Author's response to reviews

Title: Does a 10-valent pneumococcal-Haemophilus influenzae protein D conjugate vaccine prevent respiratory exacerbations in children with recurrent protracted bacterial bronchitis, chronic suppurative lung disease and bronchiectasis: protocol for a randomised controlled trial

Authors:

KerryAnn F O'Grady Dr (k.ogrady@uq.edu.au)
Keith Grimwood Prof (k.grimwood@uq.edu.au)
Allan W Cripps Prof (Allan.Cripps@griffith.edu.au)
Edward K Mulholland Prof (kim.mulholland@menzies.edu.au)
Peter Morris Prof (peter.morris@menzies.edu.au)
Paul J Torzillo A/Prof (paul.torzillo@sydney.edu.au)
Nicholas J Wood Dr (nicholW3@chw.edu.au)
Heidi Smith-Vaughan Dr (heidi.smith-vaughan@menzies.edu.au)
Andrew Wilson Prof (andrew.wilson@health.wa.gov.au)
Amber Revel Ms (amber_revel@hotmail.com)
Peter vanAsperen Prof (peter.vanasperen@health.nsw.gov.au)
Ruth Thornton Dr (r.thornton@meddent.uwa.edu.au)
Sheree M Rablin Ms (s.rablin@uq.edu.au)
Anne B Chang Prof (anne.chang@menzies.edu.au)

Version: 3 Date: 8 July 2013

Author's response to reviews: see over
05 July 2013

Editorial Board
Trials

Dear Editors

**Re: Submission of revised manuscript (M1050286566896608)**

Please find attached our revised manuscript following receipt of the peer review report. We would like to thank the reviewer and Trials for giving us the opportunity to improve our manuscript and have it considered again for publication.

Please refer to the below point-by-point response to concerns as raised by the reviewer with direct reference to the relevant sections of the revised manuscript (attached). We would like to raise with the Editors some difficulty we had with the reviewer’s comments. Many comments focussed strongly on ear disease and data from healthy young children that are not directly applicable to children with chronic lung disease. This led to an increase in length of the manuscript with respect to the background and discussion that, given the focus of a protocol paper is on the methods, may not have been necessary.

We would also like to note that since this manuscript was submitted, an amendment to the protocol has been undertaken and approved by the relevant ethics committees. This relates to increasing the upper age limit from < 12 years to less than 15 years and removing the requirement for prior PCV7. Both of these were consequent to a review of our recruitment and aim to increase the potentially eligible pool of children at the recruitment centres. These changes have been applied to the manuscript in track changes.

On behalf of the all the authors I would like to thank you for considering this application and I look forward to your response. Please do not hesitate to contact me via email (k.ogrady@uq.edu.au) or by phone (+61 7 3636 1296).

Regards,
Detailed responses

Editors comments

1. **Manuscript title to be amended to match journal requirement**: the title has been amended as requested

2. **Please specify the exact practical steps for randomization**: steps for randomization have been specified in the manuscript (track changes, page 10)

3. **Consider using negative binomial regression for the primary analysis**. Thank you for suggesting we review the analysis plan. We have discussed with our study biostatistician and the independent biostatistician on our Data Safety Monitoring Committee, who both feel the primary analysis should remain as currently described given our primary outcome measure is based on the count of exacerbation episodes over that time. While we agree with your comments about negative binomial regression, we feel this can be a secondary analysis that can incorporated into our data analysis plan with an aim of examining any differences that may be observed in our results using the two approaches.
Reviewer comments

1. Past reports on PHiD-CV efficacy on NTHi. As discussed in our paper, there are no data on the efficacy of this vaccine or its prototype in children with chronic/recurrent disorders of the airways in older children. However, although not directly applicable to children with chronic diseases of the lower airway we have expanded our background to include the most recent data available on vaccine efficacy (VE) on NTHi nasopharyngeal (NP) carriage and aquisition in older children, and the recently released data from the COMPAS study in South American children (Page 6). We emphasise that while the data are important with respect to carriage, the implications of these findings with respect to older children and those with chronic lung disease are unknown, providing further impetus for our trial. We have expanded on this issue and many of the related comments the reviewer made in the Discussion, starting at page 17 and ending on page 19.

2. Include the Veenhoven study: we have not included the Veehoven study as suggested given the more recent data provided from the studies mentioned above. The issue of acquisition, serotype replacement and changes in the NP micro of other bacterial pathogens has also been addressed in the detailed additions to the discussion starting on page 17.

3. Acquisition of new strains & van den Bergh paper. Addressed in the introduction via the additions to page 6 and in detail from page 17 to 19. In addition we have also included recently published adult data from people with chronic lung disease on responses to Hi antigens, suggesting diminished immune responses and hence the possible need for boosting with an effective vaccine to prevent acquisition of new strains (page 17). We emphasise the dearth of data examining the relationship between the nasopharynx and lower airways in children and adults with chronic lung disease and how the data from otitis media cannot be used as a proxy for that association.

4. Difference between PHiD-CV and oral vaccines: We have addressed this in the introduction (page 5) and also added that PD is only one of a number of Hi antigens being assessed as potential vaccine candidates (page 6). We acknowledge that the vaccine may not have any effect and hence the study was conceived and designed on the principles of genuine equipoise, however we believe this adds weight to the need for our study as the first step in establishing “proof of concept”. We have stated the best evidence
needed to answer many of the questions the reviewer has raised in the last paragraph of our discussion on page 19 and highlighted the evidence for using vaccine trials as probe studies to address questions relating to the relative contribution of specific bacteria to clinical disease.

5. **Last paragraph of reviewers comments.** We believe that all of these points relate to issues already raised above. We have added to the introduction and expanded the discussion considerably to address these concerns. With respect to the priming of children with PCV7, we have since removed that requirement from the study protocol and prior PCV will be dealt with in the analysis. Given randomisation, it is likely that there will be no important differences between vaccine groups that may confound VE estimates.