Author's response to reviews

Title: Non-capsulated and Capsulated Haemophilus influenzae in Children with Acute Otitis Media in Venezuela: a prospective epidemiological study

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Author's response to reviews: see over
Sirs

BioMed Central Editorial

BioMed Central Infectious Disease Journal

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Dear Editors,

We were glad to receive your e-mail of January 13th, 2012 stating that our manuscript entitled “Non-capsulated and capsulated Haemophilus influenzae in children with acute otitis media in Venezuela: a prospective epidemiological study” has the potential to be published in The BMC Infectious Diseases Journal provided that some aspects are improved.

The authors appreciate the constructive comments and have attempted to modify the manuscript as requested within the limits of the study objectives. Wherever possible, we have made the changes and corrections suggested by the reviewers. Please find attached the revised version (with changes highlighted in yellow for your convenience) of the manuscript as well as a document containing our point-by-point answers to the comments made by the peer-reviewers.

We hope that the manuscript can be accepted for publication in The BMC Infectious Diseases Journal in its present version.

Yours sincerely,

LAURA NARANJO MD.
Point by point responses to peer-reviewers:

**Reviewer 1:**

1. Main objective of this study was related to investigate the epidemiology of AOM in Venezuelan children. Nonetheless, it looks like that authors waited for results to choose the title (capsulated and noncapsulated H. influenzae). Title seems more commercially than academically driven wording.

**Answer 1:** The selected title highlights the results that are the key info to share with the scientific community. Previous studies reported non-capsulated *Haemophilus influenzae* as a prevalent agent for otitis media. Our results showed the role of other capsulated types previously not reported in other studies in the region.

2. Study was conducted in a private setting of central Venezuela. It is important to underscore this setting because epidemiological results could not apply necessarily to a more public pediatric population. Many differences can be involved. Variables include antibiotic use/abuse, day care attendance, breastfeeding rates, smoking habits, number of siblings, PCV7 and Hib vaccination availability, etc.

**Answer 2:** Agree, the discussion section has been updated to reflect this study corresponded to private setting in the discussion and potential limitations for data interpretation.

3. Besides the speculation of prior PCV7 use to explain predominance of *H. influenzae* over *S. pneumoniae*, age of enrolled children could be another factor. Mean age of subjects was 28 months, period in which NTHi AOM has been shown to be more frequent.

**Answer 3:** A clarification was included in the results explaining that most of the cases (over 40%) enrolled in the study were in children in under 2 years of age, and the results were consistent noting that *H. influenzae* was the most prevalent agent in all age groups except in 3-11 months were it was equally distributed as with *S. pneumoniae*.

4. Finally, but very relevant, authors should moderate business-oriented conclusions. I suggest, therefore, to reduce the enthusiasm in stating that PHiD-CV will covered 36% more of causing pathogens (55% vs 19%) than PCV13. First, because in the POET study, the PHID-CV prototype vaccine had an efficacy against NTHi of only 35%. And second, because protection against a membrane Hi protein D, does not warrant protection against capsulated Hi strains (capsule would impede antibody action against protein D).

**Answer 4:** The text was changed and we are presenting now the potential episodes targeted by available vaccines in the discussion, but noting that neither clinical efficacy nor effectiveness data against AOM are available for either PHiD-CV or PCV-13, and that studies with the precursor conjugate vaccines (PCV-7;11-valent pneumococcal protein D conjugate PHiD-CV predecessor vaccine) have demonstrated efficacy of <100% against the targeted pathogens.
Reviewer 2:

5. The English expression is poor and most of the manuscript is written in passive voice. The combination of these two factors leads to constant confusion and ambiguity

Answer 5: The text was modified and updated to active voice

6. The results report on details not described in the methods. I recommend and explicit approach, such that authors list the data to be collected. Data were collected include “gender, age, clinical presentation symptoms, clinical samples”. Similarly, the statistical test used to obtain p=0.38 is not described, was it a chi square, if so, this needs clarification in the methods.

Answer 6: Methods section was updated to be consistent with the results and discussion. Also we provided further details on statistical analysis done.

7. Table one can be removed and just referenced, table 2 can be removed and the findings included in text. Of note, the mean with standard deviation are reported in data are normally distributed (these do not appear so), else median and range, this can be summarized in text easily. The gender differences are insignificant, a brief note could be added in the text or an asterix * to figure 2. Figure 5 can be removed.

Answer 7: Table 1 & figure 5 were removed and table 2 (now it is Table 1) was maintained as suggested by editors, but providing age distribution of the AOM episodes

8. One major finding was that there was no Hib. This is valid as confirmed vaccine failure has resulted in Hib deaths in recent years, and there is growing fear that this trend is growing.

Answer 8: As indicated in the text, Hib was not identified in any subject enrolled. This is consistent with the Hib vaccination coverage in the subjects enrolled (>95%). Also, the discussion was updated indicating Hib is not a common etiologic agent for OM and potential reasons for this

9. The discussion is too short and does not synthesis the information adequately, this section needs more literature (international) bought in for discussion with these study results.

Answer 9: Discussion section was updated comparing these data with international literature in the region but also in Europe and US> Limitations section was updated as well.

10. Minor: the vaccine schedule for Venezuela is not discussed in the introduction, this needs to be added.

Answer 10: Introduction was updated indicating that PCV is not included in UMV, only in private setting. Hib vaccination is included in UMV. Reference was included.
11. The format of the methods and results sections needs to be reorganized and perhaps synchronized for ease of reading.

**Answer 11:** The format was reorganized and synchronised with results as suggested by the reviewer