13 October 2009

8:30–9:00 Registration
9:00–9:15 Introduction and charge to the Committee J. Hombach
9:15–9:30 Adoption of the agenda A. Hinman

Coverage Estimates at WHO-UNICEF
Rapporteur: A. Burton

9:30–10:30 — Immunization system monitoring R. Steinglass
(20’ presentation)
— Formal knowledge reasoning and L.M. Pereira
representation systems (20’ presentation)
— Outcome WHO-UNICEF B. Grenfell
immunization coverage estimates
review meeting (20’ presentation)

10:30–11:00 Coffee break
11:00–12:00 Review & discussion
— 10’ review QUIVER member & Z. Bhutta
50’ discussion

12:00–13:00 Lunch

Measles Eradication
Rapporteur: A. Dabbagh

13:00–13:15 Outcome June 2009 working group meeting A. Dabbagh
— 10’ presentation & discussion
13:15–14:05 Dynamic measles Models 1 & 2 D. Bishai* & C. Burgess
— 25’ presentation each
14:05–15:45 Review & discussion J. Edmunds
— 10’ review QUIVER member & 40’ discussion
Economic Evaluations 1 & 2
— 25’ presentation each D. Bishai* & A. Levin

15:45–16:00 Coffee break

* Participate by teleconference
Measles Eradication  
Rapporteur: A. Dabbagh

16:00–17:00 Review & discussion  
— 10’ review QUIVER member & 50’ discussion  

A. Nelson

17:00–17:30 Health systems  
V. Oliveira Cruz

17:30–18:30 Review & discussion  
— 10’ review QUIVER member & 50’ discussion  

A. Somanathan

18:30 Adjourn / Cocktail

Wednesday, 14 October 2009

Burden of Vaccine-Preventable Disease Session  
Rapporteur: P. Strebel

9:00–9:30 Estimation of country-specific measles case and death burden  
M. Ferarri

9:30–10:30 Review & discussion  
— 10’ review QUIVER member & 50’ discussion  

F. De La Hoz Restrepo

10:30–11:00 Coffee break

11:00–11:45 Update on NIH Pertussis model and feedback from Pertussis SAGE working group  
— 15’ presentation & 30’ discussion  
M. Miller

11:45–12:30 Update on Tetanus model  
— 15’ presentation & 30’ discussion  
S. Cousens*

12:30–14:00 Lunch

Post polio eradication modelling  
Rapporteur: N. Gay

14:00–15:30 Introduction  
B. Aylward  
— 5’ presentation  
Post-eradication polioviruses risk assessment model  
K. Thompson/ R. Tebbens  
— 25’ presentation  
Model appraisal by external reviewers  
N. Gay  
— 30’ presentation

15:30–16:00 Coffee break

16:00–18:00 Review & discussion  
— 30’ review QUIVER members R. Laxminarayan  
— 30’ questions for clarification  
J. Koopman  
— 60’ discussion

18:00 Adjourn

* Participate by teleconference
### Thursday, 15 October 2009

*For information session*

**Rapporteur: R. Hutubessy**

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<td>Introduction of hepatitis A, B and E models</td>
<td>S. Wiersma</td>
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<td>– 15’ presentation &amp; 20’ discussion</td>
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<td>09:20–09:55</td>
<td>Influenza social contacts and mixing patterns in South-east Asia</td>
<td>J. Edmunds</td>
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<td>09:55–10:30</td>
<td>New vaccines cost-effectiveness modelling for national policy makers</td>
<td>R. Hutubessy</td>
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<td>– 15’ presentation &amp; 20’ discussion</td>
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<td>10:30–11:00</td>
<td><strong>Coffee break</strong></td>
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<td>11:00–12:30</td>
<td><strong>QUIVER closed session</strong></td>
<td><strong>Rapporteur: R. Hutubessy</strong></td>
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<td>12:30</td>
<td><strong>Closure</strong></td>
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*Participate by teleconference*
8. List of participants
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Quantitative Immunization and
Vaccines Related Research Advisory Committee (QUIVER)
Room 27, UN E-Building, Geneva, Switzerland
13–15 October 2009

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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.