Author’s response to reviews

Title: Effectiveness of Pneumococcal Conjugate Vaccination against Invasive Pneumococcal Disease among children with and those without HIV infection: A Systematic Review and Meta-Analysis

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Author’s response to reviews:

Dear Editor,

We greatly appreciate the editorial team for providing us the opportunity to resubmit our manuscript. We also deeply thank the reviewers for their valuable comments and constructive criticisms that we believe have resulted in a substantial improvement of our manuscript.

Point by-point responses to the reviewers, comments are provided below. We hope we have adequately addressed all issues raised by the reviewers.

Yours Sincerely

To Aran Singanayagam (Reviewer 2):

1- The major concerns are with lack of clarity in writing. For example, in the abstract, the authors state that 'the effectiveness of PCV against IPD among HIV-infected children is much less limited in real situation and even it might increase overall incidence of IPD. This is not a particularly clear sentence or conclusion. Why do the authors think the vaccine might increase IPD? What do they speculate could be the reason for this, if it is true?
Thank you so much for this comment. We revised manuscript for more clarification accordingly.

In the abstract, as there was no space to justify (word limitation up to 250) and discuss why PVC vaccination may result in an increase in the overall number of IPD cases in HIV-infected children, we replaced our conclusion with the following:

Unlike the evidence on the efficacy of PCV against IPD among both of HIV-infected and HIV-uninfected children, its effectiveness against IPD among HIV-infected children is much less limited.

However, in briefs, increase in the overall (all serotypes) number of IPD cases among PCV vaccinated HIV-infected children may be due to increase in the number on IPDs by non-vaccine serotypes (but not vaccine serotypes) as a consequence of serotype replacement. In addition, in the real situations, vaccination may lead to a type of false assurance. Such false assurance could result in lower levels of efforts to protect the vaccinated HIV-infected children from exposure with pneumonia agents.

On the other hand, this increase in the overall number of IPDs have been reported by some of the primary studies which are included in our analyses (following a repeatable systematic method), and we have to pool these results and present the pooled estimate.

2- In general, the manuscript needs to be improved in terms of clarity and precision. Meta-analyses can be rather dry in subject matter, but regardless of this, the authors do not do a particularly good job of writing this in a way that will be of interest to a general infectious diseases reader. Particularly with the results section, they need to more carefully and clearly describe the reason for the analyses/sub-analyses carried out and give more justification to make it easier and more interesting to read.

Thanks to you for this. We try to revise the manuscript for more clarification and justifying some parts of applied methods along with their results. Accordingly, the results section divided into several sub-sections and then following sentences added in the revised text in the methods or results sections:

In the method section:

Considering the well-evidenced issue of the probability of serotype replacement after the PCV vaccination, and also to show if the efficacy and effectiveness of the PCV vaccination is depended on the IPDs’ causative serotypes, meta-analyses were done in three subgroups including IPDs caused by all serotypes (AT IPD, showing the overall results of the PCV vaccination); IPDs caused by vaccine-serotypes (VT IPD, showing the results of the PCV
vaccination only against serotypes which are included in the PCVs; and IPDs caused by the non-vaccine serotypes (NVT IPD, showing the results of the PCV vaccination against IPDs which their causative serotypes are not included in the PCVs, in this case if the efficacy or effectiveness be a negative value it may be an evidence of serotype replacement).

In addition, as the results reported by the RCTs show estimates of the vaccine efficacy, while reported results by the observational study show estimates of vaccine effectiveness, all serotype-based subgroup meta-analyses were repeated according to the subgroups defined based on the study design (pre-post, case-control, and RCT).

…

As in the meta-analysis studies a crucial criterion for doing meta-analysis is a relative homogeneity of the observed primary effect measures (in this study efficacy and/ or effectiveness), we assess homogeneity of the primary effect measures. In a simplified word, homogeneity means that the sampling population of each of the included primary studies is adequately similar with the sampling population of the other studies. Meta-analysis of effect measures from studies with different sampling populations results in an apple-orange juice.

…

Meta-regression is a technique to identify determinants of differences between the sampling population of the primary studies (i.e. heterogeneity).

…

In the results section:

(showing that meta-analysis is not justifiable in this subgroup),

…

showing that meta-analysis is justifiable in this subgroup.

…

(factors which may be the underlying causes of different sampling populations of the included studies).

…

showing that meta-analysis is justifiable in each of these subgroups).
(as a determinant of vaccine efficacy/ effectiveness).

...(vaccine valency is an important determinant of the PCVs efficacy and/ or effectiveness, as the preventive effect of typeable PCVs is a function of the serotypes added in the vaccine).

3- The discussion section requires some improvement - the authors need to more clearly state the importance/implications of the findings and relate to existing literature/concepts more coherently.

Thank you so much for this comment. We revised manuscript for this. Following sentences added in the discussion section, focusing on the application of our results.

Accordingly, improvement in the accessibility and utilization of the routine healthcare available for HI children in addition of extending the range of such services may be measures to increase the PCV effectiveness among this population.

...This probable serotype replacement may be a result of a type of false assurance after vaccination, and then a reduction in the healthcare provided for HI children, and consequently more exposure with NVT serotypes. Therefore, it is necessary to healthcare provider and care-givers of HI children be aware about this type of false assurance.

...However, it may be an indicating evidence on the need of booster doses to increase the vaccine effectiveness among older children.

...Accordingly, it seems that increase in the valency of the PCVs may not be a single effective measure to prevent the IPDs and it should be belong with other interventions.

...

To Albert Gabarrus, MSc (Reviewer 3):

4- Page 11, 1st paragraph. Results in the text should be referenced to corresponding figures, i.e. -6.2% (95% CI: -67.6, 32.7) (Fig 2), 65.1% (95% CI: 47.3, 76.9) (Fig 3), etc.
Thank you so much for this comment. We revised manuscript for this.

5- Fig 2 to Fig 5. In Fig 2 the VE% 95% CI is wrong, it should be (-67.6, 32.7) instead of (32.7, -67.6). On the other hand, if the percentage of efficacy or effectiveness and their 95% CI are reported in the text (page 11, 1st paragraph) it would be better to delete them from the figures in order to not duplicate information.

   Thank you so much for this comment. We revised figures for this.

6- Also in figures I would suggest to replace the last column name ES (95% CI) by the specific OR (95% CI) or RR (95% CI).

   Thank you so much for this comment. We revised figures for this.

7- And why you do not report the % weight in these figures.

   Thanks to you for this comment. As there was no influential observation and for more simplicity (less statistical presentation of the results) statistical weights were deleted. However, as our data is available for readers, ones could see these weights if she is interested.

8- Finally the title of these figures should include "Forest plot of …".

   Thank you so much for this comment. We revised manuscript for this.

9- All these comments are also applicable from online Fig 1 to 12.

   Thank you so much for this comment. We revised online supplementary file for this.

10- Page 14, 2nd paragraph. (online Fig 12-18) should be (online Fig 13-18).

   Thank you so much for this comment. We revised manuscript for this.
Page 14, 2nd paragraph. Despite the results of Egger's test showed lack of publication bias, it would be interesting the inclusion of the funnel plots as online figures for a visual examination.

Thank you so much for this comment. We revised manuscript and online supplementary file for this. Online figures 19- 24 added in to the online supplementary file.