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

Geneva, 21-22 October 2008

(Final Draft)

Contents

Table of Contents

Abbreviations and Acronyms

CHERG	Child Health Epidemiology Reference Group
CFR	Case Fatality Rate
cMYP	Comprehensive Multi Year Plan
CRS	Congenital Rubella Syndrome
FOI	Force of Infection
FSP	Financial Sustainability Plan
GAVI	The Global Alliance for Vaccines and Immunization
GBD	Global Burden of Disease
GEM	Global Epidemic Model
GIP	Global Influenza Program
GIVS	Global Immunization Vision and Strategy
ICE-T	Immunization Coverage Estimates and Trajectories
ILI	Influenza-like Illness
JRF	WHO-UNICEF Joint Reporting Form
MSP	Measles Strategic Planning
NHM	Natural History Model
NT	Neonatal Tetanus
PATH	Program for Appropriate Technology in Health
POI	Probability of Infection
QUIVER	Quantitative Immunization and Vaccines Related Research Advisory Committee
RAS	Realistic Age-Structured
SAGE	Strategic Advisory Group of Experts
SEIR model	Susceptible (S), expose (E), infectious (I) and recovered (R) model
SIR model	Susceptible (S), infectious (I) and recovered (R) model
SIA	Supplementary Immunization Activity
TAP	Targeted Antiviral Prophylaxis
TT	Tetanus Toxoid
VPD	Vaccine-Preventable Diseases
WHO	World Health Organization
WHO-CHOICE	WHO - Choosing Interventions that are Cost Effective

1. Introduction and Charge to the Committee

An introduction was made to the second meeting of the QUIVER advisory committee by the Secretariat and Chair of QUIVER. In brief, QUIVER (a technical committee advising SAGE) provides expert advice in quantitative immunization and vaccine related research to 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) on quantitative research regarding the estimation of burden of vaccine preventable diseases; and on modelling for the investigation of the impact and cost effectiveness of interventions. Currently, the advisory committee has 7 members including the chair, 2 advisory committee members have resigned. New nominations are pending.

2. Pandemic Influenza Scenario Modelling

Introduction
An introduction to the current situation in pandemic influenza modelling was given by the Secretariat. In summary, there have been large numbers of publications on pandemic influenza but these are generally limited to a few countries. The focus of the session was modelling the use of a limited supply of pandemic influenza vaccine. Modelling this aspect will aid the identification of gaps in data, clarify which data need to be collected at the start of a pandemic and identify priorities for further data collection at the current time. In addition, it could help to promote dialog between scientists, policy makers and other stakeholders on decision making processes.

2.1. Quantifying the effect of vaccination and non-pharmaceutical interventions during influenza pandemic via a simulation model

Presenter:
Professor George Milne, School of Computer Science and Software Engineering, University of Western Australia, 6009 Crawley, Australia

Presentation:
Objectives
The objectives of this project were to produce an accurate individual-based simulation model of the time-course of an influenza pandemic, which captures disease dynamics and host mobility/contact networks, and which can be used to quantitatively determine effects of alternative mitigation strategies.
Questions addressed by the model
The questions addressed by this model include: what effect does pre-emptive vaccination have on mortality; what effect does reactive vaccination have on mortality; what effect does combined reactive vaccination and school closure/aggressive social distancing have on mortality; and, is prioritising the vaccination of transmitting population groups more effective than prioritising the vaccination of vulnerable population groups?

Methods
The individual-based model was adapted from a pre-existing census-based model of an existing town with approximately 30,000 residents. Home, contact-hub (e.g. school) and random contacts are modelled. Please refer to the presentation for full details of the model. The model was run with and without each intervention and results compared to assess the impact of the intervention.
Scenarios examined
Scenarios examined were social distancing and vaccine related interventions (timing of vaccination, vaccine efficacy, prioritising vaccine recipients and levels of coverage) were assessed. Timings of vaccination were "pre-emptive vaccination" (6 weeks prior to the index case) and "reactive vaccination" (during the epidemic), and priority was given to either transmitters or vulnerable groups for vaccination. Aggressive social distancing included school closure, workplace reduction, home quarantine and reduced community contact.
Parameters/data used
Home and contact hub data are based on census results for the town in the model. The age-specific infection rate was taken from the seasonal influenza profile in 1978/1979 and age-specific mortality from 1957 data. Percentages of transmission in each location/situation were 43% in households, 28% in schools and workplaces, and 29% as community contact (based on publications relating to pandemic influenza). Influenza cases were assumed to be infectious after 1 day, symptomatic after 2 days and infectious for 5 days. Thirty percent of infected individuals were assumed to be asymptomatic. Results were calculated using R_0 values of 1.5 and 2.0. Vaccine efficacies of 35% and 70% were examined. A full range (0-100%) of vaccine coverage levels was explored.
Results
Generally, pre-emptive vaccination performed better than reactive vaccination at preventing mortality, but when reactive vaccination was combined with 3 months of aggressive social distancing it was equally effective as pre-emptive vaccination. Results for pre-emptive vaccination showed that prioritising the vaccination of transmitters is often better than prioritising the vaccination of vulnerable groups but this advantage is lost at higher vaccination coverage levels (greater than 60%) and at R_0=2.0 (compared to R_0=1.5). Results for reactive vaccination show very similar results for vaccinating transmitting or vulnerable groups first (regardless of vaccination rate) but a small advantage may exist for prioritising the vaccination of transmitters at R_0=1.5.
Results for combined reactive vaccination and social distancing showed that aggressive social distancing is more effective than school closure alone. There is little difference according to which groups are vaccinated first in this analysis but vaccinating transmitting groups first has an advantage if the vaccine is of low efficacy.
Other
Further points raised by the researchers for investigation were the effects of scaling, different demography and different contact patterns. The last of these would be difficult to implement in the current model.

Group discussion:
The positive points of the model were identified as being that different R_0s can be used and that there is sensible structuring of contact patterns. The less positive aspects were that results are not generalizable to other settings, that user-friendliness is not ideal and that costs are not included. Costs of aggressive social distancing, surveillance to detect an outbreak early in its course, and repeated pre-emptive vaccination (if there is a delay in the start of the epidemic) should be included. A general comment made was that there is a need for standardized parameters to allow comparisons of models.

2.2. Simulator of pandemic influenza intervention strategies

Presenter:
Dr Azhar Nizam, Senior Associate, Department of Biostatistics and Bioinformatics, Emory University, Atlanta, 30307 GA, USA

Presentation:

Objective

The objective of this project was to adapt the Longini influenza model to produce a desktop, user-friendly interface which can be easily modified to include new intervention strategies, different populations and updated disease natural history and transmissibility parameters.

Questions addressed

The questions addressed by this model include: can an individual-based pandemic influenza model be adequately adapted into a user friendly version; and, what effects do various non-pharmaceutical interventions (isolation, quarantine, school closure and social distancing) and pharmaceutical interventions (e.g. pre-vaccination and targeted antiviral prophylaxis (TAP)) have on influenza attack rates?

Methods

The Longini model is an individual-based pandemic influenza model, which contains age-group specific contact probabilities. The platform chosen for the new interface was ARENA due to in-house expertise with this software. The model in this software tracks the number of individuals in each state at each time point.

Scenarios examined

Scenarios examined were: home isolation and quarantine; school closure and social distancing; pre-vaccination; and targeted antiviral prophylaxis (TAP). Each of these was examined separately and grouped as pharmaceutical and non-pharmaceutical interventions. Best and worst case scenarios relating to case ascertainment (best :90%, worst 60%), minimum cumulative illness attack rate needed to initiate interventions (best 0.01%, worst 1%) and rate of compliance for home isolation and quarantine (best 90%, worst 60%) were also examined.

Parameters/data used

Age-group specific contact probabilities were obtained through model calibration (calibrated to 1957 Asian flu age-group specific attack rates). Structured populations of 2,000 and 10,000 people, including age and household size distribution (based on U.S. census demographics) were used. “Vaccination” in this model assumed 70% prior mass vaccination. Vaccine efficacy was set at 30% for susceptibility and 70% for infectiousness. Antiviral efficacy was 30% for susceptibility and 80% for infectiousness. An R_0 of 1.85 was used in analyses. “Social distancing” assumed a reduction in work, neighborhood and community contacts by 50%.

Results

The model adapted for the ARENA format can give a best- and worse-case outcome for various scenarios, allows for adjustment of mixing patterns and parameters, and can be adapted to new populations and intervention strategies. It is limited by the lack of information on country specific mixing patterns and by the current algorithms needing to be made more efficient. Web-based implementation might be possible.

There were no new data generated in this procedure, but instead a replication of results produced by the model on which it was based. Example model results showed that school

closure and social distancing produce the largest reductions in overall attack rates and isolation and quarantine the least, with pre-vaccination and TAP producing moderate results (see presentation for specific details). This is the case in both best and worst case scenarios (described above) and both population sizes (2,000 or 10,000).

Group discussion:
The usefulness for policy makers was discussed and it was clarified by the presenter that this format is aimed to be a planning simulator rather than an end-user tool. There was discussion that more elaboration (e.g. of input and output formats) was required to simplify use. It was also discussed that sensitivity analysis on the structure (e.g. the number of schools) might need to be conducted. It was mentioned that complex models may help to develop certain setting typologies, from which policy options could be developed.

2.3. Vaccination strategies against pandemic influenza: Mexico as a case study.

Presenter:
Dr Gerardo Chowell**,** School of Human Evolution and Social Change, Arizona State University, Tempe, 85282 Az, USA

Presentation:
Objective
The objective of this project was to develop an age-specific transmission model for allocation of limited pandemic influenza vaccines in a middle-income country, using Mexico as an example.
Questions addressed by the model
The questions addressed by this model include: what effects do different (age-group based) vaccination strategies have on clinical cases/hospitalisations/deaths in a pandemic scenario; and, do these effects vary depending on whether mortality and morbidity profiles resemble 1918-like or 1957/68-like profiles?
Methods
The model developed is a dynamic, compartmental, age structured model for pandemic influenza
Scenarios examined
Scenarios examined were: a uniform vaccine allocation strategy (vaccines are allocated proportionally to age group size); an optimal vaccine allocation strategy (vaccine is allocated to age groups to minimize the peak/total of hospitalization and mortality); and an adaptive vaccine allocation strategy (vaccine is distributed proportionally to the age-specific cumulative number of hospitalizations when vaccination starts).
Parameters/data used
The age groups used were 0-5 years, 6-12 years, 13-19 years, 20-39 years , 40-59 years and 60 years and over. These age groups were populated based on census data for Mexico (2000) and the relevant parameters were based on Mexican influenza associated hospitalization and death patterns. Contact patterns were based on data from the Netherlands. The model was calibrated using pneumonia and influenza mortality data from Mexico. Parameter values for latent period (2 days) , recovery period (4 days) , fraction of clinical infections (0.1) , relative infectiousness of clinical individuals (0.003) and age specific mean vaccine efficacy (75-80% for age groups younger than 65 years and

17-53% for those older than 65 years) were taken from publications. See presentation for specific sources. R_0 values of 1.6-5 were used (results for 1.-2.5 presented). Time after pandemic onset at which vaccination started ranged from 10-50 days and vaccination coverage ranged from 10-50%

Results

Uniform vaccination starting 20 days after the onset of pandemic, in the 1957/68 scenario, showed substantial (up to 90%) reductions in clinical cases, hospitalisations and death for all R_0, although this was less marked for R_0 =2.5 (the highest examined in this analysis). Adaptive vaccination shows benefits over uniform vaccination in the 1918 scenario, particularly when vaccination is started earlier and there is higher vaccination coverage. However, this advantage is almost eliminated at higher values of R_0 (2.5-3.0) if vaccination is started late. In summary, the adaptive vaccination strategy is better than uniform vaccination in the 1918 (young adults heavily affected) pandemic scenario, and vice versa for the 1957 scenario. This difference between the 1918 and 1957/68 scenarios is due to the age structure in Mexico.

Other

Limitations identified (and common to all models) were uncertainties about disease parameters and model assumptions, and uncertainty about vaccination parameters. Conclusions were that the groups with highest contact rates should be targeted to reduce overall morbidity.

Group discussion:

The model was viewed as being well thought out and likely to be useful to inform policy. However, there were a few points which were thought not to be ideal. Firstly, the adaptive strategy depends on good data collection in the early phases of spread and this might not occur. Secondly, mixing patterns were based on data from the Netherlands which might be different from Mexico (and within Mexico, patterns might be different in rural and urban settings) and thirdly, the age grouping might be too broad in young children, and disaggregation of age 1-5 year should be envisaged. Additionally the data on which the model was calibrated included bacterial pneumonia as well as influenza which might affect results. General comments included that baseline data from developing countries are often not available but are essential here, and that R_0 ranges might be much higher in reality and so higher values than 2 should be included in all analyses.

2.4. Modelling cost-effectiveness of pandemic influenza vaccination: developing an international model piloted in 3 countries

Presenter:

Professor Maarten Postma, Groningen Research Institute of Pharmacy (GRIP), University of Groningen, 9713 AV Groningen, Netherlands

Presentation:

Objective

The objective of this project was to develop a model to estimate the cost effectiveness of pandemic influenza vaccine.

Questions addressed by the model:

The questions addressed by this model include: what is the cost effectiveness of various influenza vaccination interventions in a pandemic situation; and, is this cost effectiveness sensitive to changes in case fatality rates, complication rates and vaccine prices?

Methods
A pre-existing dynamic, age-structured, compartmental model, calibrated to 1957/1958 pandemic data (Mylius et al) was extended. The extensions include epidemiological modifications, the addition of costing, the examination of various scenarios, and the addition of sensitivity analyses. In brief, epidemiological extensions include: the addition of POLYMOD contact matrices; and varying R_0, vaccine availability and vaccine efficacy. Costing analysis includes treatment costs, production losses, vaccine costs and opportunity costs.
Scenarios examined
Scenarios examined were: pre-pandemic vaccination; late onset of pandemic vaccination (2months) targeted at the elderly; late onset targeted at the young; early onset of pandemic vaccination (20 days before peak) targeted at the elderly; and late onset targeted at the young.
Parameters/data used
R_0 values of 1.5, 1.7 and 2.5 were used. Availability of vaccine was set at 35% for pre-pandemic vaccine and at 15-20% for pandemic vaccine. Vaccine effectiveness of 30% for pre-pandemic vaccine, and 80% for pandemic vaccine (56% for 65 years and over) was used. The cost of pandemic vaccine was set at €32 and opportunity costs for stockpiling pre-pandemic vaccine at €100.
Results
For the Netherlands and at R_0=2.5, the interventions had little impact on influenza-like illness (ILI) and hospitalisations. The exceptions to this were pre-pandemic vaccination (effects for both ILI and hospitalisations) and "early elderly" (effect for hospitalisations only). At R_0=1.7, all vaccination interventions reduced hospitalisations compared to no intervention. The most marked reduction was with "early elderly" vaccination). For ILI, "early elderly" and pre-vaccination produce the most marked reduction. A similar pattern was seen at R_0=1.5 with all vaccination strategies markedly decreasing hospitalisation ("early elderly" and "late elderly" showing the most effect). For ILI "early young", "late young" and pre-vaccination showed the most effect with the other interventions showing markedly less effect.
Indirect costs (through production losses) contribute a majority of the costs. For example, in an uncontrolled pandemic indirect costs account for 94% of the total costs (Netherlands results). Savings can be made as long as indirect costs are taken in to account and R_0 is not the highest of the 3 examined (R_0=2.5). Pre-pandemic vaccination is generally least cost effective due to the relatively high price of the vaccine. Differences between countries will occur due to different contact matrices, unit costs and discount rates.

<u>Group discussion:</u>
It was suggested that the cost analysis should be widened to include other costs such as human life costs. The examination of social distancing was discussed but this would be difficult to include in the current model (other than by altering mixing matrices). Comparability of models through specified parameters was again mentioned, as was the need for more accurate mixing matrices (in various settings).

2.5. Modelling for determining the optimal use of limited quantities of pandemic influenza vaccines: global and Russia-specific model.

Presenter:
Dr Georgiy Bobashev, Senior Research Statistician, RTI International, Research Triangle Park, 27709 NC, USA

Presentation:

Objective

The objective of this project was to examine, at a global and Russian scale, the importance of various vaccine related strategies including vaccine stockpiling (and sharing of the stockpile) and pre-pandemic vaccination.

Questions addressed by the model

The questions addressed by this model include: given limited amount of vaccine, how much would global collaborative strategies help to reduce global attack rate; how much would the 50million-course stockpile of pandemic vaccine help to contain and mitigate disease at the source; how important is vaccination with pre-pandemic vaccine; how can the influenza surveillance data be used in building a country-specific model; and, what will be short and long-term economic impacts (GDP loss) of pandemic under different mitigation scenarios?

Methods

The analysis was based on the Global Epidemic Model (GEM). GEM is a patch-structured equation-based stochastic/deterministic SEIR model, which covers 105 regions and the entire world's population. Major metropolitan areas are connected by airline travel and travel to non-metropolitan areas is taken into account. The model creates outputs by calculating S, E, I and R values for each location by age group and then collapsing them by defined populations.

Scenarios examined

The scenarios examined were 10 situations in which use of anti-virals/quarantine/travel restriction, the presence of a vaccine stockpile, the collaborative sharing of a vaccine stockpile, time of disease detection and the percentage of people immune were varied. See presentation for more details.

Parameters/data used

Results are calculated using R_0s of 1.4 and 1.9. Latent and infectious period distributions are based on estimates from past pandemics, and mortality is a free parameter. World population data is based on the World Census. The age groups used are <2 years, 2-14 years, 15-64 years and over 65 years. Age-specific disease transmission rates (based on peer-reviewed publications) are used. Vaccine efficacy is course- and age-dependent and based on peer-reviewed and expert sources. It is assumed that vaccine delivery will occur 1-2 weeks after pandemic detection, and that antiviral will be delivered to 10% of the population Asymptomatic infected person are considered to be 50% less infective (based on peer-reviewed publications), and 30% of those infected are asymptomatic.
Density-specific contact rates are used (3 levels <200, 200-900, 900+ people/km^2) and are based on modeling outputs and published estimates.
Airline travel links are based on IATA transportation data. Travel to non-metropolitan areas of 1% weekly is assumed. Seasonality is included in the model (based on peer-reviewed sources).

Results
Results include: having 50million courses of vaccine stockpiled is helpful but does not lead to critical containment/mitigation effects; the sharing of stockpiles with countries already infected with pandemic influenza is counterproductive; the timing of influenza detection is critical for containment at low R_0s (when early stages can also be masked by seasonal influenza); and pre-vaccination with pre-pandemic vaccine can play a large role in disease mitigation. Maximal GDP losses with no intervention were approximately 1.1% worldwide.
Other
The limitations of this model were considered to be mainly related to uncertainty of parameters and structural uncertainty.

Group discussion:
It was considered to be useful that transmission was scaled with population density but the presenter noted that there were still problems with lack of contact matrices to do this more accurately. The age structure was also not seen to be ideal.

2.6. General Discussion

The main discussion points were that input values and output measures should be standardized and that contact matrices need to be determined (or at least standardized) to allow more accurate models. The establishment of various typologies on contact matrices for the developing world was considered priority. Surrogate data (e.g. intra-familial transmission of other diseases) might also be helpful in this regard. Priorities need to be set in addressing these points. It also needs to be established if additional contact data already exist or could be readily collected. Additionally, it was thought that stockpile costs, costs of school closure and indirect costs needed to be described more completely. It was observed that different answers were given depending on the question asked so matching is needed between public health questions and modelling goals.
In other discussion, there was concern that social distancing was not dealt with in compartmental models although social distancing might be difficult in reality. Additionally, models might need to take more account of changing behaviours with higher mortality rates which might change contact patterns. It was also considered better not to rely on just one model or model type and that different models and model types can give different insights.

It was recommended that WHO should make recommendations in relation to the definition of appropriate public health questions that could be addressed by mathematical modelling and key parameters in these models, in particular Ro, incubation period, the population age structure and vaccine efficacy.

3. Burden of Vaccine Preventable Disease Session

3.1. Neonatal Tetanus model review

Introduction:
A summary of difficulties with the previous model used for calculating the global neonatal tetanus (NT) burden was presented. See presentation for details of the previous model. The summary was based on discussions in the 2007 QUIVER meeting. The difficulties presented included:

- Different country classifications are used through the model, and country classifications were maintained unchanged over time.
- Some of the assumed rates (e.g. for notification efficacy or case fatality rate (CFR)) were imprecise, lack heterogeneity, and were kept unchanged over time.
- The literature review had been done in a non-systematic manner.
- The model was built to incorporate pre-vaccination NT mortality data, without the possibility to also incorporate more recent data, including NT mortality data in the presence of immunization.
- The interaction between clean delivery and tetanus toxoid is complex and difficult to quantify.
- Pre-immunization NT mortality rates were all model-generated, instead of using survey data for countries where such survey data existed.
- The calibration that was done for 15 countries was not well documented
- In terms of outputs, a large discrepancy was noted between the estimates generated by the model for 1990, and the estimates by Galazka for the last 1980s, which were mainly based on community surveys.

Presenter: Dr Jos Vandelaer, Expanded Programme on Immunisation (EPI), Immunisation, Vaccines and Biologicals (IVB), World Health Organization (WHO), 1211 Geneva 27, Switzerland.

Presentation:

An outline for a new method for calculating the global burden of NT was presented. This model would be used to calculate NT deaths in low- and middle-income countries, not cases or other outcomes. The model is based on the concept that the probability of a tetanus death is based on the proportion of children who are born without effective immunity, the proportion of these children who become infected and develop NT, and the proportion of NT cases who die. The major problem is that these proportions are largely unknown and/or vary by setting. The proposed solution is to identify suitable proxies for the three probabilities, review literature to identify community based studies with data on NT death and proxies, fit a statistical model to obtain parameter estimates relating outcome to proxies and use these estimates to predict death in specific populations. Uncertainty ranges would be calculated using a jack-knife approach. Refer to the presentation for a list of potential proxies. The main advantages over the previous model are that, in addition to data on pre-immunisation NT mortality rates, also more recent data can be used, and that data on proxies might be more readily available than data on the probabilities of interest.

As the model had not been finalized, it was not possible to present output data from the model.

Group discussion:
It was agreed that this appears to be an improvement on the previous model, but that methods would need to be developed to calculate morbidity. Proxies were recognized as having their own limitations, and it was suggested to examine whether existing data could not be used instead of proxies. (e.g. case fatality rates are all facility-based, and no (or very few) data exist on CFR outside a facility-setting; if it can be shown that most NT cases are brought to facilities for treatment, then such facility-based CFR could be used in the model). There was some concern that non-independence of the probabilities was still an issue. It was also mentioned that opportunities should be seized to validate proxies with empiric data, and in that context the fair number of tetanus serology projects was highlighted being conducted in context of the meningitis vaccine project or a number of HIV studies. In summary, the new model should move ahead taking into account the raised suggestions.
The general discussion also raised the issue that WHO needs to clearly define the objectives of its burden models: are estimates needed for morbidity, mortality, trends, or other reasons?

3.2. Global Burden of Disease Estimates

Presenter: Dr Colin Mathers, Measurement and Health Information Systems (MHI), Evidence and information, World Health Organization, 1211 Geneva 27, Switzerland.

Presentation:
A summary of the WHO 2004 Global Burden of Disease (GBD) estimates was presented. The update was produced using similar methods to 2002 estimates, but with new data where available. There were updates on the analysis of death registration data and estimates for under-5 and neonatal causes of death (IVB estimates used but reasonably consistent with CHERG estimates). See presentation for expanded cause lists, and details of methods and estimates. Burdens of disease estimates have changed due to both real changes and changes in estimation methods. A new assessment will be conducted for 2005 GBD with the objectives of creating new disease, injury and risk factor estimates for 1990 and 2005 for 21 regions, and to create simplified analytical tool for burden of disease studies. Issues for WHO include ensuring estimates are consistent (e.g. IVB and CHERG, and additionally , that the sum of individual causes do not exceed totals), coherence with other agencies and how to deal with updating estimates annually when there are no new data for inputs.

3.3. Child Health Epidemiological Reference Group (CHERG)

Presenter: Dr Cynthia Boschi-Pinto, Newborn and Child Health and Development (NCH), Child & Adolescent Health (CAH), World Health Organization (WHO), 1211 Geneva 27, Switzerland.

Presentation:
A summary of CHERG's objectives and activities was presented. Full details are available in the presentation. In summary, CHERG was founded in 2001 with the main objectives of providing leadership in the estimates of cause-specific morbidity and mortality estimates for children under five, addressing methodological issues and assessing the contribution and impact of interventions on reducing under-five mortality. The general strategy for estimating cause-specific morbidity and mortality estimates for children under-five consists of using vital registration for countries with good systems for this, or by using published literature for other countries. Published literature is also used to validate vital register data. Single- and multi-cause models as well as other available sources are triangulated to reach final results. Causes are distributed within the mortality envelope to ensure that the sum of deaths from each cause does not exceed the total expected deaths. For the most recent results, please see the presentation.

3.4. Programmatic data needs for immunization

Presenter: Mr Tony Burton, Expanded Programme on Immunization (EPI), Immunization, Vaccines & Biologicals (IVB), World Health Organization (WHO), 1211 Geneva 27, Switzerland.

Presentation:
Data are needed to inform decisions for vaccine introduction, monitor the impact of vaccine introduction, and report on progress towards goals. The basic data required are cases and deaths of vaccine-preventable disease (VPD), and cases and deaths of VPD prevented. These should explicitly incorporate the impact of immunization. Consideration has to be given to the level of resolution required for data (age groups, geographic regions etc). Data need to be consistent over time to demonstrate trends and ideally there should be country-specific annual updates with certainty bounds.

3.5. Global burden of disease discussion

Group discussion:
There needs to be an understanding that groups with different goals will produce different results in these analyses. Resources continue to be directed towards the improvement of vital record systems to improve estimates (with an aim to reduce the need for "estimates").

3.6. Use of measles strategic planning (MSP) tool for burden estimates.

Introduction:
Approaches taken by WHO to estimate global measles deaths have evolved over time since the 1980's with stepwise improvements in the models in keeping up with the quality and availability of information from Member States, need for precision, and funding available. The question remains as to which is the most appropriate method for use by WHO. The options are to use the method published in the Lancet (Wolfson et al. 2007) which is a

static model that tends to over-estimate deaths, use the measles strategic planning (MSP) tool without modification, use a refined version of the MSP tool or to use a fully dynamic model (for which the essential data elements may be lacking for many countries).
Two presentations were given outlining firstly, the usefulness of potential "fixes" to the MSP tool (compared to a fully dynamic age-structured model), and secondly, the level of accuracy of the MSP tool when compared to surveillance data.

Presenter: Dr Pejman, Rohani, Associate Professor, University of Georgia, Athens, 30602-2202 GA, USA;

Presentation 1:
The outputs of the MSP tool were compared to the outputs of the natural history model (Stein et al) and a fully dynamic, stochastic, SEIR, realistic age structured (RAS) model under a variety of assumptions and intervention scenarios. In addition 2 potential "fixes" to the MSP tool were also explored.
It has been speculated the cause of the MSP tools consistent overestimation is due to the static probability of infection (POI) curve. In reality the POI varies with fluctuations in population susceptibility and fluctuations in measles prevalence. Two potential methods of adjusting for this were suggested. The first ("fix 1") is to use the fitted fraction susceptible (*S*) and the aggregated cases in the previous year in the model. The second ("fix 2") is to use the fitted *age-specific* fraction *S* and aggregated cases in previous year.
For full details of the RAS model, see the presentation. In brief it is a fully dynamic, stochastic, SEIR, age structured model with an age dependant pattern of contacts. For the purposes of this analysis, the outputs of the RAS model were assumed to represent "truth" These true data were simulated for 50 yrs and used as training data. Then one step ahead predictions (from 51 years) of the different models [natural history model (NHM), MSP tool, MSP tool plus fix 1 and MSP tool plus fix 2] were compared with reference RAS data. See presentation for full results, but in summary, the MSP tool with either fix performed better than either the MSP tool or the NHM unless there were extreme departures from training data assumptions (e.g. in the per capita birth rate). In theory adding vaccine uptake and birth rates to the fixes is possible, but a fully dynamic model might yet prove a better alternative.

Group discussion:
There was discussion around whether it was possible to include other factors in the fixes (e.g. seasonality) and to deal with the issue of poor performance with extreme departures for training data assumptions. It was concluded that, although this is technically possible, the computational capacity required to obtain the training data would be prohibitively large. An alternative strategy of using a Bayesian approach to incorporate cases from the previous year was suggested.

Presenter: Dr David Mercer, Surveillance, Monitoring and Evaluation, WHO Europe, Copenhagen, Denmark.

Presentation 2:
A comparison of the MSP tool's predictions to surveillance data was presented. The POI curve was once again highlighted as the driver of the MSP tool estimates. Surveillance data were collected from a number of sources including case data routinely reported to WHO by countries, published reports, supplementary immunization activity (SIA) coverage data and

imputations if data were missing for a given year. It was acknowledged that reported cases might be severe underestimates but trends will often still be captured (if detection and reporting methods remain the same). For full details of results see presentation. In summary, data from the AFRO region fitted reasonably well to predictions except for there being faster rebounds after SIA in the model than in reality (due to POI not being influenced by the number of cases in the previous time step). In the two SEARO countries that were taken as examples (Indonesia and Myanmar) the MSP tool did not predict the real data as well as in the AFRO region. In conclusion, the MSP tool fits real data reasonably well in some conditions but might need refinement for other situations. The POI might need adjustment, potentially using Bayesian methods, to include information on cases from the previous year.

Group discussion:
There was discussion of reported data being an underestimate of real data and that time trends might also not be realistic if case detection and reporting methods change over time. Bayesian methods were discussed as a potential "fix" to the model.

General discussion:
In the general discussion of the MSP, it was clarified that the MSP tool serves two purposes: the one is a planning tool for countries to assess impact of planned measles immunization scenarios. The second is to serve for the production of annual estimates of global measles mortality. While the first function has been endorsed by QUIVER in 2007, the second function was subject of discussion here. In that context two questions were identified:

1. Which tool is the best to use over the next 2 years (i.e., for measurement of progress towards the 2010 goal of a 90% reduction in global measles deaths compared with the 2000 level)?, and
2. In the long term, is it better to continue with the MSP tool or to develop a completely different model?

There was general agreement that an MSP tool with some additional fixes would be a substantive improvement of the current methodology, but that a different, more sophisticated model would be more suitable in the long term. It was also noted that in the long-term, measles mortality estimates should increasingly rely on case-based reporting data.

3.7. Rubella model review

Presenters: Dr Elisabeth Adams, Health Protection Agency, London, NW9 5HT, UK
Dr Emilia Vynnycky, Modelling and Economics Unit, UK.

Presentation:
Models for the estimation of the annual incidence of rubella infection and congenital rubella syndrome (CRS) were presented. Different methods were used for countries in which rubella-containing vaccine has been introduced and where it has not. In those where it has not, a simple catalytic model (as previously published by the presenter) with susceptible and immune states was used. Age specific data (from literature review) were fitted in this model to determine the proportion infected prior to reaching child-bearing age and the force of infection among individuals of child-bearing age. In this model it was assumed that the FOI was identical for all individuals of child-bearing age and that the risk

that a child is born with CRS is 65% if infection occurs in the first trimester of pregnancy. CRS incidence per 100,000 pregnancies was calculated using the proportion of susceptibles from the model (see presentation for calculations). For countries where rubella containing vaccine has been introduced, an age-structured model describing the transmission of rubella in the given setting prior to rubella vaccination was developed into which vaccination coverage could be introduced. The model was then fitted to obtain the FOI, by year, amongst individuals of child bearing age (see presentation for details of methods). CRS incidence per 100,000 pregnancies was then calculated in the same way as for countries without rubella vaccination. The problems highlighted relate mainly to the availability, quality and form of data in the literature. Further work includes completing the literature review, accounting for the sensitivity of the rubella anti-body test, using a transmission model in setting without rubella vaccine, and validating the model.

Group discussion:
It was highlighted that criteria need to be established for the inclusion or exclusion of data found in literature review. It was also suggested that it might be safe to presume in countries without rubella vaccination the epidemiology is similar enough to use meta-analysis values for FOI. In addition, in countries with vaccination, the model might not need to be as complicated since the model will always predict no cases of CRS if there is a catch up scheme.
There was some concern that childbearing age could be less than 15 years (the age from which cases are currently calculated from here) in some locations, and additionally that calculating based on births (rather than live births) does not account for pregnancy loss. Seasonality might be worth examining and the robustness of assumptions (e.g. 65% of infections if first trimester result in CRS) should be examine e.g. by literature review. The potential use of POLYMOD contact matrices in this situation should be examined. Consideration should also be given to private sector use of rubella vaccine.

3.8. Pertussis model review

Presenters: Dr Hélène Broutin, Fogarty International Center, National Institutes of Health, Bethesda, 20892 MD, USA.

Presentation:
A generic cohort model describing country specific burden of pertussis, and the effect of vaccination was presented. The model provides burden estimates by age group (using 104 age groups, including adults) and includes consideration of benefits of incomplete vaccination, and waning immunity (10 years immunity after vaccination and 15 years after natural infection). FOI varies between high and low coverage countries and over age groups (see presentation for model structure and equations). Cases and deaths for each age group are calculated based on the proportion susceptible, the age specific force of infection, vaccination coverage and vaccine efficacy. Validation is being performed by comparing outputs with reported cases in the WHO database. Limitations include the non-fully-dynamic nature of the model, seasonality not being included, the absence of data on country specific mixing patterns and uncertainty around several disease parameters (e.g. FOI and CFRs). Future research could include the effect of booster doses, more accurate estimates of waning immunity, improved measures of CFR and incorporating sub-national levels in the model structure.

Group discussion:
It was highlighted that more data are needed to inform the choices of CFR and FOI. The methods were seen to be appropriate given the limited data but a fully dynamic model would be preferred because it could incorporate the influence of adult infection. It might be preferable to have some refinement of the model for developed and developing country settings. Duration of immunity also needs more elaboration as many factors might affect this and maternal immunity might need some consideration. Economic analysis will be important once the model is refined. Objectives might need to be more clearly defined by WHO.

4. Measles Session

A brief introduction was given to the topic of using decision analysis models to assist in determining policy options for introduction of a 2nd dose of measles vaccine. Current questions were outlined including what the economic and epidemiological criteria should be for introducing a second routine dose of measles vaccine and whether second doses should be delivered through routine services or in campaigns. The purpose of presenting the models to QUIVER was to evaluate their methods and determine if they could be used to develop policy. QUIVER was not being asked to evaluate the actual policy options as this is the focus of the SAGE Working Group on Measles.

4.1. Measles second dose review - RFP 1

Presenter: Dr Mark Miller, Director, Division of International Epidemiology and Population Studies, Fogarty International Center, National Institutes of Health, Bethesda, MD 20892, USA.

Presentation:
Two models which can be used simultaneously to explore scenarios were presented. The first model was based on the analysis of individual age-cohorts by year. Specific demographic data for a country can be used and scenarios can be simulated with 3 vaccination opportunities. Dependence or independence of receipt of doses can be included in the model. For further details of model structure, see the presentation. Outputs of this model are the number of susceptible person, cases, and deaths by age and year. The second model was a dynamic model with iteration by generation which looks generically at a country (and can also be used at the sub national level). The interface system is excel-based with modifiable default values. It was noted that cost was likely to increase substantially in increasing vaccine coverage from 70% to near 100 % and that the cost-effectiveness of a second vaccination opportunity would depend greatly on the dependence or independence of receipt of the first and second dose.

Group discussion:
The main concern with this presentation was the static nature of the first model although it was considered useful that the FOI changed with vaccine coverage. The generic nature of the model was seen as a potential benefit. A move towards a fully dynamic model (possibly stochastic) which includes seasonality was suggested. The second model was hard to assess given the limited availability of results and the economic analysis needs to be expanded substantially. Validation of the model would also be useful. It was also highlighted that the policy question might need to be refined in order allow appropriate analyses to be performed.

4.2. Measles 2nd dose review - RFP 2

Presenter: Dr Anne Levin, , Health Economist, Bethesda, 20817 MD, USA.

Presentation:
A dynamic, age-structured, deterministic SIR model for the evaluation of the introduction of both the introduction of a second dose and the cessation of a third dose (where this occurs) was presented. For full model structure and parameter values, see the presentation. In this model, transmission is weighted by age. Various scenarios were examined where a baseline intervention (e.g. only one vaccination opportunity was given) was compared to the intervention of interest. The scenarios were broadly: adding a second opportunity, adding a third opportunity and removing a third opportunity (see presentation for full elaboration).Dependence/independence of doses were considered in these scenarios. Measures of effectiveness include measles cases averted, measles deaths averted and DALYs averted. Costs at health system level were examined but cost savings were not evaluated due to the lack of data on the costs of treating measles in developing country settings. The costs which were considered related mainly to service delivery. Output measures are cost per case averted, cost per death averted and cost per DALY averted. A probabilistic, Monte Carlo based sensitivity analysis will be conducted. Limitations of this model highlighted by the presenter include generalizability to other populations, an assumption of homogeneous mixing at country level and limited cost data.

Group discussion:
A positive point of this model included its dynamic nature and the consideration on the independence of vaccine doses. However, the age structure element and mixing patterns were not seen to be very clearly described. Maternal immunity should also be included in the model
The need for validation was highlighted and the possibility of using a model with partial differential equations (based on the McLean model) was raised. The need for more field data (including mixing patterns) was once again highlighted. The data needed include sero-prevalence in a representative sample of the population, measles incidence, the age distribution of cases and the independence of vaccine doses. Results on cost effectiveness are still to be produced.

4.3. Feasibility of global measles elimination

Presenter: Dr Alya Dabbagh, Expanded Programme on Immunization (EPI), Immunization, Vaccines & Biologicals (IVB), World Health Organization (WHO), 1211 Geneva 27, Switzerland.

Presentation:
A presentation of the feasibility of global measles elimination was given. Global measles elimination was defined as the absence of endemic measles cases worldwide for a period of 12 months or more in the presence of adequate surveillance. For full scope of work, see the presentation. The key considerations for assessing the feasibility and appropriateness of global measles elimination were identified as programmatic, biological, economic, health systems impacts, vaccine market, and global context along with political feasibility. See presentation for further elaboration on these aspects. A specific focus in the presentation was given to the cost effectiveness analysis, in order to inform a subsequent call for

proposals. The analysis proposed considers the cost effectiveness of global measles elimination compared to achieving and sustaining the current global goal of a 90% reduction in measles mortality by 2010 (compared to 2000 levels). In order to do this, a fully dynamic model would be required, allowing cases, deaths and DALYs averted to be calculated for a number of scenarios. The costs should be calculated based on country-level estimates of operational and health systems costs. A separate analysis should be conducted of the additional costs and benefits of using MMR or MR vaccine to control rubella and CRS.

Group discussion:
There was discussion on factors other than cost presenting substantial barriers to elimination. These other factors include sustainability of programs, decisions within countries being based not only on their own measles situations but also that in their neighbours and the high transmissibility of measles. In addition, if vaccination cannot be substantially reduced after elimination, cost effectiveness is reduced. There is little information on treatment cost, and opportunity costs will also be difficult to capture. The need for dynamic (trans-national) models was acknowledged but the lack of good quality data to parameterize models was emphasized. The group suggested that timeline for the completion of the proposed studies (by August 2009), was too ambitious and more time would be needed for quality and a comprehensive economic analysis.

5. Information Session

5.1. Global Immunization Vision and Strategy (GIVS) costing

Presenter: De Carol Levin, Program for Appropriate Technology in Health (PATH), Seattle, WA 98107-5136, USA.

Presentation:

A summary of a WHO/IVR technical review meeting in June 2008 in Seattle, USA hosted by PATH on the Mini-GIVS costing tool was presented. Global Immunization Vision and Strategy (GIVS) costing is an approach to estimate the cost of scaling up immunization and to examine this for different vaccines in a standard way. The original full GIVS costing tool was initially developed to estimate the cost of achieving the WHO-UNICEF Global Immunization Vision and Strategy for 2006-2015. The model is based on: the Comprehensive Multi-Year Plan (cMYP) and the Financial Sustainability Plan (FSP) for baseline immunization spending; Immunization Coverage Estimates and Trajectories (ICE-T) for projecting coverage goals; FSP, Choosing Interventions that are Cost Effective (WHO-CHOICE) data base and WHO-UNICEF Joint Reporting Forms (JRFs) for costs of scaling up health systems; and a bundled vaccine platform for estimating average costs of vaccines and injection supplies. It therefore includes costings of maintenance of current routine system costs, vaccine costs, costs of scaling up routine systems and the cost of campaigns. Due to the complex structure of the GIVS tool, a smaller version was designed (i.e. Mini-GIVS) with the objective to make it less complex and more user friendly. The benefits of the Mini-GIVS version are considered to be that it is useful for estimations of costs for scaling up immunization programmes on a global or regional basis, and can also

estimate costs for the introduction of new vaccines. It might also be suitable for limited country level use by expert user to start policy dialogue on introduction decisions with national policy makers. Further adaptations need to be made to enhance user friendliness and to facilitate for uncertainty and sensitivity analysis.

Group discussion:
QUIVER's potential contribution to the development of this tool was discussed. It was suggested that QUIVER could provide advice on whether the Mini-GIVS tool should be adapted to country level and provide comment on how costings are calculated. It was decided that a working group should be formed with TORs to be defined .
Specific points raised in discussion included: whether ICE-T had been adequately validated; if it was possible to increase documentation so there is clarity on the basis of estimates; whether costing should be based on what would or should be done within health systems; whether the cost elements of some of the newer vaccines are plausible, and that proxies might need to be adapted if the tool is used at country level.

5.2. HIV Vaccine modelling - HIV VaccSim

Presenter: Dr Daniel Barth-Jones, School of Medicine, Center for Healthcare Effectiveness Research and Department of Internal Medicine, Wayne State University, Detroit, MI 48201, USA.

Presentation:
A deterministic, equation-based, dynamic model for determining the optimal distribution of an HIV vaccine to limit the HIV epidemic in scenario countries was presented. The model is aimed at enabling policy makers to determine potential epidemiological impacts of an HIV vaccine, and to conduct cost effectiveness analyses. The model (HIV VaccSim) runs on the VenSim platform. The compartmental differential equations model incorporates age, gender, risk groups, behaviour and transmission data, natural history of HIV, treatment and vaccine characteristics. The model needs to be adapted, fitted and validated to each county's epidemic (by concentrated team effort). The hypothetical vaccine modelled was assumed to produce only a modest reduction in susceptibility but a more substantial reduction in infectivity (if given pre-infection). It was also assumed to be in limited supply. Results are, as yet, uninterpretable due to the large number of uncertainties (e.g. how the vaccine will work). Limitations include having uncertainty in data and having no consistent system for dealing with this uncertainty. For a full list, see the presentation. A Bayesian approach might help to deal with model calibration and validation difficulties.

Group discussion:
There was discussion on the value of continuing with the model when a vaccine is not imminent, and parameters for any future vaccine are unknown. The value was seen to be in guiding decisions on data collection and also to examine how close a vaccine could bring R_0 to 1. There was seen to be only limited possibility to incorporate interventions other than vaccines in to the model. Interventions which require compartment structure changes would be relatively difficult to incorporate. HIV experts should be asked whether this model has enough utility to continue with prediction. A change in question from how to target limited vaccine to how to reduce R_0 to below 1 was suggested.

6. Meeting agenda

Quantitative Immunization and Vaccines Related Research Advisory Committee
QUIVER
21-22 October 2008
Conference Center Varembé, Room B, Geneva, Switzerland

Chair: Alan Hinman
Overall Meeting Rapporteur: Pippa Scott

TUESDAY, 21 OCTOBER 2008		
08:30	Registration	
09:00	Introduction and Charge to the Committee	J. Hombach
09:15	Overview of QUIVER 2007 activities	A. Hinman R. Hutubessy
	Pandemic Influenza Scenario Modelling Session	***Rapporteur: S. Briand***
9:30	Quantifying the effect of vaccination and non-pharmaceutical interventions during influenza pandemic via a simulation model	G. Milne
10:00	Simulator of pandemic influenza intervention strategies	K. Tsui
11:30	Vaccination strategies against pandemic influenza: Mexico as a case study	G. Chowell
11:00	***Coffee break***	
11:30	Modeling cost-effectiveness of pandemic influenza vaccination: developing an international model piloted in 3 countries	M. Postma
12:00	Modeling for determining the optimal use of limited quantities of pandemic influenza vaccines: global and Russia-specific model	G. Bobashev
12:30	General Discussion	L. Garrison (moderator)
13:00	***Lunch***	
	Burden of Vaccine Preventable Disease Session	***Rapporteur: A. Dabbagh***
14:00	Neonatal Tetanus model review - feedback on QUIVER 2007 - discussant	J. Vandelaer S. Cousens[1] N. Crowcroft
	Disease Burden Estimates at WHO	***Rapporteur: A. Burton***
15:00	Global Burden of Disease Estimates	C. Mathers
15:20	Programmatic data needs for immunization	A. Burton
15:40	Child Health Epidemiological Reference Group (CHERG)	C. Boschi-Pinto

[1] Participate via teleconference

16:00	***Coffee break***	
	Burden of Vaccine Preventable Disease Session (Ct'd)	***Rapporteur: A. Dabbagh***
16:30	Use of MSP tool for burden estimates	P. Rohani / J. Drake[*] D. Mercer
17:30	Rubella model review	E. Adams E. Vynnycky
18:30	***Cocktail***	

WEDNESDAY, 22 OCTOBER 2008		
	Burden of Vaccine Preventable Disease Session (Ct'd)	***Rapporteur: A. Dabbagh***
08:30	Pertussis model review - presentation reviewer	M. Milller N. Crowcroft
	Measles Session	***Rapporteur: P. Strebel***
9:30	Measles 2nd dose review - RFP 1	M. Miller
10:30	***Coffee break***	
11:00	Measles 2nd dose review - RFP 2	A. Levin
12:00	Feasibility of global measles elimination	A. Dabbagh
13:00	***Lunch***	
	For Information Session	***Rapporteur: R. Hutubessy***
14:00	GIVS costing	C. Levin
14:45	HIV Vaccine modeling - *HIV VaccSim*	D. Barth-Jones
15:30	***Coffee break***	
16:00	Closed Session (AC Members only)	
18:00	***Closure***	

[*] Participate via teleconference

7. List of Participants

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