Author's response to reviews

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

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Author's response to reviews: see over
**Title:** Cost-effectiveness and cost utility analysis of new pneumococcal conjugate vaccines in children of Peru

**Version:** 1  **Date:** 5 March 2013

**Answer to Reviewer:** Lesley Tilson

- *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.*

**Choice of Model**
The model can estimate and compare different accumulated conditions of a birth cohort over a lifetime: unvaccinated, vaccinated with PHiD-CV, and vaccinated with PCV-13 at steady state which means that the vaccine effect is fully implemented within the cohort.

It was explained in the manuscript, and previously validated and published (1,2). Is an age-compartmental, deterministic (= non-random), and static (= non-dynamic) Markov-process cohort model with specific health states spread over time (= age). The different health states highlight specific disease stages to which disease management processes in a decision tree are added with specific changes in cost and/or Quality Adjusted Life Years (QALYs). The model runs from birth over a life-time and the cycle length in the Markov process is 1 month. For example, if a subject lives precisely 100 years, he/she will run through 1,200 monthly cycles before being death.

Monthly cycles were chosen in order to estimate the effect of the vaccination precisely in the first 2 years of life. The vaccine is given at months 2, 4 and 12. In order to account for partial early protection at months 2 and 4 we subdivided the model into monthly cycles. It is important to precisely estimate the effect of the vaccines in the <1 age group because the burden of disease amongst pediatric population is the highest in this age group. Vaccine efficacy estimation by month has previously been explained (2).

The key model assumptions were validated with international pneumococcal vaccine expert meetings that were held in 2007-2008 (see appendix for details of participants on the AB), and it has been previously validated and published (1,2).

**Serotype distribution**
As explained in the manuscript, serotype distribution for Peru was obtained from the Latin American Network for Surveillance of Pneumonia & Bacterial Meningitis Agents (SIREVA II). This network is sponsored by PAHO and provides information of most Latin American countries. We have used average data specifically reported for Peru between years 2000 to 2006 (n = 222), as reported in the supplementary data file (3, 4). The epidemiological data used to calibrate the model for Peru is prior to the introduction of pneumococcal conjugated vaccines (PCV-7 in 2009).

Peru reports to this network typing results of 17 to 50 cases per year. Although minor differences are reported in type distribution year by year, no clear trend is observed over time and the annual sample size is not adequate to assure that the scenario of any individual year will represent a significant epidemiological change. For all these reasons, we decided to use average data of pneumococcal types.
distribution covering many years before vaccine introduction in the analysis.

**Indirect effects**
To estimate the economic consequences of a herd effect through a cohort model, a fixed net indirect effect value stratified by age is introduced as a reduction in disease frequency across all ages for those diseases for which it is expected that the herd effect will be important. We estimated fixed net indirect effect data based on PCV-7 impact on unvaccinated children in the US. To date US has the longest history of PCV vaccines introduction. We opted for a starting effect of a 15.4% reduction in IPD disease in children <5 years and a 29.0% in those ≥5 years old (5, 6).

The net indirect effect in IPD was not included in base-case direct comparison of the vaccines, since the potential difference in herd protection induced by these vaccines is not known. The inclusion or exclusion of equal (not differential) herd effect for all vaccines should not impact on the results, because the incremental differences between them would be the same with or without inclusion of the indirect effect.

To demonstrate the impact of the indirect effect assumption on results presented in the base case, we conduct a scenario analysis with inclusion of herd effects for PHiD-CV (Fig 3). In addition, we have analyzed the inclusion of herd effects in the incremental QALYs and cost results for PHiD-CV when compared to PCV-13 to confirm that they are the same as base-case results (data not shown).

**Cross protection**
This practice of including assumptions regarding clinical effectiveness not specifically cited in a vaccine’s label is not only widespread in all pneumococcal vaccine models but is also methodologically appropriate because data in vaccine labels can vary from country to country and can often be incomplete (7, 8). Criteria to include vaccine data in the label also differs from usual practice of public health impact and economic modeling.

Cross-protection occurs when a vaccine demonstrates an effect against serotypes which are not included in the vaccine but belong to the same serogroup as those included in the vaccine. For example, Whitney et al (9) reported PCV-7 vaccine effectiveness against IPD of 76% for serotype 6A and 26% for serotype 19A. We have used these data to assume cross protection for PCV-7 and PHiD-CV, and the rationale for that assumption with the corresponding references are included in the manuscript.

**NTHi Disease**
To date regulatory authorities have largely relied on the studies of Eskola et al (10) and Prymula et al (11) in granting indications against acute otitis media protection, and the international pneumococcal vaccine experts collaborating with us in model development agreed that these studies should represent the sources of AOM efficacy values in the health economic modeling assessment.

Efficacy of PHiD-CV against AOM caused by NTHi was included in the base cases of studies published in international peer-reviewed journals (12-19). Moreover, inclusion of NTHi into a base case has been published in a number of European countries (13, 16-18).

VE efficacy against AOM caused by NTHi was also evaluated in the COMPAS trial (20). Similarly to Prymula et al (11) and in contrast to Eskola et al (10), COMPAS showed positive point estimates for VE against AOM caused by NTHi and showed no evidence for replacement of VT with non-vaccine
pneumococcal serotypes (NVT) or other pathogens (20).

PHiD-CV is licensed in more than 115 countries and in 58 of these, the vaccine is indicated to prevent NTHi AOM. PHiD-CV is also licensed against NTHi AOM in the following Latin American countries: Bolivia, Argentina, Mexico, Chile, Panama.

In addition, we assumed in the base-case analysis that the use of protein D from NTHi as a carrier protein in PHiD-CV may offer additional protection against NTHi invasive disease (ID). The vaccine efficacy of PHiD-CV against NTHi-associated ID was assumed to be the same as that reported for NTHi-associated AOM (35.3%) (11). This assumption was considered conservative as the vaccine efficacy of PCVs against ID is much higher than for mucosal diseases. For example, vaccine efficacy of PCV-7 against IPD (vaccine types) is ~95% (9), while its efficacy against mucosal diseases has been reported to be 58% (in pneumococcal AOM) (10, 11). NTHi burden on ID was based on data reported by the previously mentioned SIREVA II network (21). We have assumed that the ratio of *S. pneumoniae* to NTHi meningitis was 11:1 and *S. pneumoniae* to NTHi bacteremia was 17:1. The relatively low burden of NTHi associated ID used for the analysis, limited the potential benefit of the vaccine against this outcome and it is clearly seen in the manuscript.

**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.**

We agree with Dr. Tilson. The conclusion of the study is that PHiD-CV is predicted to be a dominant intervention compared to PCV-13 and PCV-7. The analysis was based on the available scientific evidence and our analysis is presented transparently and with all the required details. We have answered in previous paragraphs the questions regarding NTHi disease, cross protection, and herd immunity. We have mentioned in the discussion that the most important assumption made is the paucity of efficacy data for these new vaccines and we then explained the assumptions and limitations observed for these data. Although there are a few clinical trials for PHiD-CV (11, 20, 22, 23), there are no trial for PCV-13 so we have tried to estimate vaccine efficacies objectively for all vaccines. As an example, presently there are significant doubts about the efficacy of PCV-13 against *S. pneumoniae* type 3 (24), but full efficacy was considered in the base-case analysis.

**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.**

Our analysis shows that PCV-13 vaccine provides greater health gains at a higher cost in the scenario not considering Quality of Life that presented health benefits as Life Years gained. A reduction on PCV-13 vaccine prices could have changed the results, but that scenario is not related to present reality in Latin America. We have used the vaccine costs reported by the PAHO Revolving Fund for all these vaccines. PCV-7 was the 1st conjugated pneumococcal vaccine available at the PAHO RF and Peru have introduced PCV-7 in 2009 at a cost of 20 dollars per dose. PCV-7 was discontinued in 2010 and its last price at the PAHO RF was 20 dollars per dose (25). PHiD-CV was introduced in 2011 in Peru when it was
the only PCV vaccine available at the PAHO RF (26). PCV-13 and PHiD-CV have been available at the PAHO RF since 2012 and their prices per dose were 16.34 and 14.24 dollars (27), as used in present manuscript. This scenario is still present (2013) at the PAHO RF and it is the scenario we consider when we decided the vaccine prices to be used in the analysis. We tried to reflect as close as possible the scenario of the PAHO RF because Peru and many other countries in Latin America acquire vaccines under this framework.

- 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…

We have introduced this comparison in the updated discussion, particularly with the cost effectiveness analysis of PCVs developed for Latin American countries.

- Modelling approach

We used a static cohort Markov model as previously described, because it is one of the most frequent tools used in health economic studies for PCVs, but it also provides the right balance between accuracy and simplicity. A more complex transmission model would have the difficulty of being much less transparent and would require a lot more inputs for country calibration. These are important limitations to consider for health economic analyses in a setting like Peru. The appropriate information to populate transmission models is not available from this country and authorities will have difficulty understanding and manipulating them. In addition, as previously mentioned, we have decided not to include indirect effects against IPD in the base-case analysis for vaccine comparison, since the potential difference in the herd protection induced by them is not yet known. Therefore, our decision on the model to be used not only considered the primary goal of the study but also the setting where this study was being developed.

- Serotype distribution data

This point was previously described in detail. We have reviewed the data reported by SIREVA II network for Peru between 2007 and 2011, and no increase in the prevalence of pneumococcal types 6A & 19A were identified.

- Indirect effect of vaccination.

This point has previously been described in detail. As explained in the manuscript, a fixed herd effect was evaluated in the scenario analysis for PHiD-CV. Incidence reductions of IPD of 15.4% and 29.0% among children <5 years and ≥5 years, respectively, were assumed based on the PCV-7 experience in the USA (5, 6). As mentioned in the manuscript, a slightly greater effect on QALYs gained was seen (21%) in this scenario.

- Cross protection
This point has previously been described in detail. This practice of including assumptions regarding clinical effectiveness not specifically cited in a vaccine’s label is not only widespread in all pneumococcal vaccine models but is also methodologically appropriate because data in vaccine labels can vary from country to country and can often be incomplete (7, 8). Criteria to include vaccine data in the label also differs from usual practice of public health impact and economic modeling.

The rationale for using cross protection is explained in the manuscript. Cross-protection against \textit{S. pneumoniae} serotypes 6A and 19A for ID was considered for PCV-7 and PHiD-CV. Immunogenicity studies have shown that PHiD-CV provides cross-reacting functional (opsonophagocytic) antibodies against 6A and 19A (28, 29). These studies have shown that PHiD-CV and PCV-7 provide similar levels of cross-functional antibodies against serotype 6A, but PHiD-CV provides higher levels of cross-reacting functional antibodies against serotype 19A than PCV-7. Cross-protection of PCVs against \textit{S. pneumoniae} type 6A has been reported in several studies (9, 10, 30), and Hausdorff et al. have suggested that cross-protection against \textit{S. pneumoniae} serotype 19A for vaccines covering \textit{S. pneumoniae} serotype 19F is a likely assumption (31). After implementation of PHiD-CV into UMV in a number of countries (Brazil, Canada, Finland) a trend towards decrease of 19A have been observed (32, 33), in line with the observation of Hausdorff et al. (31).

Therefore, we included cross protection for these vaccines (PHiD-CV & PCV-7) at levels of 76% against \textit{S. pneumoniae} type 6A ID and 26% against \textit{S. pneumoniae} type 19A ID, based on the data reported by Whitney et al. (9).

**Vaccine efficacy against NIPD**

Dr. Tilson mentions that we assumed that the effects of vaccination on AOM and pneumonia for PHiD-CV and PCV-13 would increase proportionally with the increase in serotype coverage for IPD. This statement is not right. We assumed vaccine efficacies against AOM based on the results of two clinical trials (10, 11), and provide details in the manuscript. In addition, we assumed \textit{similar} vaccine efficacies against hospitalized all-cause pneumonia (23.4%), and against all-cause ambulatory pneumonia (7.3%), based on the data of the COMPAS trial developed in Latin American countries (34). We totally agree with the limitation mentioned by Dr Tilson. The scenario described by her was used in a recent study of PCVs developed in Argentina (35). Urueña et al. used different vaccine efficacies against pneumonia based on the different type coverage of PCV-13 and PHiD-CV vaccines in IPD. This assumption introduces significant bias in the analysis but was not used in our analysis. We are including these comments in the discussion to highlight this potential bias.

**Vaccine efficacy against AOM**

Vaccine efficacy against AOM associated to NTHi has previously been detailed. To date, regulatory authorities have thus largely relied on the studies of Eskola et al (10) and Prymula et al (11) in granting indications against AOM protection, and the international pneumococcal vaccine experts collaborating with us in model development agreed that these studies should represent the sources of AOM efficacy values in the health economic modeling assessment.

The practice of including assumptions regarding clinical effectiveness not specifically cited in a vaccine’s label is not only widespread in all pneumococcal vaccine models but is also methodologically appropriate because data in vaccine labels can vary from country to country and is often incomplete (7, 8). Criteria to
include vaccine data in the label also differs from usual practice of public health impact and economic modeling.

PHID-CV is licensed in more than 115 countries, and in 58 of those, the vaccine is indicated to prevent NTHi AOM. PHID-CV is also licensed against NTHi AOM in the following Latina American countries: Bolivia, Argentina, Mexico, Chile, Panama. The labeling information of PHID-CV in Peru mentions that it provides protection against AOM at a similar level as observed in the Prymula et al study (33.6%; (11)) completed with the precursor 11-valent vaccine. The labeling information of PCV-13 in Peru also mentions that it provides protection against AOM. Although it mentions there is no clinical trial with PCV-13, the document described the vaccine efficacy observed in PCV-7 trials against AOM (Eskola et al study (6%; (10)). After the assumptions explained in the manuscript to estimate vaccine efficacy against AOM, the overall efficacies of PHID-CV, PCV-13, and PCV-7 against AOM in our analysis were 11.9%, 6.6% and 3.1%, respectively (see Table 2). In our opinion, these results are in line with the available scientific evidence on these vaccines and also with the prescribing information for these vaccines in Peru.

- **Duration of Immunity**

We modeled the duration of vaccine efficacies as previously described for PCVs (2, 36). To simulate how vaccination protection alters over time, the model considers three distinct periods of protection: pre-vaccination, vaccination, and post-vaccination. Individuals of pre-vaccination age (0–2 months) and post-vaccination age (>9 years) are considered to be not directly protected by the vaccine. Those within the vaccination age range (2 months to 9 years) are sub-divided into three additional time periods: an initial ramp-up phase that occurs over the course of vaccine administration (2–13 months), a full efficacy phase (13 months to 2 years) and a waning efficacy phase (2–9 years). We use different duration of protection of 10 years for 3+1 schedule (not in this study) and 9 years for 2+1 schedule. This estimation of waning efficacy was based on the opinion of a board of experts and previous observations of efficacy with PCV-7. To simulate waning over these time periods, the model linearly adjusts vaccine efficacy each month. This assumption is not expected to have an impact on incremental differences between vaccines since the duration of protection is equal for all of them.
Title: Cost-effectiveness and cost utility analysis of new pneumococcal conjugate vaccines in children of Peru

Version: 1 Date: 28 December 2012

Answer to Reviewer: Carlos A Castañeda-Orjuela

- **Major Compulsory Revisions**

1. *Background, last paragraph*...
   We agree with the suggestion and it was modified.

2. *Background, last paragraph (2)*...
   We agree with the suggestion and it was modified.

3. *Methods. The authors should describe better the model.*
   We think the model was adequately described. The reviewer, Lesley Tilson, has mentioned that the study was methodologically sound and well described. We have included additional explanations about the model on this answer to reviewer’s comments, but all of them were taken from previously published studies with the model and all of them are referenced in the manuscript.

4. *Methods. ‘modeling approach’ section, First sentences: does the model only evaluated*...
   Paragraph was modified accordingly.

   We have previously explained the reason for the monthly cycle in our answers to Dr.Tilson. Model inputs are annual incidences described in the Supplemental data file. Monthly cycles were used to assess vaccine efficacy, as previously described (2, 36). To simulate how vaccination protection alters over time, the model considers three distinct periods of protection: pre-vaccination, vaccination, and post-vaccination. Individuals of pre-vaccination age (0–2 months) and post-vaccination age (>9 years) are considered to be not directly protected by the vaccine.

Those individuals within the vaccination age range (2 months to 9 years) are further sub-divided into three additional time periods: an initial monthly ramp-up phase that occurs over the course of vaccine administration (2–13 months), a constant efficacy phase (13 months to 2 years) using full vaccine efficacy as published and described in the manuscript, and a final phase with a linear waning of vaccine efficacy (2–9 years) until efficacy disappears. As mentioned, this modeling of vaccine efficacy was discussed and agreed with experts on PCVs vaccines and modeling during 2007 & 2008 (see Supplemental data file for details in participating experts).

6. *Table 1. Define better the perspective*...
   Table 1 was modified.

7. *Table 1. What is the reference and the values for considering the cross protection*...
   The manuscript mentioned that cross protection was used for PHID-CV and PCV-7. That statement was further clarified including the word “similar”. The manuscript also mentions the rationale to include cross protection in the analysis and the values and reference used for them in the following
sentences: … cross-protection levels of 76% against *S. pneumoniae* type 6A and 26% against *S. pneumoniae* type 19A for PCV-7 and PHiD-CV in ID were assumed, based on Whitney et al. (9).

8. **Table 1. It is not logic that the price of PCV-7 (US$ 20.00) was higher than…**
As previously explained, we have used that price scenario for PCV-7 because that was the last vaccine price for PCV-7 in Peru (in 2010) before the introduction of PHiD-CV in 2011. All of this information was updated in the manuscript so that the rationale for our vaccine price selection is now much clearer.

9. **Table 1. Reference for the immunity duration of 9 years.**
This was an assumption based on expert opinion. The Supplemental data file contains the names of the experts collaborating with us in these definitions. In addition, all these assumption for modeling vaccine efficacy have previously been described and published (2, 36).

10. **Table 1. I suggest that all the parameters and assumptions of the cost-effectiveness and …**
The goal for Table 1 was to describe the assumptions used to generate the base-case scenario analyzed. The parameters used in the model are described in Supplemental information file Tables 1 to 7, and the ranges used for additional analysis are shown in Table 8. It is not possible to include all these information in one unique table. Table 8 was reviewed and completed with information regarding parameter distributions used and some lacking values and references. In addition, these data were obtained in a multi country study mentioned in the manuscript (37) that was presented at the ISPOR Latin American meeting in 2011, was submitted for publication and we expect it to be published before the present one.

Finally, to demonstrate the robustness of the model, sensitivity analysis was undertaken. Each input parameter was systematically varied to quantify its influence over the corresponding predicted outcomes. Mainly, one of three approaches were used to select the ranges of variation: data were varied up and down for all age groups at the same time by ±20% (or ±50%) of the base case value; data were varied to the reported 95% confidence intervals; or a weighted average of studies was calculated to derive suitable values. All these details are presented at the updated Table 8 of the Supplemental data file.

11. **Methods. Model inputs. Epidemiological burden. Supplementary data should be summarized to be presented in the parameters table in the main text…**
We decided to include all these information in the Supplemental data file to be able to detail all data inputs used in order to improve transparency of the manuscript.

12. **Methods. Model inputs. Epidemiological burden. All the information required validation. You should describe better the source information of the occurrence data, and the proportion due to *S.pneumoniae* and NTHi.**
Table 8 of the Supplemental data file was reviewed and completed with information regarding parameter distributions used in the analysis and some lacking values and references. All inputs are detailed in Supplemental file Tables 1-8 with its corresponding references (sources). The detailed process to obtain some of the input was described in a multi country study mentioned in the manuscript (37) that was presented at the ISPOR Latin American meeting in 2011, was submitted for publication during 2012 and we expect it to be published before the present manuscript.

13. **Methods. Model inputs. Epidemiological burden. Last sentence. I do not agree with the estimation**
methods of burden of NTHi. SIREVA data is a passive surveillance system. Although this data presents valuable information, the tendency analysis (with linear regression), based in data from six years is a miscalculation. I think that a better calculation could use a average…

We used data reported by the SIREVA II surveillance system (21) between 2000 and 2005. Gasbastou et al have shown an increase in the distribution of non-typeable strains of *Haemophilus influenzae* (2000-2005). This observation is most probably due to a reduction on the distribution (%) of *Haemophilus influenzae* type b cases after the introduction of the vaccine. We do not agree that using average values will simulate reality better than considering the reported trend. We estimated the relative frequency of invasive disease associated to NTHi in reference to the reported frequency of pneumococcal invasive disease. Based on these data, it was assumed that NTHi meningitis would be equivalent to 8.8% of all pneumococcal meningitis and NTHi bacteremia would be equivalent to 6.1% of all pneumococcal bacteremia. Therefore, the ratio of *S. pneumoniae* to NTHi meningitis was calculated to be 11:1 and the ratio of *S. pneumoniae* to NTHi bacteremia was 17:1. Therefore, the incidence of NTHi ID is estimated by the model based on the incidence of IPD (shown in Supplemental data file) and the previously described ratios.

We did not use 38% as the proportion of ID associated to NTHi. This process generates a scenario of low burden of NTHi in ID as can be seen in Table 2 of the manuscript.

14. Methods. Model inputs. Economic Burden. Why you have a lot of differences between the three sceneries? How many are the proportion of population attended in each scenario?
Please could you clarify your question? The population covered by the 3 vaccination programs is detailed in the manuscript.

15. Methods. Model inputs. Economic Burden. The sequels’ costs are considered annually?
Yes, the sequels costs were considered annually.

16. Methods. Model inputs. Vaccine efficacy assumptions. This section is very har. It not clear the source of the information, the differences between vaccines, and the strength of the information used into the model. It is a important weakness of this version that not collaborates with the transparency of the model.
We specifically dedicated a significant amount of the methods section to explain the assumptions, the values and the references used to simulate vaccine efficacy in our analysis. We have reviewed all the methods section and added further clarifications on specific points. We think we have presented a complete description of all the inputs used and their rationale and corresponding references.

As previously described, we assumed in the base-case analysis that the use of protein D from NTHi as a carrier protein in PHID-CV may offer additional protection against NTHi invasive disease (ID). The vaccine efficacy of PHID-CV against NTHi-associated ID was assumed to be the same as that reported for NTHi-associated AOM (35.3%) (11). This assumption was considered conservative as the vaccine efficacy against ID is usually much higher than vaccine efficacy for mucosal diseases. For example, vaccine efficacy of PCV-7 against IPD (vaccine types) is ~95% (9), while its efficacy against mucosal diseases has been reported to be 57% (pneumococcal AOM) (10, 11). NTHi burden on ID was based on data reported by the previously mentioned SIREVA II network (21). The low burden of NTHi associated ID estimated for the analysis, and the reduced efficacy assumed, limited the potential benefit of the vaccine against this outcome and it is clearly seen in the results section of the
18. Methods. Model inputs. Vaccine efficacy assumptions. Vaccine efficacy against AOM. Why you took the same effectiveness against AOM for PCV7 and PCV13. It is necessary to adjust it by some increase in coverage.

Yes, we used the same vaccine efficacy against covered pneumo types (58%), based on the results of Eskola et al (10), but we used different coverage for each vaccine based on Bardach et al (38). In our analysis PHiD-CV covers 76.2% of the isolated pneumos in AOM; PCV-13 covers 89.5% and PCV-7 covers 69.8%. This information was included in the Table 8 of the Supplementary data file.

19. Methods. Cost-effectiveness analysis. Why did you use different coverage rates to each alternative?

We used different coverage for PCV-7, PCV-13 and PHiD-CV, as mentioned in the methods section. We used a reduced coverage for PCV-7 (83%), as reported by WHO Vaccine-Preventable Diseases Monitoring System for 2010 (39), because the introduction of this vaccine in Peru only lasted for 1-2 years and it was not used long enough to reach the expected coverage for these vaccines in Peru. We used the expected coverage of 95% for PHiD-CV and PCV-13, considering the experience with other vaccines in Peru.

20. Methods. Scenario analysis. Herd effect was equally considered for three vaccines?

Herd effects were evaluated for PHiD-CV as explained in the scenario analysis to show its potential benefits, but were not considered (as previously explained) in the base-case analysis. It was not shown for PCV-13 or PCV-7 as previously explained. No incremental differences between vaccines would occur if shown.

21. Methods. Scenario analysis. What happen if you include a more relevant sceneries like non-effect of PCV-10 against AOM due to NTHi.

The model calculates overall efficacy against AOM based on the efficacy against covered pneumo types, uncovered pneumo types and NTHi. If we do not consider the vaccine efficacy against NTHi AOM its overall efficacy against AOM will be reduced.

Vaccine efficacy against AOM associated to NTHi has previously been detailed. To date, regulatory authorities have thus largely relied on the studies of Eskola et al (10) and Prymula et al (11) in granting indications against AOM protection, and the international pneumococcal vaccine experts collaborating with us in model development agreed that these studies should represent the sources of AOM efficacy values in the health economic modeling assessment.

PHiD-CV is licensed in more than 115 countries and in 58 of those the vaccine is indicated to prevent NTHi AOM. PHiD-CV is also licensed against NTHI AOM in the following Latina American countries: Bolivia, Argentina, Mexico, Chile, and Panama.

The labeling information of PHiD-CV in Peru mentions that it provides protection against AOM at a similar level than observed in the Prymula et al study (33.6%; (11)) completed with the precursor 11-valent vaccine. The labeling information of PCV-13 in Peru also mentions that it provides protection against AOM. Although it mentions there is no clinical trial with PCV-13, the document described the vaccine efficacy observed in PCV-7 trials against AOM (Eskola et al study (6%; (10)). After the assumptions explained in the manuscript to estimate vaccine efficacy against AOM, the overall effectiveness reached with PHiD-CV, PCV-13, and PCV-7 against AOM in our analysis was 11.9%, 6.6% and 3.1%, respectively (see Table 2). In our opinion, these results are in line with the available scientific evidence on these vaccines and also with the prescribing information for these vaccines in
Peru. We do not think that reducing vaccine efficacy against AOM will generate a more relevant scenario. Other studied in our region have used similar assumptions and considered a greater efficacy against AOM for PHID-CV than PCV-13 (35, 40).

22. Methods. Were did you take the QALYs weights. Do you have national weight to evaluate preferences in this population? I think that in developing countries where the population have a important mortality due to infectious disease the analysis with years of life saved (YLS), or disability adjusted life years (DALYs) are better options.

Peru does not have a set of health state values to assess the health-related quality of life preferences of its population. The utilities sources to calculate QALYs are referenced in the Table 7 of the Supplemental data file. We are using the same utility values used in many other cost-effectiveness analyses of PCVs. It is widely accepted to use international utilities when local ones are not available. The high mortality associated to infectious disease in developing countries has no differential effect in the QALY or DALY calculation. Although DALYs are widely used in health economic analysis, they were originally developed for other types of study. QALYs are the traditional indicator used in health economic analysis when considering quality of life, they are widely accepted in all countries and we prefer its use due to the intrinsic limitations of DALY calculation on pediatric diseases when age adjustment is required.

23. Result. Table 2. If the time horizon was the life expectancy why you only show the results of the fist ten years?. How are the result after the first 10 ten years?

We are showing the impact of the vaccine on disease and economic burden before 10 years of age because vaccine efficacy is zero after that date and no vaccine effect is observed after that point. As this is a cohort model, reporting vaccine impact on the disease/economic burden after a lifetime would not modify the number of cases averted but would modify the total number of cases. As a consequence, the percentage of cases averted would not adequately show the potential impact of the vaccination program.

In contrast, the total cost and QALY calculations require considering a life expectancy time horizon. These differences are clearly indicated in the Tables.

24. Results Tables 3, 5, and 6. Why are different between the QALYs and YL averted reported in table 3 and the values used to construct the ICER. Is it related to difference in the observation period (life expectancy vs. 10 years period), or using discount rates?

No, the QALYs & LY are reported for the life time horizon in all tables. Table 3 contains undiscounted data (as it is mentioned in the footnote), while Tables 5 and 6 contains discounted data as it is required for ICER calculation.

25. Results Tables 5 and 6. Why the LYG are higher than QALYs to each vaccine. If LYs are considered within the QALYs the avoided burden considering QALY should be higher.

Our cohort lives (discounted data) 12,988,553 LYs without vaccines and 12,992,507 LYs with PCV-7 (3,954 LYs gained). This calculation does not include quality of life (QoL). Perfect healthy life equals 1 in QALY calculation and any disease will decrease that value. One year of life suffering a certain disease can value 0.8 (as an example) instead of 1 (1 being equal to perfect life). Therefore, our cohort lives (discounted data) 11,586,536 QALYs without vaccines and 11,590,206 QALYs with PCV-7 (3,670 QALYs gained).

26. Results. Costs. All the costs should correspond to the same base year. You have treatment cost in 2009 currency and vaccine prices in 2012 currency.
We generated treatment cost for Peru by microcosting, in 2009 Nuevos Soles. We estimated the cost of different outcomes in the public health sector, the EsSalud sector (social security system for the salaried population) and the private sector. Finally, we weighted average these costs using the reported coverage for each health system.

The costs of PCV-13 & PHiD-CV are from 2012 because that was the 1st year both vaccines were available at the PAHO RF with published costs. Only PHiD-CV was available in 2011. The cost of PCV-7 was from the PAHO RF 2010 because that was its last year of its availability.

We could have inflated the treatment costs to 2012 using Consumer Price Index to be aligned with international guidelines. The CPI measures the price of a particular set of goods and services through time. It is not sure that changes in the price of this basket will reflect accurately the inflation of prices from the health sector, and it is even more difficult to estimate if the inflation rate is similar for the different health sectors analyzed. As we were unable to identify more detailed data like health-sector specific indices of inflation, and we have only 3 years differences (2009-2012) with low inflation rates in Peru, we prefer to use nominal values for the analysis knowing that our decision would generate a scenario less favorable for the interventions being evaluated.

27. Results. Cost utility and cost-effectiveness analysis. The approach of reporting the results of each possible pairwise comparison is not appropriate. The comparison of all vaccines against no vaccination is not appropriate. The 4 strategies (no vaccination, PCV7, PCV10, PVC13) are mutually exclusive and should be assessed together in the ‘competing choice’ framework. Tables 5 and 6 should be reconstructed using this logic. You should arrange the alternatives of the lesser to most costly (using net costs) and the columns would show Total Cost, Total Effect (QALY or LY), Incremental Cost, Incremental Effect, and Incremental Cost-effectiveness Ratio (where the incremental values are compared to the next most effective EFFICIENT strategy. When one intervention is more costly and less effective it should not be included in the comparison.

We have ordered the different studied alternatives in Tables 5 & 6 from the ones with less health effects (less QALYs gained) to those with highest health effects. There is no unique way to present the ICER calculations tables. Both methods are very well accepted in the scientific literature and the final results for the ICER calculations are totally similar. We prefer to rank the interventions based on their health effects because we think that the most important consequences of a vaccination program are aimed to improve health.

The second part of tables 5 and 6 (columns 7-9) analyze both PCV-13 and PHiD-CV as mutually exclusive interventions in a competing choice framework, as suggested. We do not include PCV-7 in this analysis because this vaccine was already introduced in the EPI program of Peru (2009-2010) and later withdrawn for the market. Therefore, PCV-7 was not a competing intervention for PCV-13 & PHiD-CV, but it was the reference scenario. That was the reason to use the PCV-7 as the reference scenario for the competitive analysis of PCV-13 and PHiD-CV. Incremental costs and QALYs/LYs are compared to the next most effective strategy to estimate the ICER, as suggested. Minor modifications were included in Table 5.

In addition, we think it is valuable to present the ICERs of all these vaccines (including PCV-7) in comparison to the “no vaccination” scenario. These data are presented in columns 4, 5, and 6. It will be useful for authorities to see the ICERs of each vaccine against the scenario without any of these interventions. These ICERs demonstrate that all these vaccines are highly cost-effective interventions in the PAHO RF vaccine price environment. Even PCV-7 is a cost-effective intervention at PAHO RF
prices for Peru and this was not the case for the initial international health economic analysis completed for this vaccine.

These 2 tables (5 & 6) contain a lot of very useful information for authorities. ICERs of the competing new vaccines (PCV-13 & PHiD-CV) versus the current standard (PCV-7); ICERs of each vaccine versus the no intervention scenario and all of them are presented with and without considering the effects of vaccines over the quality of life. These are valuable tables and minor changes were included following your suggestion.

28. Result. Sensitivity analysis. Did you have sensitivity analysis by each parameter by each vaccine?, because in Figure 1 you report parameter to all vaccine together, and it is important to evaluate the sensitivity by vaccine, especially when exits uncertainty at the vaccine level.

Yes, we have performed SA for all parameters for each vaccine. Figure 1A shows the analysis for PHiD-CV and Figure1B shows the analysis for PCV-13.

29. Discussion. The authors need to review more widely the literature about the health economic evaluation in countries similar to Peru (i.e. Castañeda-Orjuela et al. / Vaccine 30 (2012) 1936–1943, Sartori, et all J Epidemiol Community Health; 2012 Mar;66(3):210-7, Muciño-Ortega et al, Value Health, 2011 Jul-Aug;14(5 Suppl 1:S65-70, and Ureña et al. Vaccine. 2011 Jul 12;29(31):4963-72, interalia), to compare your model and results. With the additional review the authors could make a strongest discussion about the validity and implication of their results.

We agree with the suggestion and included it in the discussion of the manuscript.

30. Discussion. Additional more in depth discussion is required about the validation of the model parameter and results, You could compare your data, obtained by the model, with the official records, for example with the mortality report by syndromes considered.

We have reviewed the discussion as suggested. We used the official records to estimate the mortality rates used in the analysis (input data).

31. Discussion. The authors should considerer that based many parameters obtained by experts opinion, does not guaranty the validated of their results and it is not mention in the discussion as a limitation of the study.

We have reviewed the discussion as suggested.

- Minor Essential Revisions

1. Title: It should be: Cost-effectiveness and cost-utility analyses of three pneumococcal conjugate vaccines in children of Peru, because the study present 2 analysis, and the PCV-7 isn't a new vaccine.

Title was modified as suggested

References


24. Joint Committee on Vaccination and Immunisation (UK). Pneumococcal sub-committee. Minute of meeting on Wednesday 30 May 2012. 


vaccine-eligible children in Finland. 31st European Society for Paediatric Infectious Diseases. May 28 to June 1 2013, Oxford, UK


