Author's response to reviews

Title: A prospective study of urinary pneumococcal antigen detection in healthy Karen mothers with high rates of pneumococcal nasopharyngeal carriage

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19th March 2011

Dr Liang Chen, BMC Infectious Diseases

Dear Dr Chen,

Re: MS 6631497675088183: A prospective study of urinary pneumococcal antigen detection in healthy Karen mothers with high rates of pneumococcal nasopharyngeal carriage

We thank the editor and reviewers for their constructive comments on the version of the above manuscript. We have ensured that the revised manuscript is formatted correctly and include a point-by-point response to the reviewers concerns here.

Reviewer 1 (David Murdoch):

Minor Essential Revisions:

(1) The use of the chi-squared and Fisher's exact tests are mentioned in the methods section, yet it is unclear whether any data has been analysed in this manner. Similarly, it is not apparent which continuous data are presented as median and IQR. Some of this information may have been carried over from another paper.

Response: We apologize for the errors in the statistical analysis section: we did indeed analyse some of variables by chi-squared or Fisher’s exact tests in a previous draft, but these analyses were dropped from the final version of the paper. The mother’s ages are described by the median and range. We have amended this section of the manuscript accordingly.
(2) Should "odds" really be "odds ratio" in the results section?
Response: Yes, we have amended the text to “odds ratio” in both the abstract and the results section.

(3) The data in Table 1 need not be repeated in the text.
Response: We have removed the duplication as suggested (results section).

Discretionary Revisions:
(1) The company producing the BinaxNOW test has recently changed again to Alere. The authors may wish to include this detail.
Response: We agree that this information will be useful for readers and have added this detail in the background section.

Reviewer 2 (Yanan Zhao):
Minor Essential Revisions
(1) Unlike other studies on evaluation of the BinaxNOW S. pneumonia urinary antigen test, this study was assessing the performance of this commercial kit in healthy adults with higher S. pneumoniae colonization rate instead of pneumonia patients. It is an interesting way to look at the false positivity caused by the nasopharyngeal colonization, however, it also creates problem of comparing results with studies performed in patients with pneumonia. Because of the different choice of study population, the diagnostic test parameters have different meanings. For instance, the specificity in this study means the possibility of getting a true negative diagnosis on person who is neither having pneumonia nor colonized with S. pneumonia. The same term might mean differently, as the possibility of obtaining the negative diagnosis when the person does not have pneumonia but is possibly colonized with S. pneumonia, in another study performed in pneumonia patients. Thus, be cautious about this difference posed by the study population difference. Where such comparison is made (eg: page 7, the second last line), please make the transition by using the correct calculation or state the difference to avoid the implicity.
Response: We agree that comparison of specificity results should be done cautiously since we focused entirely on the relationship between urinary antigen detection and pneumococcal nasopharyngeal colonization rather than disease (pneumonia). However given that colonization is an essential requirement for subsequent infection (either mucosal or invasive) the test specificity might not be dissimilar between the two groups. The study of Boulware et al included 63 non-pneumonia controls (46 HIV-negative and 17 HIV-positive), one (HIV-positive) control had a positive BinaxNOW test (i.e. 2% false positive rate overall, 6% within the HIV positive sub-group). We have added this control group false positive data to the discussion: “This 3% (95% CI: 0 – 9%) false positive rate is similar to that found in the systematic review and prospective study of Boulware and colleagues, who reported an overall specificity of 94% (95% CI:
93-95%) for adult pneumonia diagnosis and a 2% false positive rate (1/63) in their non-pneumonia controls (17 HIV positive, and 46 HIV negative).

(2) The number of positive BinaxNOW test in this study is really low largely due to the specific study population. Such a small number might explain that authors did not observe any significant association between colonization and positive urine antigen test. As the postulation of this study is sensitive to the sample size, please explain how the sample size was determined.

Response: We assumed that 30% of participants would be colonized by S. pneumoniae, based on our overall cohort carriage data, which documented a pneumococcal carriage prevalence of 27% in mothers when their infants were 12 months old (the mothers were sampled for the BinaxNOW evaluation when their infants were >12m of age). Based on published specificity data from pneumonia diagnostic studies and healthy infant carriage studies, we estimated that there would be a 5-20% false positive rate in the BinaxNOW test. Therefore, we expected to see between one and six positive BinaxNOW test results with a sample size of 100 women, assuming that false positives were only seen in those women colonized by S. pneumoniae. Whilst this sample size would lead to wide confidence intervals if the lower false positive rate were true, we felt that this sample size was reasonable since the data on BinaxNOW performance in pneumococcal colonized adults is extremely limited and data from colonized children suggested that a higher rate of false positives might be seen. The 3% false positive rate we found still has a relatively small 95% CI (0 – 9%), suggesting that our sample size was not unreasonable.

We have now included a specific comment regarding sample size in the discussion: “The main limitation of our study was the relatively small sample size: we may have missed a small association between pneumococcal colonization (particularly if this is related to colonization density) and a positive BinaxNOW test as a result of the small numbers of positive urinary antigen tests in our participants. Further studies, either a larger study in our population or in a setting with an even higher prevalence of adult pneumococcal colonization, are warranted to confirm our findings.”

(3) I would suggest authors to modify this manuscript as a note instead of a full article due to the abundance of the data. Or else, more substantial data should be included, such as the association between colonization density and the false positivity of the BinaxNOW test.

Response: We agree with the reviewer that our study was small, however we feel that the findings are robust and enough for a standalone publication. Since we did not test infant urine specimens by the BinaxNOW test we could not formally test our colonization density hypothesis. Although the “note” format might better suit this manuscript, this does not seem to be a format supported by BMC Infectious Diseases, whose readers we feel would be an appropriate target audience for the paper.
The authors should also describe the limitations of this study in the context, eg. small sample size.

Response: Answered above (Reviewer 2, Comment 2).

We hope that these modifications will be satisfactory to both the editor and reviewers.

Yours sincerely,

Dr Paul Turner