Using mathematical model to evaluate the impact of different PCV schedules:

Preliminary results from the West Africa epidemiological scenario

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Executive summary

Aims and Objectives

- To explore how mathematical modelling techniques can provide supplementary information to address key policy questions on immunization schedules in a specific epidemiological setting.
- To assess various PCV schedules using data on Streptococcus pneumoniae infection and pneumococcal vaccine effectiveness in a West African setting.

Key policy questions for review

- What is the impact of alternative PCV vaccination schedules in the West African setting, including the indirect effects of the vaccine (herd immunity and serotype replacement)?
- How do these alternative PCV schedules compare in terms of cost-effectiveness?

Process

- A mathematical model originally developed to assess the impact of PCV7 vaccination strategies in England and Wales (Melegaro et al., 2010) was used as the foundation for this exercise.
- This model has been modified to be able to assess PCV impact in the West Africa scenario and to deal with the demography of low income countries.
- Data from Burkina Faso and The Gambia were used to parameterize the model. This data included carriage prevalence and pneumococcal meningitis incidence rates from Burkina Faso¹ and invasive and non-invasive pneumococcal disease incidence from MRC The Gambia².
- The model structure and its methodological assumptions were reviewed by QUIVER (WHO Geneva, October 5th 2010).
- A panel of key pneumococcal experts provided inputs on the model structure, the underlying epidemiological assumptions, and the current parameters for the West Africa setting (WHO Geneva, October 6th 2010).
- Comments received from these reviews are currently being addressed where data permits.

Key policy findings

- The model currently reproduces the country-specific epidemiology of invasive pneumococcal disease estimated for Burkina Faso in the pre-vaccination era, and then projects the number of cases under the alternative vaccination schedules in the years post-PCV introduction.
- Schedules under consideration by local policy makers can be assessed and the number of life-years gained can be estimated for each alternative programme.
- The cost-effectiveness of these programmes can be evaluated using the estimated life-years gained and the net programme costs.
- Under initial preliminary epidemiological and economic assumptions, all proposed routine schedules appear to be cost-effective at commonly accepted thresholds.
- Catch-up programmes considerably increase the number of life-years gained in the first years of a programme, though at substantially higher cost than routine vaccination schedules alone.
- Incremental analyses can identify the schedules that provide best value for money.

¹ Data from Agence de Médecine Préventive, Centre Muraz, Acute Bacterial Meningitis surveillance and carriage studies (Reference person: Dr. Judith Mueller)
² Data from The MRC The Gambia (Reference person: Dr. Grant Mackenzie)
**Limitations of the model and the data used to parameterize the model**

- QUIVER considered that overall structure of the model was sound and appropriate. The possibility of incorporating both the mechanism of herd immunity and of serotype replacement was noted as essential to properly assess the effectiveness and cost-effectiveness of alternative PCV schedules.
- QUIVER recommended incorporating natural immunity, and non-invasive disease endpoints into the model.
- The recommendations of the panel of PCV experts included further stratification of serotypes (in particular the “epidemic” serotypes, e.g. ST1) in the model, and the need to clarify the derivation of the vaccine efficacy parameter estimates.

**Overview of preliminary results**

**Main interim conclusions of this PCV modelling exercise:**
Development of the model as well as discussions with key PCV experts on model assumptions allowed the workgroup to identify the critical aspects of the current work and the existing gaps in the data available.

The model reproduces the epidemiology of pneumococcal disease as estimated for the West Africa setting. The dynamic transmission framework and the mechanism for competition between vaccine- and non-vaccine serotypes and cause the model to exhibit both herd immunity and serotype replacement effects, which may be important influences on the overall effectiveness and cost-effectiveness of the vaccination programme. Direct comparisons of country-specific schedules can be performed and the number of life-years gained can be estimated.

The following schedules have been assessed in the interim analysis: 1+0 dose, 2+0 doses, 3+0 doses, 2+1 dose though all possible alternatives can be evaluated. The schedules considered have been assessed as routine infant programmes only or in parallel with catch-up campaign (either 1-2 years old or 1-4 years old). Interim results provide the following general conclusions:

- Under initial preliminary epidemiological and economic assumptions, all proposed routine schedules appear to be cost-effective at commonly accepted thresholds.
- Catch-up programmes considerably increase the number of life-years gained in the first years of a programme, though at substantially higher cost than routine vaccination schedules alone.
- Incremental analyses can identify the schedules that provide best value for money.

**Lessons learnt**

**On methods**

- The transmission model of *S. pneumoniae* carriage enables investigation of the potential effects of infant PCV vaccination strategies. It builds on previous *S. pneumoniae* models and, by including realistic demography and non-invasive disease, it allows investigation of the impact of different vaccination schedules on the age-specific incidence of pneumococcal disease in middle/low income settings.
- The transmission model results provide the basis for an economic analysis of alternative schedules.
- Knowledge on pneumococcal infection and the effect of the vaccine at the individual and population level is far from complete. Modelling results should reflect this uncertainty in mechanisms and parameter values – uncertainty should reduce as more data becomes available.

**Additional model refinements**

Three developments to the model were recommended by the groups of experts:

- include non-invasive pneumococcal pneumonia as an endpoint – this has now been implemented;
- consider additional sub-grouping of serotypes – this will be achieved by separate consideration of “epidemic” serotypes;
- incorporate natural immunity in the model – generation of acquired immunity to pneumococcal serotypes is too complex and poorly understood to be incorporated in the present model structure, but will be considered for inclusion in future versions of the model.
OVERVIEW OF THE PCV MODEL

Attempting to evaluating the effects of PCV clearly presents a daunting challenge to modellers as the epidemiology and vaccinology of pneumococcal infection is considerably more complex than any other vaccine preventable infection. More than 90 serotypes exist and each is characterised by a different potential for transmission, duration of carriage and capability of causing invasive as well as non-invasive disease (Brueggemann et al., 2003; Sleeman et al., 2006; Melegaro et al., 2007; Greenberg et al., 2010). Moreover, evidence of multiple colonisation is now building up (Auranen et al., 2010; Brugger et al., 2010) and the understanding of the interaction between different competing types is far from complete as well as the knowledge of the determinants of the immunological processes and whether serotype-dependent (Weinberger et al., 2008) vs. serotype-independent (Granat et al., 2009) acquired immunity to pneumococcal carriage exist. Nevertheless some progress can still be made using a model with many simplifying assumptions and investigating the robustness of model results to changes in parameter values.

Model description

The model is a transmission dynamic model with realistic age structure that aims at describing the natural history of S. pneumoniae infection and progression to pneumococcal disease and capable of a mechanistic investigation of herd immunity and serotype replacement effects. Vaccination strategies can be implemented and the model keeps track of the number of doses received and the level of protection achieved (unprotected, partially protected and fully protected).

Model assumptions

The main model assumptions are described in the following table where indication is also provided on the planned activities in relation to these assumptions and after QUIVER and PCV expert review.

<table>
<thead>
<tr>
<th>MODEL ASSUMPTIONS PRE-QUIVER</th>
<th>NEXT STEPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease outcomes</td>
<td>Only IPD considered</td>
</tr>
<tr>
<td>Mixing patterns</td>
<td>Ranges from fully assortative to proportionate, (Garnett &amp; Anderson, 1993).</td>
</tr>
<tr>
<td>Serotype grouping</td>
<td>Two groups only: VT and NVT, assuming homogeneous characteristics within these groups</td>
</tr>
<tr>
<td>Immunity</td>
<td>No acquired immunity</td>
</tr>
<tr>
<td>Competition</td>
<td>In acquisition of a new serotype rather than in clearance (Auranen et al., 2010)</td>
</tr>
<tr>
<td>Vaccine efficacy</td>
<td>Separate parameters for degree of protection against: – acquisition of carriage of vaccine-serotypes – development of disease in carriers (baseline assumption is of total protection against VT pneumococcal disease for vaccine protected individuals)</td>
</tr>
</tbody>
</table>
Data used to parameterize the model

The model is currently parameterised with data from Burkina Faso and The Gambia and generates estimates of the number of life-years gained from and overall cost of the alternative schedules. Healthcare costs avoided due to the reduction in disease burden are not yet included. Vaccination coverage has been set to the values reported for developing countries setting and the possibility of having delays in the actual age at vaccination is also included as an additional scenario (Clark & Sanderson, 2009).

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>BASE VALUE (RANGE)</th>
<th>SOURCE OF DATA/COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-vaccination epidemiology</td>
<td>Age-specific</td>
<td>Cross-sectional carriage prevalence study in Burkina Faso Meningitis incidence by serotype from Burkina Faso Pneumonia incidence from The Gambia</td>
</tr>
<tr>
<td>Mortality</td>
<td>Age-specific</td>
<td>UNPD</td>
</tr>
<tr>
<td>Population age-structure</td>
<td>Age-specific</td>
<td>UNPD</td>
</tr>
<tr>
<td>Duration of carriage by age</td>
<td>0-1 yr: 72 days;</td>
<td>Analysis of longitudinal data for England and Wales (Melegaro et al., 2004, Melegaro et al., 2007). Studies from developing countries yield similar estimates</td>
</tr>
<tr>
<td></td>
<td>2-4 yrs: 28 days;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-17 yrs: 18 days;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18+ yrs: 17 days</td>
<td></td>
</tr>
<tr>
<td>Relative rate of acquisition of VT if colonised with NVT</td>
<td>0.5</td>
<td>Assumed</td>
</tr>
<tr>
<td>Relative rate of acquisition of NVT if colonised with VT</td>
<td>0.50 (0.00-1.00)</td>
<td>To be varied in the sensitivity analysis</td>
</tr>
<tr>
<td>Assortativeness of age-specific mixing pattern</td>
<td>0.85 (0.00-1.00)</td>
<td>To be varied in the sensitivity analysis</td>
</tr>
<tr>
<td>Average duration of protection against carriage acquisition</td>
<td>5 years</td>
<td>A shorter duration of protection was suggested by the PCV expert review panel</td>
</tr>
<tr>
<td>Degree of protection against carriage acquisition</td>
<td>65%</td>
<td>(Rinta-Kokko et al., 2009) Parameterization of the model with final figures on degree of protection with alternative schedules is ongoing (Low et al., draft report 2010)</td>
</tr>
<tr>
<td>Discount rate</td>
<td>3.5%</td>
<td>To be varied in the sensitivity analysis</td>
</tr>
<tr>
<td>Time horizon</td>
<td>25 years</td>
<td>Long time horizon allow investigation of longer term effects. However, shorter time horizons (5, 10 years) can also be considered</td>
</tr>
</tbody>
</table>

Immunization schedules being assessed

The vaccination programmes outlined below are the ones highlighted by the PCV expert group to be of interest. However the consideration of these schedules will critically depend on the availability of data to parameterise vaccine protection. Here, preliminary estimates of vaccine efficacy against VT colonisation provided from the systematic review of RCTs of pneumococcal vaccines (Low et al., draft report 2010) and previous analyses were used. Routine infant programmes were considered either alone or in parallel with catch-up campaigns.
Routine infant programmes
- **Strategy 1+0**: Routine vaccination at e.g. 14 weeks
- **Strategy 2+0**: Routine vaccination at e.g. 6 and 14 weeks
- **Strategy 3+0**: Routine vaccination at e.g. 6, 10, 14 weeks
- **Strategy 2+1**: Routine vaccination at e.g. 6 and 14 weeks and booster at 12 months

Each strategy can be adapted by adjusting the ages at which each primary dose is given to, say, 2, 3 and 4 months or 2, 4, and 6 months; or by moving the booster to, say, age 9 months or 15 months. The impact of all these adjustments can be evaluated.

Catch-up campaigns
In addition to routine vaccination, there is an opportunity to conduct a “catch-up” vaccination campaign at the onset of the vaccination programme. Such campaigns accelerate the reduction in circulation of vaccine serotypes. The target age range for the catch up campaign can be varied in the model, to investigate the impact of different options e.g. a catch-up campaign for those aged 1-2 years, or for those aged 1-4 years.

Cost-effectiveness analysis
The cost-effectiveness of alternative schedules is assessed by projecting the outcome of vaccination from the dynamic infectious disease model on the number of cases of pneumococcal disease and associated QALY loss and estimating the overall costs of the programme and healthcare costs avoided. Incremental cost-effectiveness analysis is then performed to compare the QALYs gained from and net costs of alternative programmes. Our preliminary analysis considered life years gained (rather than QALYs) and used programme costs only (excluding healthcare costs). We used the potential long-term cap price of $3.5 per dose of PCV as suggested by AMC, and a wastage of 7.5% (varied in the range: 5-10%). In addition an average programme cost per child and per dose of $6 ($2-$10). Discount rates have been fixed to 3.5%. Multivariate sensitivity analysis can be performed to show the variability of LY gained and costs of each schedule.

Preliminary Results
Introducing PCV vaccination decreases carriage of vaccine serotypes in the population and consequently reduces the incidence of disease from vaccine serotypes. Vaccination has eliminated carriage of vaccine types in developed countries, but it is not yet clear that this will also occur in developing countries (a higher pre-vaccination prevalence of carriage is indicative of more intense transmission and thus a higher $R_0$ and threshold for elimination). Some increase of carriage and disease caused by non-vaccine serotypes is expected, the extent of which remains uncertain. Adding catch-up campaigns on top of routine programmes causes a greater impact in the first few years of the vaccination programme.

Calculation of the effectiveness and cost-effectiveness of the vaccination programme takes into account the impact on all pneumococcal disease. Under initial preliminary epidemiological and economic assumptions, all proposed routine schedules appear to be cost-effective at commonly accepted thresholds. Catch-up programmes incur substantially higher costs than routine vaccination schedules alone. Incremental analyses can identify the schedules that provide best value for money.

Interpretation and discussion
This model is part of a larger project to examine the evidence related to vaccination schedules in middle/low income countries and to develop a framework to identify the optimal schedule for a particular country or setting. In this respect, the current work has accomplished not only the task of developing a tool that can evaluate a specific vaccination programme, such as PCV, taking into account the most critical mechanisms,
but has also demonstrated productive interdisciplinary collaboration which is essential for making progress with such complex problems.

We use a transmission dynamic model to allow the consideration of short and long term direct and indirect effects of the vaccination programme and which could have been parameterised with the available data. While the process of incorporating experts’ suggestions and refining parameter estimates is still ongoing, the potential of this modelling approach for addressing policy-relevant questions can be can already be seen. The short and long-term, direct and indirect effects of alternative schedules can be explored in the same (model) population within a feasible time-scale. What would be the optimal dosing strategy in a particular setting: 2+0, 3+0 or 2+1 doses? Is there a preference for a particular timing of the doses in this setting: 6, 10, 14 weeks or 2, 4, 6 months? Would a catch-up campaign (to 2, 5 or even 10 years) add significant benefit and justify its cost?

Once the model is developed and parameterised, the identification of the optimal schedule is still not trivial. Performing a comprehensive uncertainty analysis is also necessary to explore the robustness of the model output and the effects that variations in model parameters and/or assumptions may have on the estimated life-years gained and net costs of each vaccination schedule considered, and on the order of preference of different schedules. Examination of the epidemiological conditions or vaccine parameters that change conclusions regarding the preferred schedules can also be informative.

The specific example addressed here, evaluating the effects of PCV, clearly presents a daunting challenge to modellers considering the complexity of pneumococcal infection. Nevertheless some progress has been made using a model with many simplifying assumptions and investigating the robustness of model results to changes in parameter values. Further analysis and interpretation in this and other epidemiological scenarios for PCV and other vaccines are planned.


