Author's response to reviews

Title: Childhood Tuberculosis and its treatment outcome in Addis Ababa: a 5-years retrospective study

Authors:
Dereje Hailu (deramass@gmail.com)
Woldaregay E Abegaz (woldearegay.erku@aau.edu.et)
Mulugeta Belay (mulg2002@yahoo.com)

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Authors’ response to Reviewers’ comments

Childhood Tuberculosis and its treatment outcome in Ethiopia: a 5-years retrospective study

Dereje Hailu¹, Woldaregay Erku Abegaz², Mulugeta Belay²*

¹Dereje Hailu, Addis Ababa Health and Research Laboratory, Addis Ababa, Ethiopia, P.O.Box 30738
email: deramass@gmail.com

²Woldaregay Erku Abegaz, Aklilu Lemma Institute of Pathobiology, Addis Ababa University, P.O.Box 1176, email: woldearegay.erku@aau.edu.et

²Mulugeta Belay, Aklilu Lemma Institute of Pathobiology, Addis Ababa University, P.O.Box 1176, email: mulg2002@yahoo.com

*Corresponding author: mulg2002@yahoo.com
Dear Editor,

We thank the reviewers for reviewing our manuscript critically. We have addressed the comments given by the reviewers. Besides, a point-by-point response to each comment has been provided (in blue) in this cover letter. We hope we have addressed the concerns raised by reviewers.

**Reviewer: Alan Altraja**

1. What this study adds to the pre-existing knowledge in this area of TB?
   Rationale for the study has been included and the introduction section has now been expanded.

2. The first two large paragraphs of the Materials and Methods section („Diagnosis and treatment of TB among children in the study area“ and „Study area“) do not entirely represent „methods“. Although proper description of the background is important for this kind of studies, the Materials and Methods section should be shortened by placement of most of the descriptive contents into the Introduction. This has been corrected as suggested.

3. Did the study cover the entire Addis Ababa? How does this reflect the situation in the whole country?
   This study included all health centers providing TB treatment for at least one year. The majority of TB patients are treated at health centers but hospitals do also provide TB treatment to a lesser extent. We believe those treated at health centers represent children with TB in Addis Ababa. However, it is difficult to propose that our findings could be generalized to the country as a whole.

4. Standard definitions of the Ethiopian NTLCP guidelines were used in this study. Why were not WHO definitions used? In the sub-section „Definitions for treatment outcomes (FMOH, 2008):“ , the definitions are given in full. However, the full definitions can be deemed redundant if correct references were used in the former sub-section.
The Federal Ministry of Health of Ethiopia adopted WHO definitions and the reason we cited this reference is because diagnosis as well as treatment is implemented in the country according to the country’s guideline. The full definitions are omitted and a reference is cited.

5. In the paragraph „Study design and data collection“, a more thorough description of what data were namely collected, by whom etc., is needed. Variables available in the TB unit registers were extracted and this has been described under “Study design and data collection”. A trained nurse extracted the data and one of the authors supervised data collection as described under “Study design and data collection”.

6. How was the main database for this study created? Data were extracted from TB unit registers using a pretested data extraction sheet and entered into excel; subsequently data were exported into SPSS for further analysis (described under “Data analysis”)

7. How were the missing data handled or were the data missing in the TB registries of each health center pursued in some way? Those with missing treatment outcome and those with complete treatment outcome were compared and since there was no significant difference, they were excluded from further analysis.

8. Were separate TB registries present at each health care center? Yes, each health center has a separate TB unit register. On page 4, line 206, it is mentioned that the data were extracted from TB unit registers.

9. In the paragraph entitled “Data processing and analysis”, how were the data checked for completeness and accuracy? Data were checked for completeness and accuracy after running simple frequency analysis. The result was examined closely to look for missing values as well as inaccurate values. For inaccurate and missing values, we checked the TB registries as
well as the data extraction sheet to correct errors introduced during data extraction as well as entry.

10. The description of statistical analysis seems to be either incomplete or badly vague. What is meant under “Descriptive statistical methods” (page 5, line 125)? What was Chi-square test used for (lines 126-127)? This has been further elaborated.

11. Results: although the coverage of testing for was HIV increasing with years, the HIV serostatus was unknown for as large proportion as 52.1% of children; among those tested, 26.8% were co-infected with the virus. It would be interesting to know, what could be the proportion of HIV positivity among the untested population (in Discussion)? It has been, however, mentioned that children with unknown HIV sero-status had poor treatment outcomes (Discussion, page 8, line 214). The Discussion is a bit inconsistently written, which makes it difficult to follow, e.g. the HIV issue is revisited later on this page (page 8, lower paragraph).

The discussion section has been improved in line with the comments given.

12. Discussion: there are numerous pretty serious limitations mentioned, e.g. the lack of socioeconomic data. Some data were confessed to be incomplete. What data? Furthermore, the authors claim that some data collected from registries may be inaccurate. What data? Major discussion is needed to evaluate the influence of the absence of data not collected at all (socioeconomic data), but other input data must be at least correct. The limitations also include the retrospective nature of the study.

We acknowledged the concerns raised by the reviewer. Because of the retrospective nature of our data, we don’t have any control on what information has been registered and to what extent the quality was assured. This is an inherent problem of any retrospective data. The registration of selected information is mainly for programme
evaluation and follow-up purposes. However, TB units are better off in terms of registering a good quality data compared to other health programmes. We collected all the information available from TB unit registers (as described under “Study design and data collection”) and caution was taken to avoid errors during data extraction. The specific variables available in the TB unit registers were also described under “Study design and data collection”. Therefore, we discussed the limitations of a retrospective data and not our study as such to remind readers that the data has to be interpreted in view of the limitations of a retrospective data.

Table 1: Without referral to the text, it is not clear for the reader, what does “PTB-“ mean? Smear-negative pulmonary TB? Why there are no statistical differences mentioned? Why are some of the treatment outcomes marked as “NA”?

Proper descriptions of abbreviations included under table 1. The reason we preferred to omit values of measures of statistical differences is because we have table three that describes the predictors of poor treatment outcome. Statistical differences (p-values) have now been included.

Some treatment outcomes were marked as NA (not applicable) since it does not apply to these labels. In this regard, “cured” and “treatment failure” don’t apply for extrapulmonay and smear negative pulmonary TB patients.

Figure 1 may not depict the most important finding from this study. Instead, a forest plot of the main results would be of more value. Forest plot, to our knowledge, is a graphical display designed to illustrate the relative strength of treatment effects in multiple quantitative studies.

The reason for including Figure 1 is to show the age distribution of TB among our study participants.

Reviewer: Daniel Datiko
The article addresses important areas of public health interest and clinical significance. Give that the study was based on retrospective review should indicate the trend over five years which could be used as a measure of the program implementation and patients care. However, there areas to be improved. The discussion part needs to be rewritten after revision. 

We have now included a figure (Figure 2) describing the trend of poor treatment outcomes over five years. The treatment success didn't vary as such over the years.

Major revision

Introduction:
1. the introduction is briefly written and does not clearly justify why the study was done
The introduction is expanded and the rationale for the study has been included
2. clinical, diagnostic and patient care challenges which could justify the need for review is missing
This has now been incorporated in the introduction part especially paragraph 3.

Methods:
3. Diagnostic and treatment deception is given. Otherwise there is no clear algorithm be it international or National on which the case finding was based.
We have cited the national guideline for diagnosis and treatment of TB. Three diagnostic algorisms are included in the national guideline of Ethiopia (one is for children without HIV infection, the second for children with close contact with known smear positive TB patient and the third is for children with HIV infection). Since including three diagnostic algorisms will take a substantial space, we opted for citing a reference so interested readers could refer for further information.

Study design and data collection
4. it does not describe which facilities, how and why they were selected is not clearly shown
This has been described under “study area”- kindly please refer to the manuscript. We included all (23) health centers which were providing TB treatment for at least one year prior to data collection. The main reason we included health centers is because the
majority of TB patients are treated at health centers as described in the manuscript. The reasons we didn’t list the names of the 23 health centers included in this study is because we thought the list is long.

5. the exclusion criteria for hospitals, if at all excluded and their importance in the diagnostics of childhood TB is missing

We acknowledge that hospitals play a significant role the diagnosis of TB especially among children. Our study is a retrospective analysis of treatment outcomes of children with TB in all health centers in Addis Ababa offering TB treatment for at least one year before data collection. To this end, 23 health centers were included. The main reason we included health centers only is because the majority of TB patients diagnosed at hospitals end up being referred to the nearest health facility closest to patients’ residence before initiation of treatment.

Results

6. Page 5, last sentence described new cases, what about retreatment t cases?

This has now been included

Discussion

7. The paper does not describe the importance of parents in the adherence to treatment which is very important in childhood TB

We completely agree with the reviewer that parents play key role in supervising and administering medication to their children especially during the continuation phase. We have included a statement under Discussion: paragraph 4, line 4

References

8. The discussion is based on few studies and does not make thorough

Comparison

Additional references (6,7,13,14,15, 17,20) are included and discussion has been elaborated further

9. Mainly based on guidelines and needs to be more of published articles than guidelines which reflect the interest of the organizations.

In the discussion section, we included research articles/reviews published in peer-reviewed journals and removed guidelines.

Minor revision
1. page 3, third sentence under diagnosis and treatment should go to introduction and described better

This part was moved to the introduction part

2. page 5, 9th sentence describes unsatisfactory outcome which may be written as poor outcomes

corrected as suggested

3. under data processing and analysis: TB registration books should be TB Unit Registers

Corrected as suggested

4. page 6, line 3 – 5, the words like vast majority should be omitted

Corrected as suggested

5. Page 6, line 7, Mann Whitney is not described under the methods and should be described and why?

Described as suggested