Reviewer's report

Title: Cost-effectiveness and cost utility analysis of new pneumococcal conjugate vaccines in children of Peru

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Reviewer: Lesley Tilson

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This study explores the cost-effectiveness of universal vaccination with the new pneumococcal conjugate vaccines in children of Peru. This is a topical issue, following the recent introduction of the 10-valent and 13-valent pneumococcal vaccines. There are numerous publications in the literature comparing these vaccines with PCV-7 in various countries but as far as I am aware this is the first study to describe the cost-effectiveness of these vaccines in Peru. In general, the cost-effectiveness study was methodologically sound and well described. However, I have a number of comments and concerns in relation to the base case assumptions and consequent conclusion that was drawn from the results of this study.

My comments focus on the choice of model, the serotype distribution data, the inclusion of indirect effects of vaccination, cross protection and the benefits of PHiD-CV in reducing NTHi disease.

The overall conclusion from this study is that PHiD-CV is predicted to be a dominant intervention compared to PCV-13 and PCV-7. I would have concerns that this conclusion is underpinned by the assumptions related to benefits of PHiD-CV against NTHi disease and cross protection, as well as the exclusion of the herd immunity effect from the base case scenario. The results show that the PCV-13 vaccine is associated with greater health gains which come at a higher cost. A reduction in the price of PCV-13 would result in PCV-13 being a cost-effective option compared to PCV10 with overall greater health impact. This is not clearly highlighted in this paper.

Other evaluations
There are many publications comparing the cost-effectiveness of the pneumococcal vaccines and there is considerable variability between these studies (e.g. Chuck, Rozenbaum, Beutels, Newall). The discussion section of the paper did not refer to any of these studies and did not offer any explanations for differences in findings between studies. Comparison of the findings of cost-effectiveness evaluations of the 10 and 13 valent pneumococcal vaccines is difficult because of the differences in the base case assumptions and data inputs between studies. Some studies do not include the indirect effect of vaccination or the impact on AOM in their analysis. Therefore the benefit of vaccination is lower in these studies. While all studies conclude that PHiD-CV and PCV13 are more cost-effective than PCV7, conclusions regarding the cost-effectiveness of
PHiD-CV compared to PCV13 are variable. One of the most important explanations for variation in results and conclusions seems to be the impact of different assumptions regarding cross protection, efficacy against AOM, indirect effects and the vaccine price.

Modelling approach
A static cohort model was used in this study. This is consistent with the majority of other studies of the pneumococcal conjugate vaccines. Transition dynamic models offer the potential to predict the dynamics of underlying herd immunity and serotype replacement. However, they need to be underpinned by detailed pneumococcal carriage studies which are currently lacking in many countries. The only country to date to evaluate the cost-effectiveness of PCV vaccines using a transition dynamic model is the UK. This was made possible by the availability of UK data on nasopharyngeal carriage and the indirect effects of vaccination.

Serotype distribution data
IPD cases caused by 6A and 19A may be a determining factor in cost-effectiveness estimates. More detailed information regarding the pneumococcal serotype distribution would be of value. For example, has the serotype distribution changed over time; is 19A or 6A increasing post introduction of PCV7 vaccination in 2009 in Peru? It appears that data from a Panamerican database was used in model. Was country specific data from Peru used? It appears that the serotype data included in the model was from the year 2006. If this is the case, the impact of the introduction of PCV7 vaccination in Peru in 2009 would not have been captured in the model. Please clarify.

Indirect effect of vaccination
Although there is a lack of data for potential herd immunity effect, it is important that this is captured in the model. Studies show that introduction of PCV7 vaccination resulted in a substantial decline in pneumococcal disease in older patients through a herd immunity effect. On page 14 of the manuscript the authors state that “when herd effects are considered, a slightly greater effect on QALYs gained was seen (21%)”. However, the impact on the cost-effectiveness of PHiD-CV vs PCV13 is not clear.

Cross protection
This study assumes cross protection against serotype 6A and 19A for invasive disease. There are concerns in relation to the evidence available to substantiate this. The EMA (2011) state that “there is insufficient evidence that PCV10, will provide cross protection for serotypes not contained in the vaccine, including 6A and 19A”.

Vaccine efficacy against NIPD
It was assumed that the effects of vaccination on AOM and pneumonia for PHiD-CV and PCV13 would increase proportionally with the increase in serotype coverage for IPD. A major limitation of this approach is that it is not known what
serotypes cause non-invasive pneumonia or AOM in Peru. The impact of each vaccine will depend on the relative importance of different serotypes in different diseases (i.e. IPD, pneumonia, AOM). There is currently no evidence that there is an incremental effect on NIPD with incremental serotypes as a result of vaccination with PHiD-CV or PCV13. This limitation should be highlighted in the discussion.

This study assumes that the efficacy of PHiD-CV in preventing AOM caused by not only vaccine serotypes of S. pneumoniae but also those caused by NTHi is the same as the efficacy of the PCV11 vaccine which was demonstrated in the POET study. Per protocol analysis of the POET study demonstrated a clinically significant reduction in the overall incidence of AOM in the PCV11 group (33.6% (95%CI 20.8-44.3%)) (Prymula R 2006). Of note, PCV11 contained 11 different polysaccharide serotypes, each was conjugated to a protein D carrier protein. In contrast, eight of the serotypes included in the PCV10 vaccine are conjugated to protein D carrier protein, 18C is conjugated to tetanus toxoid and 19F to diphtheria toxoid carrier protein. Therefore, the investigational PCV11 differed from PCV10 in the use of protein D as a conjugate protein. Based on review of comparative NTHi immunogenicity between PHiD-CV and PCV11, the EMA noted in their review for vaccine registration “there is insufficient evidence that Synflorix provides protection against pneumococcal serotypes not contained in the vaccine or against NTHi. Synflorix does not provide protection against other micro-organisms” (EMA 2011). Therefore, I would have concerns in relation to the inclusion of the benefit of PHiD-CV against NTHi disease in the base case analysis, and consider it would be more appropriate to include in a scenario analysis.

Duration of immunity

Finally, it was assumed that the duration of protection from vaccination was 9 years. Justification should be provided for this.

In conclusion, I would recommend that alternative, more conservative, parameters should be included in the base case model and that the existing base case scenario should be presented as a scenario analysis.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I have no competing interest to declare