Author's response to reviews

Title: Do pneumococcal conjugate vaccines provide any cross-protection against serotype 19A?

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RESPONSES to REVIEWERS’ COMMENTS

Reviewer Hanna Maria Nohynek

MAJOR COMPULSORY REVISIONS

1. As suggested by the reviewer, we now provide the incidence of 19A IPD before and after PCV-7 in the US (p.3, penultimate paragraph, in Background).
2. As suggested by the reviewer, the table now includes the absolute numbers of 19F and 19A cases and the numbers of subjects where applicable. In addition, the subjects, case numbers, and vaccine efficacies of each of the 4 studies included in the cited metanalysis are now listed in Table 1 separately as well.
3. As suggested by the reviewer, Table 2 now includes the absolute numbers of 19F and 19A colonized individuals and numbers of subjects. Confidence intervals are provided where available from the papers.
4. When referring to reference #13, we now provide the timing of the doses and when the NP sampling was taken (2nd paragraph of the Discussion).

MINOR ESSENTIAL REVISIONS: The 3rd bullet point was deleted due to other reviewer comments.

Reviewer Shabir Madhi

MAJOR COMPULSORY SUGGESTED REVISIONS

1, 2. As suggested by the reviewer, the abstract (Discussion portion) has been modified to note that protection of 19F-containing vaccines against 19A is modest and not statistically significant, and that no impact on 19A colonization has been seen.
3, 9. As suggested by the reviewer, the summary of the abstract now states that the magnitude of the public health benefit of the modest cross-protection against 19A from PCV7 would be dependent, in part, on the magnitude of the disease burden occurring when the protection is expected to occur (after the booster dose). This theme is also mentioned in the Conclusion on pp. 6-7, noting that a vaccine providing some protection after the primary series might offer more protection for this reason, and is further captured in the third and fourth bullet points of the Summary at the end.
4. Following the reviewer’s suggestion, Table 1 is now split into sections, separating IPD from AOM for the conjugate vaccines, as well as a third section with the single study of the polysaccharide vaccine (reference 34). Although the reviewer questioned inclusion of this latter study in the table, we have maintained it because we believe it is very relevant to the principle of the paper (that 19F-containing vaccines may provide clinical protection against 19A disease), as antibodies to the 19F polysaccharide capsule are presumably mediating cross protection whether the vaccine is a free polysaccharide or conjugated. Of course, with conjugates T-cell help is involved too.
5.7. As suggested by the reviewer, the paper now explicitly states that it is the “onset” of the rise in 19A which correlates with the shortage of 7vCRM in 2001 and 2004, but that the rise indeed continued for several years (p.5). We also note in the conclusion that the limited activity was insufficient to prevent or reverse the net rise in 19A disease in the US (p.6). The reviewer also suggested to include in the table a later summary of 19A IPD vaccine effectiveness from the US than the Whitney paper; however, as the focus of the paper is on the potential for direct protection by the vaccine against 19A disease, we only chose to include in Table 1 (and Figure 1) the initial analysis of vaccine effectiveness against 19A rather than those assessed several
years later when additional elements, such as herd impact, secular trends, antibiotic forces etc, may be at work. As noted above, the later summaries are however discussed throughout the text.

6. We had considered conducting a formal meta-analysis, but as is now noted in the Methods section we felt there were too many methodological and design variables between the studies to fairly conduct one, including, efficacy vs effectiveness endpoints, different vaccines, different dosing regimens, etc.

8. We now explicitly note that ELISA—as well as the OPA mentioned in the paper—does correlate with clinical effectiveness (p.5).

10. We agree with the reviewer that the effect of any other vaccine formulation on 19A colonization can’t be predicted, although in the absence of clear correlates of protection it remains unclear how much antibody is really needed—recent unpublished data may suggest that the levels are lower than commonly assumed. To highlight the uncertainty of protection, we now include in the conclusion a sentence explicitly noting that whether other vaccines offer any cross-protection against 19A colonization remains unknown (p7).

Reviewer Shally Awasthi
MAJOR COMPULSORY REVISIONS:
1. Abbreviations in Table 1 were expanded, as requested.
2. As now explicitly noted in Table 1 (and its legend), the meta-analysis only covered 4 efficacy studies, while there are also other efficacy and effectiveness studies needed to be included in a systematic and fulsome review.

MINOR ESSENTIAL REVISION
1. On page 2 (abstract summary) and page 6 (conclusion) we now explain that antibiotic selection pressure may increase colonization of antibiotic-resistant strains, including (but not limited to) antibiotic-resistant clones of 19A.
2. On page 5 (lines 7-8) we now highlight that contradictory colonization effects have been reported even within the same study site (US Navajo Apache), further supporting the lack of a consistent effect.

DISCRETIONARY REVISION
1. We removed this sentence from the summary point (although it continues to be discussed in the discussion section). The observation that the only detectable functional antibody seen with 7vCRM occurs after the booster dose is what led us to speculate that after the booster dose is when efficacy is most likely to be apparent.
2. We removed this statement from the summary, as requested.
3. We now state in the methods why a formal meta-analysis was not done (see response to comment 6 of Referee Madhi).