Author's response to reviews

Title: Cost-effectiveness of Pediatric Pneumococcal Conjugate Vaccines: A comparative assessment of decision making tools

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Author's response to reviews: see over
Dear Editors,

We would like to thank the Reviewers for their useful comments and suggestions.

Please find below our point-by-point response to the concerns and comments of the reviewers. Enclosed you also find a revised version of the manuscript in ‘tracked-changes’.

With best wishes,

On behalf of my co-authors

Raymond Hutubessy
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Point by point response to Reviewer’s report

**Reviewer 1 (John Grabenstein)**

*Major revisions*

1. page 5

We have adopted the list as proposed by the WHO Guide for standardization of economic evaluations of immunization programmes on page 6 i.e model structure, attributes, input parameters and key assumptions.

Both in the background (p5 we have inserted “input parameters”) and results sections (p8-11, headings to each paragraph are added) we have applied the list consistently.

2. WHO reference 37

As laid out in the manuscript overall three models adhered to the WHO Guide.

An exception might be the lack of discounting in the SUPREME model. The model developers justify a 0% discounting rate since a population model focuses on the immediate and important benefits (such as herd protection and serotype replacement due to vaccination) across different age groups making up the whole population at the time of the assessment (see p. G34, Standaert et al. 2010 (reference 38 in the manuscript)).
3. Page 15

The strengths and limitations of each model are listed and summarized in the discussion section. Several are listed below.

- As pointed out on p14 the SUPREMES model may be useful for budget impact analysis and requires less data inputs and easier to use but the user needs to agree with several implicit assumptions embedded in the modeling approach.

- Or as stated on p13, each model evaluates different vaccines: PneumoADIP assessed the CE of PCV, TriVac assessed the CE of PCV, Hib and rotavirus vaccines while SUPREMES appraised PHiD-CV.

- In terms of user-friendliness on p15 it is stated that all models do not provide a manual to the tool but that: “The TriVac model has an advanced user-friendly and self guided function enabling users to properly interpret the research findings.

Minor revisions

1. Title

On p1 the title has been revised to “Cost-effectiveness of Pediatric Pneumococcal Conjugate Vaccines: A comparative assessment of decision making tools”.

2. Abstract

On p3 we have added twice “national pediatric immunization programmes” in the abstract.

3. Acronyms

Acronyms have been spelled out as indicated by the reviewer.

4. Abstract, results, correct syntax in first parenthetical remark

We are not sure what the reviewer wants us to correct.

5. Page 6

S is removed from inputs parameters.

6. Page 6 last sentence:
We have added the following sentence on p7:

“A cohort model focuses on the accumulated benefit over time for individuals within the cohort, whereas for the population model the focus is on the immediate benefit across different age cohorts making up the population at the time of the assessment”.


Yes, SUPREMES varies every parameter +/- 20%.
PneumoADIP allows for manual changes which in fact means that the user needs to re-run the model for each scenario.
TriVac has default min and max values if the user does not provide input parameters for sensitivity analysis

8. Page 10, middle and upper paragraph.

They all apply to PneumoADIP.

9. Page 10, last sentence

We have taken out the sentence as it is not applicable anymore.

10. Page 13, Discussion, paragraph 1, line 5

We suggest to use the word “data needs”.

We agree with the reviewer that different model results are not only because of differences in assumptions and inputs. We acknowledge this further in the discussion section where we state that:

“differences between models are not only due to the approach and data requirements, but are difficult to distinguish without a fully transparent user manual”

11. Page 13, Discussion, paragraph 2, line 5: add a clause about why fewer data inputs are needed – is it because the model already assumes them implicitly?

Aggregate population models require fewer input data because the model approach evaluates the impact of an intervention in the population across different age cohorts at one cross-sectional time period under static conditions. We amended the text accordingly on p14 as follows:
The latter model evaluates under static conditions an entire population at specific time point using the total population size and its specific age distribution to estimate the impact of a new vaccine program on total population health during a fixed time period (usually 1 year) and therefore requires fewer data inputs.


We have revised the sentence accordingly.

“users would need to agree with several implicit assumptions embedded in the modeling approach.”

13. Pages 13-14

Redundant text spanning has been removed.


We meant to say for the comparison exercise we have used the August 2009 version of each model. Since the evaluation was done models have been updated and revised.

On p14 we have added: “since the evaluation in August 2009”

15. References

Special characters have been corrected

16. References need additional details

17. Table 3

We have added the following footnote to Table 3:

“default means the outputs using the pre-defined model inputs. Standardized means the outputs using the standardized model input”

18.

p23 Influenza has been corrected in influenzae.
p25 (in years) behind life expectancy at birth has been added
p25 case fatality has been corrected in fatality
Reviewer 2: Maria Hortal

- Abbreviation in title (PCV) has been deleted from the title
- Abbreviations and acronyms has been clarified in the text
- *H Influenza* has been corrected (see also minor edit nr 18 from reviewer 1)
Reviewer 3: Maarten Postma

- Page 7:
  “a” has been replaced by “one”

- Page 13

We have explained why the SUPREMES model does not allow for discounting.

*For the SUPREMES model, discounting was not allowed as population models evaluate the impact of interventions in the population across different age cohorts at one cross-sectional time period [1]*

- Page 7

As the SUPREMES model is a population based model we wanted to point out that the modeling approach chosen by its developers (who in turn were motivated by the decision to be informed) is an influential driver to the results hence might explain the difference between SUPREMES and the other models assessed.

Furthermore, the model developers informed us that they also had developed cohort model with consistent results compared to the population model. However, at the time of the evaluation the cohort model was not publicly available.

- Page 7

The model developers only provided access to their tool and explained the modeling framework to the investigators (also stated on p6 in the method section). They were not actively involved in the actual modeling comparison exercise (i.e. the WHO consultants (NC and RS) ran the standardized data sets and scenarios using their models) and not involved in the data analysis nor writing up of the manuscript.

Therefore, we are of the opinion that it is appropriate to mention them in the Acknowledgements section.
Reviewer 4: John Kim Andrus

- We have added the following sentence in the conclusion of the abstract.

…and provide analysts and decision makers with a more in-depth view behind the disease dynamics. Adherence to the WHO guide of economic evaluations of immunization programmes may also facilitate this process

- The sentence on p5 now runs as follows:

The availability of a 7-valent pneumococcal conjugate vaccine (PCV7), which is efficacious in preventing IPD, pneumonia, and Acute Otitis Media (AOM) [2-4], has prompted policy makers to ponder whether or not this vaccine should be included in the national immunization program.

- We did provide the SUPREMES modelers with a standardized data set. However, it was not straightforward for the model developers to adapt the data intended for cohort models in a population based model, however they managed.

- Halloran et al [5] distinguishes direct and indirect effect of the intervention. The direct effect of an intervention in an individual receiving it is the difference between what happens with the intervention and what would have happened without the intervention, all other things being equal. The indirect effects of an intervention program are the protective or detrimental effects that are mediated by intervention-induced changes in transmission. Indirect effects result from the dependent-happening structure of events (1) of many infectious diseases, where the number of persons becoming infected depends on the number of persons already infected. One way an intervention program can have indirect effects is by changing the immunologic status of a population of hosts with respect to the organism of interest. This collective immunologic status is called "herd immunity."

We therefore have rephrased the sentence as follows:

This assumes the benefits of herd immunity in both vaccinated (direct effects) and unvaccinated (indirect effects) people. The PAHO TriVac model assumes indirect effects only within the cohort that is targeted for vaccination.

- We tried to point out that PneumoADIP model was the only model that did not include default values for disease burden estimates, while the other two models provided default values. This might place burden to users to find values for the model. In fact, input values used in all models need to be justified regardless of the availability of default values.
• This comment might be covered by the major comment nr 3 of Reviewer 1.

We believe that the reviewer misunderstood. In fact, we stated clearly in our text that “Trivac allows to make an explicit direct adjustment for serotype replacement over time”. In addition, our statement was consistent to Table 1.

Reference List


5. Halloran ME, Haber M, Longini IM, Jr., Struchiner CJ: Direct and indirect effects in vaccine efficacy and effectiveness