Author's response to reviews

Title: Otitis media in children vaccinated with either 7-valent or 10-valent pneumococcal conjugate vaccines: a cross sectional comparison

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Author's response to reviews: see over
We are very grateful to both of the reviewers for their detailed scrutiny of our article. We agree with the suggested revisions and have substantially re-written the paper. A statistician has assisted with the multivariate analysis and we believe the paper is substantially improved, thank you again to the reviewers for making this point.

REVIEWER ONE

MAJOR COMPULSORY REVISIONS

1) In the current form I would not accept the main finding of differences between the vaccination programmes (see below). The current main finding would be the sustained high morbidity despite vaccination programmes.

We agree that the main finding is the sustained high morbidity in this population, first line of Abstract conclusions “Otitis media remains a significant health and social issue for Australian Indigenous children despite PCV vaccination”, and main Conclusions “Our study identifies ongoing high rates of ear disease and other infections in Indigenous children living in remote regions.”

2) Title: This is not cross-sectional comparison, but a comparison of two different consecutive PCV vaccination programmes with data collected in cross sectional design.

We have changed the Title: “Otitis media in children vaccinated during consecutive 7-valent or 10-valent pneumococcal conjugate vaccination schedules”

3) Mainly the text is clear and well-written, but the whole manuscript is not at the level of extreme carefulness needed for manuscript submission as there are several typos and poorly phrased sentences, see below for some examples.

See below for corrections to typos and improved phrasing

4) Risk differences are mainly reported in statistical analysis. First, in cross-sectional design the concept of risk is not fully valid due to lack of follow-up time. Therefore, prevalence is suggested instead. Second, only risk (=prevalence) differences are reported. Prevalence ratios would also be interesting, even though differences would be regarded as the primary analyses.

We have included a univariate and multivariate analyses to provide Odds Ratios for the estimate of PCV effect, and other measured factors, on suppurative OM.

5) There are a multitude of variables collected and reported in the study which might (partly) explain the differences in addition to or instead of the two different vaccination programmes:
a. age distribution of participants  
b. vaccination schedules (3 PCV + PPV23 vs. 3+1 PCV) and number of doses actually received  
c. impact of the PPV23  
d. season of data collection (not reported)  
e. gestational age, birth weight  
f. other health problems, respiratory symptoms  
g. prior antibiotic use  
h. number of children in household  

Therefore, multivariate analysis would be recommended or a justification for univariate analyses only. A statistician’s review would be highly recommended.

We have included a multivariate analysis as suggested and confirmed the approach with our statistician, Mr Mark Chatfield who has agreed to be a co-author.

6) If the primary aim is to compare the different vaccines as the exposure, then restriction of data analysis to children with equal number of vaccine doses without any additional vaccines would be clearer for the reader. Is this possible? Now the table 1a gives a very complicated mix of the exposure in the two groups.

We include an analysis of children having received a non-mixed schedule of either PCV7-alone or PHID-CV10-alone. The results are very similar. Table 1a is indeed complicated, but this is the reality of our data from this particular period of surveillance.

7) The main findings of the study presented in table 2a are the different designations for the OM outcomes; i.e. more AOMwoP in the first group and more OME in the second. However, this is highly dependent on the subjective otoscopical assessment. Therefore, more emphasis on the description of this assessment is needed in the methods. The value of the assessment would be higher if there had been elements of objective assessment, blinding etc. Furthermore, AOMwoP is defined as bulging but no symptoms are required contrary to the most common definitions for AOM. Lastly, in case the definitions were defined a priori and not post hoc would be important to report.

We have provided definitions of all OM diagnoses and combination categories which are consistent with the Office of Aboriginal and Torres Strait Islander Health Guideline “Recommendations for Clinical Care Guidelines on the Management of Otitis Media in Aboriginal and Torres Strait Islander Populations.”

Almost all children have a type B tympanogram, so we are dependent on otoscopic assessment to discriminate between OME (flat or retracted TM) and AOMwoP (bulging TM).

L140: Our assessments were made using a tympanometer (Grason Stadler GSI 38), a LumiView (Welch Allyn) with Siegel’s speculum for pneumatic otoscopy, and a video-otoscope (Welch Allyn macroview or MedRx video-otoscopes).
The video can be re-run to confirm the diagnosis, so we are confident that AOMwoP can be discriminated from OME.

We report the proportion of children with ear pain, this is around 6% overall. Whilst a greater proportion of children with bulging or perforated TMs report pain (11%), the sensitivity is poor.

L168: We have included a statement regarding the a priori status of our clinical definitions.

**MINOR ESSENTIAL REVISIONS:**

**ABSTRACT**

Abstract methods: data collection dates have been added

“We conducted standardised surveillance of OM in children in remote Indigenous communities between September 2008 and December 2012.”

Abstract results: we have clarified as follows

“Multivariate analyses confirmed a strong and independent negative association between suppurative OM and PHiD-CV10 compared to PCV7 (Odds Ratio = 0.58 [95%CI 0.41 to 0.80] p=0.001). Additional children in the household were a risk factor for OM (OR = 2.42 [95%CI 1.5 to 4.0] p=0.001 for the third additional child), and older age and male gender were protective. Other measured risk factors were non-significant. Similar clinical results were found for children who had received non-mixed PCV schedules.”

**INTRODUCTION**

**Row 91**, pre-introduction data for OM morbidity is cited in the Abstract Background and has been published - reference [1]. We have changed the text in the Introduction to read

“Community based surveillance pre- and post-introduction of seven-valent pneumococcal conjugate vaccine (PCV7) indicates that less than 10% of Australian Indigenous children living in remote Northern Territory (NT) communities have normal middle ears and around 20% have tympanic membrane perforation, TMP (either acute otitis media with perforation (AOMwiP), dry perforation (DP), or chronic suppurative otitis media (CSOM)).[1, 2]”

**METHODS**

**Row 122: Study dates** are clarified as follows: This report includes cross sectional data from 25 communities participating in the later years of PCV7 and/or first years of PHiD-CV10 between September 2008 and December 2012.
Row 138: “Overarching” – overarching refers to the whole of surveillance inclusion criteria. We clarify this by removing “overarching” and adding “For this report we limit analysis as described below (Statistical analysis).” This section now reads “Inclusion and exclusion criteria” Aboriginal children between 0 and 6 years of age, resident in participating communities, and whose parents or carers provided signed consent, were eligible for surveillance. For this report we limit analysis as described below (Statistical analysis).”

Row 146: “voroscope” is a locally used term which refers to the name of the Australian, Dr John Vorrath, who invented the prototype called Vorotech, of the Welch Allen LumiView. Text has been changed to “a voroscope LumiView (Welch Allyn LumiView).”

Row 155: Data collection for antibiotics – This refers to the action taken by research staff for children assessed during the survey. “Antibiotics and other treatments or referrals were provided to participants according to local guidelines.” This would include both topical and systemic antibiotics.

Handling of missing data:
Row 154: Under General health measures: “We categorised ‘not sure’ as absent.” Unsure refers to data collected by research staff if they were unsure of the presence of a general health problem. In this instance we considered unsure to be absent, rather than missing.

Row 203: “Missing data: Where participants declined a clinical assessment, a swab or an interview question, or were unsure, the data were coded as missing. Missing data were then excluded from the denominator for summary statistics.” “Unsure” refers to a response by the carer to an interview question. In this instance we considered unsure to be missing, rather than absent.

Row 208: Funding: We have added the years to indicate relative contributions. “The study was funded by the Australian National Health and Medical Research Council (project #545232) for the years 2008 to 2010, and by GlaxoSmithKline for the years 2009 to 2012.”

RESULTS

Row 214. Were there recurrent visits by some children?
Yes there were repeat visits of the same child and these were included in the original analysis if the time between visits was more than 120 days. However this revision has been undertaken with repeat visits excluded. To be more explicit in the results, we suggest the following section be added:

Row 213: “Participant exclusions and PCV vaccination status (Table 1): We enrolled 1,027 children and made 1,088 child visits. Only the first visit per child is included in this analysis. Forty one children had received PCV13 only. We excluded a further 91 children on
the basis of their vaccination status; 33 children who had not been vaccinated, 25 who had only a single dose of one or both vaccines, 30 children who had received 2 doses of each vaccine, two children who received two doses of PCV13, and one child who had received two or more doses of more than one PCV. Of 895 children in this analysis, 444 were in the PCV7 group and 451 in the PHiD-CV10 group. All had received two or more doses of appropriate vaccine and less than one dose of any other PCV. Most children had received 3 or more PCV doses.”

**Row 223:** We have also added the following to clarify the season of data collection “**Region and communities:** All communities were in the tropical Top End region of Australia. Visits were made each year between early February and mid-December, the majority being the between April and December, during the dry and pre-cyclone season.”

**Row 233 and throughout:** Where appropriate, RD is replaced by Difference and the unit added.

**Row 286** “**Comparisons restricted to 3 dose recipients .. were almost identical...**”
We have further restricted the comparisons to recipients of non-mixed PCV schedules and added these data to Table 2a. The text has been changed to clarify the comparisons.

“Comparisons of OM prevalence between recipients of non-mixed PCV schedules showed almost identical differences in prevalence of OME (RD = 12% [95%CI 5 to 20] p=0.001), any suppurative OM (RD = -16% [95%CI -24 to -8] p<0.0001), and any TMP (RD = -3% [95%CI -8 to 3] p=0.41) as were seen for the primary comparisons of recipients of at least 2 doses of PCV and less than 2 doses of an alternative PCV (Risk Differences of 10%, -12% and -3% for OME, any suppurative OM and any TMP, respectively).”

**Row 303:** Failure to undertake multivariate analyses
We have included univariate and multivariate analyses of risk factors for any suppurative OM, including vaccine type (Table 4).

**DISCUSSION**

**Row 326:** During the PCV era has been added.

**Row 309 (now 363)** Reason for low compliance
The reasons for non-consent to the risk factor questionnaire were not sought from participants.

**Row 322 It is not known whether compliance outside .. not self explaining.**
We have removed this comment.

End of Discussion – introduce RCTs mentioned in the abstract.

**Table 1:** Query: PPV23 not included
We have included PPV23 vaccinations in Table 1a, and Row 293 to 297: “PPV23 was received by 138 children in the PCV7 group. Compared to 39 age-eligible children in the PCV7 group who did not receive PPV23, there was no significant association between PPV23 and suppurative OM, although TMP was significantly more common in the PPV23 group (24%) than the non-PPV23 vaccinated group (8%) (RD 16%, 95%CI 5 to 27) p=0.026”).

Table 2a and 2b

Table 2a “Participant characteristics, by vaccination group”
General Health data moved from Table 3a to Table 2a.
Any skin problem has been removed to reduce confusion – multiple concurrent skin conditions were found, in 15 PCV7 children and 30 PHiD-CV10 children.
The denominators for numbers of children assessed for cough and runny nose, or who had a recent haemoglobin test result, are now provided separately, rather than a range of denominators.

Table 2b “OM risk factors, by vaccination group”
No. children consented has been changed to No. parents consented

Table 3a: Query: Columns do not add up due to combination categories.
“Table 3a: Prevalence of otitis media including combination categories of any suppurative OM, any TMP, and any pain, by vaccination groups.”
I have added a Sub-Title “Combination OM categories”.
The numbers are
150+27+40 = 217, and 111+24+34 = 169 for AOMwoP + AOMwiP + CSOM = any suppurative OM
27+8+40 = 89, and 24+5+34 = 63 for AOMwiP + Dry Perforation + CSOM = any TMP.
I have also added results for bilateral OME and unilateral OME (as requested by reviewer 2), and for the parental question regarding ear pain (under category).
I have added a Sub-Title “Non-mixed PCV schedules” to Table 3a
Results of the comparison between children receiving PCV7-only and PHiD-CV10-only have been added.

Table 3b: Prevalence of any suppurative OM in each age group, by vaccination group.

Table 4. Univariate and multivariate analyses of risk factors among 380 children with and 459 children without suppurative OM (AOMwoP, AOMwiP and CSOM), adjusted for community.

REVIEWER TWO
MAJOR REVISIONS

Abstract, page 2, line 61. A definition of OM is beyond the word limit of the abstract, however we have used the term “all forms of OM” to inform the reader that we acknowledge the complexity of the diagnosis. We provide definitions under our METHODS section.

Abstract, page 2, line 67. The increase of OM with effusion should be included in the Results and also in the discussion without citing again the numbers.

We have added prevalence of OME to the Abstract (Line 68) and Discussion (Lines 341) and Conclusion (Line 408),

Methods, page 5, line 130: Were parents asked to have their child examined if he/she was ill? Or independently from his status?

We have changed the wording to reflect our target population being all eligible children. “Consent was sought from parents of all children less than 6 years of age (regardless of ear health status or history) for their child to have an ear examination, nasal swab, swab of ear discharge if present, and general child health check.

Methods, page 7, line 154. AOM: any bulging without any symptom would be AOM? If this is the case, then this type of AOM does not equate the definition of AOM of most guidelines, including the latest AAP 2013, which includes also “mild bulging of the TM and recent onset of ear pain or intense erythema of the TM”.

The Australian Guidelines for OM in Aboriginal and Torres Strait Islander populations define AOM as “the presence of fluid behind the eardrum plus at least one of the following: bulging eardrum, red eardrum, recent discharge of pus, fever, ear pain or irritability.” This is due to research that identified a very small proportion of children present with ear pain, despite the high prevalence of TM perforation. In this cohort, the child’s ear pain was reported by 51 of 745 (7%) parents/carers (Table 3a)

Methods, page 8, line 183. No questions about the father habit to smoke? And why was the information regarding TMP asked only for the mother and the siblings?

Information about paternity is considered sensitive, the father is often not spoken of and is rarely present at research visits. Even when mothers were asked about their own ear health history, 70% were unsure, so results of this question could not be used. We have since expanded our questions on smoking to include household members, indoor and outdoor smoking, smoking near the child.

Results, page 11, line 269. “97% had at least one ear successfully assessed”. Does this mean that if only one ear was checked and this was normal then the other one was considered normal as well? Or if the assessed ear was pathological, then the other one was pathological?
Yes to both these questions. We have added two rows to Table 3a to indicate that 27(6%) children in the PCV7 group and 13 (3%) in the PHiD-CV10 group had a diagnosis based on unilateral examination.

And how much severe?
Of the 40, 5 (13%) were normal, 17(43%) were OME, 14 (35%) were AOMwoP, 1 (2%) was a child with AOMwiP and 3(7%) had CSOM.

In other words, how was the “other” ear considered?
The other ear was considered to be no better and no worse than the examined ear.

How many were the children with both ears checked?
92%

Were all the children having one normal ear considered to have with normal bilateral ears?
Yes, if only one ear was assessed. This was the case for 5 children.

If the children with a bilateral assessment were only few, then stating that “less than 10% had bilateral normal middle ears” seems to be inappropriate.

We made bilateral assessments in 92% children; 5% had unilateral assessments and 3% were not assessed.

Results, page 11, line 278. It would be interesting to know if OME was bilateral (more severe) or unilateral (mild). The comment about the increase of OME should be modified accordingly.

We have added data to Table 2a that shows that there was no difference in the prevalence of unilateral OME whereas there was a significant increase in bilateral OME in the PHiD-CV10 group compared to the PCV7 group. Please note that laterality of OME could only be determined where bilateral assessments were successful.

Results, page 11. Why a multivariate analysis was not performed regarding risk factors?

We have included a multivariate analysis (Table 4) which confirms a significant independent association of PHiD-CV10 with a reduction in prevalence of suppurative OM. Age and number of children less than 5 years of age in the household were also significant independent predictors of suppurative OM.

Discussion, page 13. The lack on nasopharyngeal sampling has to be included as a limitation. NP carriage will be reported in subsequent paper.

Table 2a : a column with p value should be added.
We have added a column for reporting the differences and the p value.

MINOR REVISIONS

Abstract, page 2, line 66. Prevalence … “were”. I would say “was”. This has been changed.
Abstract, page 2, line 64. Most … I would replace with “most relevant”. The sentence has been removed.
Abstract, page 3, line 72. I would say “combined” and not “combine”. This has been removed.

Methods, page 7, line 167. Why were 5 weeks chosen (instead of the usual 4 or 2 weeks)?

We have used 5 weeks in previous studies, so it provides a consistent comparison when comparing data over these time periods. The reason for 5 weeks is because Indigenous children are often on longer courses than usual, so prescription within 5 weeks provides the time required for a longer course to have been completed.

Methods, page 9, paragraph on Ethical approval and funding. The first sentence is a repetition of the sentence included in the first paragraph of the methods. The sentence of funding could be included also in the first paragraph.

We changed this paragraph to Funding, and the years funded by the two sources are provided. “The study was funded by the Australian National Health and Medical Research Council (project #545232) for the years 2008 to 2010, and by GlaxoSmithKline for the years 2009 to 2012.”

Table 1a and 1b. The % sign close to the numbers in the column might be deleted because it is included at the top of the column.

We have de-cluttered the Tables, but have left the % symbol – we would remove this if the journal require it.