Author's response to reviews

Title: High incidence of pulmonary tuberculosis in children admitted with severe pneumonia in Uganda

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Author's response to reviews: see over
To: Dr Jose Ricardo de Mello Brandao  
Journal Editorial Office  
BioMed Central

Dear Sir,

RE: RESPONSES TO REVIEWERS COMMENTS ON ARTICLE TITLED “HIGH PREVALENCE OF PULMONARY TUBERCULOSIS IN CHILDREN ADMITTED WITH SEVERE PNEUMONIA IN UGANDA”

Below are my responses to the reviewer’s comments

Reviewer: Stephen Graham

Minor Essential revisions
1. Background. line 5 page 1. Pneumonia mortality is not ”50%” in Africa - what you mean I think is that in Africa there is 20% of the world's children but African children account for 50% of all child pneumonia deaths globally.

Response: This sentence has been edited to reflect the correct figures.

2. Results. It is very unusual to have positive blood culture for M.tb from children. This is a novel finding esp the 5 month old. Was there anything remarkable about these two cases in terms of likelihood of heavy bacillary disease or amount of blood actually taken for culture?

Response: There was only one child aged 5 months that grew mycobacterium from the blood culture. There was nothing remarkable about this child. The child had had cough for 14 days, was HIV exposed but Negative, had moderate malnutrition (Z score -2.5), no household smear positive contact and no physical findings suggestive of disseminated disease.
3. Discussion. Too long when comparing to other studies. Note that they were all from South Africa - Zar (3); Moore (16), Madhi (17) and McNally (5) - because availability of culture. Note that McNally may have had a higher TB (and HIV) prevalence but that study had selection bias in that it was a study of severe "treatment failure" cases i.e. those not responding to first-line antibiotics so one might expect a different prevalence of unusual pathogens.

Response: I have looked at the discussion and merged some of the sentences to make the discussion more precise.

Reviewer: Alok Kumar

Major Revisions
1. Results
   a) was there any difference in the results of the blood counts such as total WBC counts OR the differential WBC counts among those who had TB and those who did not have TB?

Response: We did not show that data but there was no difference between the two groups; e.g mean WBC : 13,680 in PTB Vs 14,299 in No PTB, p = 0.8. Lymphocytes; 6567 in PTB Vs 7178 in No PTB, p=0.4. I have included the data in the revised manuscript.

b) was there any difference in the chest xray finding among children who had TB as compared to those who did not have TB?

Response: Yes. The was a significantly higher proportion of children with abnormal chest Xrays among TB cases compared to those without TB. I have reflected this data in the results text.

c) was a blood culture or other cultures to exclude coexisting bacterial pneumonia in these children with TB?

Response: we did blood cultures for mycobacteria only. we did not assess for presence of other micro-organisms.

d) was there a way to exclude Pneumocystis jiroveci pneumonia in children who had HIV and Tb coinfection?

Response: We did not investigate for Pneumocystis jiroveci pneumonia due to limited financial resources. Otherwise there is a way we could have determined PjP.

2. Discussion
Page 8 line 5 through 10
a) Authors have argued that the access to ART may have been a possible factor for the reduced incidence of Tb seen in this study. How many of the children with confirmed or probable Tb and HIV coinfection were on ART in this study? It will be nice to have the data on the immune status and the therapy data including any prophylaxis in those children who had HIV coinfection.

Response: 41 children were HIV positive. 14 had PTB and 27 had No TB. Only 1 of the 14 TB cases was on ARVs while 6 without TB were on ARVs. None was on INH prophylaxis. We did not obtain information on cotrimoxazole prophylaxis. I have included this data in the results text.

Minor revisions
1. Methods
Line 3 - HIV seroprevalence of 10.6%,
   a) does the author refer to seroprevalence in the entire population or the childhood population? if it is for the entire population ten what is the seroprevalence among children?

Response: This is sero-prevalence in the general population. I have corrected the rate to 8.5%. The sero-prevalence on childhood population below 5 years in the study area is estimated at 2.2%. I have added this information in the manuscript.

Line 8 - pneumonia admissions accounting for 20%,
   b) 20% of what, all the pediatric admission? or all the admissions at that hospital?

Response: this refers admissions in the paediatric emergency unit. This has been clarified in the manuscript.

2. Results
Page 6 Line 11 - 17 children had culture confirmed Tb,
   a) In 2 children Tb was cultured from blood and in one Tb was cultured from both the blood and the sputum, was in the remaining 14, Tb cultured from sputum? Author should mention the culture medium in the remaining 14 children.

Response: All the 14 had positive TB culture from only sputum. The manuscript has been edited to reflect this clarification.

3. Discussion
Page 8 Line 9
“Our study was however not designed to establish the prevalence of culture confirmed Tb in children admitted with severe pneumonia” So what was the objective of this study. I think this need to be clearly explained in the methods section.

Response: the statement was intended to mean that we were not powered enough to determine culture confirmed prevalence. Our definition of a TB case included clinical diagnosis cases. The manuscript has been edited to clarify this. Otherwise our study met its intended objective.

Reviewer: Paulette Douek

Major Compulsory Revisions
1. The objective cannot be to establish the prevalence of TB, a priori, the cases of TB in treatment were excluded. One suggestion would be to use "ratio of diagnosis made for pulmonary TB,” rather than prevalence.

Response: I do appreciate the observation. I have edited the manuscript to reflect that these are newly identified cases by using incidence ratio.

2. It would be interesting to discuss whether there was any bias due to cases excluded for being in TB treatment (17) or not having achieved a sputum sample (19) and from the 15 lost ones.

Response: we acknowledge that the exclusion due to failed sputum and the lost results could have influenced the results. We did not intend to study children already on TB treatment but rather new cases where delay in TB treatment is likely to occur. We believe that these results would only have a modest influence on the final estimation assuming 50% positivity in all the samples. This explanation has been included in the manuscript.

3. Table 1 - It would be important to put the absolute number of children in each age group.

Response: I have included the absolute numbers.

4. Table 1 - I think it would be interesting to calculate the percentages of the features shown, according to the total number of children in each age group.

Response: There is no missing data for the all the features shown. I have edited to include the total population. The percentages are according to the groups shown.

5. Missing the summary.
Response: I presume this was the abstract. An abstract has been included in revised manuscript.

Minor Essential Revisions
1. In the first paragraph, the data is reported as being from 2010, but the reference cited is from 2006.

Response: This has been updated to reflect the 2011 WHO TB Report.

2. It would be interesting to put the reference for "WHO / STOP TB strategy".

Response: Reference inserted in the manuscript

3. Figure 1 - The 58 cases were excluded from the 343 children aged 2 to 144 months and not the 1432 children with pneumonia, therefore, the arrow is in the wrong place.

Response: this has been appropriately edited.

4. Table 1 - The second column refers to children aged 1 to 5 years (and not from 1 to 4 years).

Response: Thank you. I have edited in the manuscript

5. In the second paragraph of Results, there are 51 children (instead of 54), with pulmonary TB.

Response: I have edited in the manuscript.

6. Note the reference years for numbers: 13, 14 and 16.

Response: All the years for the references inserted in the manuscript.

7. Start the title of the Table 3 in capital letters.

Response: I have edited accordingly.

Discretionary Revisions
1. As a suggestion, include a list of abbreviations used in the text.

Response: I have ensured abbreviations are written in full the first time they are used in the text.