Reviewer's report

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

Version: 2 Date: 25 August 2009

Reviewer: Shabir A Madhi

Reviewer's report:

This review centers around determining whether cross protection exist against serotype 19A by including serotype 19F in PCV. The manuscript is generally well written, however should consider providing a more balance perspective in relation to small-modest cross protection that is evident against serotype 19A largely argued due to occur primarily following a booster dose of PCV containing 19F. This needs to be interpreted and discussed in the context of that the greatest burden of 19A pneumococcal disease in most settings occur in children prior to them being eligible for a booster dose of vaccine. As such, apparent lack of evidence of cross protection against 19A in studies where a booster dose of PCV was not included, is unlikely to have an influence on the public burden of pneumococcal disease from serotype 19A in children.

- Major Compulsory Suggested Revisions

1. Abstract (2nd line under discussion)- suggest indicating clearly in the abstract that whatever cross protection is apparent against 19A is small-modest and not statistically significant.

2. Include statement in abstract on of lack of effectiveness against 19A colonization.

3. Summary of abstract should include that perceived dependency upon a booster dose for modest cross-protection against 19A has limited public health benefit as would miss the greatest burden of disease.

4. Table 1: Would suggest that the table be clearly split into two sections, i.e one dealing with PCV and 19A IPD and the other with PCV and 19A associated AOM. Additionally, its unclear why reference 34 has been included, as it add little to the debate on PCV containing 19F vaccines protecting against 19A disease. The inclusion of this study with 19F polysaccharide vaccine has little to add to the debate, considering how different the immune responses are to PPV and PCV vaccines.

5. Ref 19- suggest that this data be updated with more recent data available form the USA effectiveness study which show that disease from 19A has actually increased in the USA in vaccinated children, compared to baseline.
6. Consider including a meta-analysis (separately for IPD and AOM), despite the inherent biases based on the type and numbers of available datasets to look at 19A cross protection.

7. Pg 5 Line 1-2: need to include that the trend in serotype 19A increase has continued beyond the time point when there was vaccine shortage and the increase remains significantly greater compared to pre-vaccine incidence rates.

8. Pg 5 line 15: the suggested threshold of OPA titre >=8 correlating with clinical effectiveness is a further extension of the putative serotype-specific antibody concentration presumably associated with community-protection against IPD. This needs to be clarified.

9. Pg 6: 3rd line conclusion: need to tighten up to that possible cross protection against 19A disease is likely only to occur in children after they receive their booster dose of PCV, which will have diminished public health benefit in settings where the bulk of pneumococcal disease occurs during early childhood.

10. Pg 7 line 3: the potential effect against 19A colonization by non-CRM PCV vaccine formulations need to be qualified. This would include that the concentration of antibody required to prevent colonization is likely to be greater than that required to protect against IPD. Accordingly, considering the lower GMCs associated with a formulation such a PHiD-CV, this or any other vaccine with lower GMCs would require substantially higher quality of antibody to induce such cross-protection against 19A colonization.

**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:**

Reviewer is associated as follows to GSK and Wyeth: 1. received honorarium; 2. on speakers bureau; 3. acted as consultant; 4. received research support