Author’s response to reviews

Title: Tuberculosis lymphadenitis in Southwest Ethiopia: a community based cross-sectional study

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Author’s response to reviews: see over
To: BMC Public Health

Subject: Re-submission of an article

Dear Editors,

We hereby re-submit our article titled “Tuberculosis lymphadenitis in Southwest Ethiopia: a community based cross-sectional study” after accommodating the comments of the reviewers line by line. We have attached the line by line responses to the comments by reviewers in the following pages.

With kind regards,

Gemeda Abebe, MSc, Assistant Professor

Corresponding author
Reviewer 1: (Subhash Chandir)

We appreciate the reviewers for their constructive comments which we have used to improve the quality of the paper. We have accommodated the comments line by line. We have made editorial revisions to avoid spelling and grammatical errors.

Reviewer's report:

Major Compulsory Revisions

Comment 1. What is the age of majority in Ethiopia? How were >15 years old defined as adults? Please consider using the appropriate terms rather than labeling all >15 years as adults.

Response: In the text now we replace the term adult by “individuals 15 years or older”.

Comment 2. In line 60, please provide total number of TB cases in Ethiopia.

Response: Now we indicate in the text that “The WHO and the Ethiopian TB control program estimate that the proportion of extrapulmonary TB among the total number of new TB cases (156,928) is about 32% [3, 5].”

Comment 3. Why data from entire 1 Kebele was incomplete? Can you please explain the bias it may have introduced.

Response: The data from one kebele was incomplete as the samples were lost on transportation. The total number of adults in the Kebele was 2443 which is 8.1% of the total study site. To minimize the bias we have excluded the kebele from analysis.

Comment 4. Further information should be provided on consent procedures eg was consent taken from 30,040 adults before administering questionnaire. Furthermore number approached and refusals should also be documented.

Response: First the head of the house gave consent. Subsequently depending on the information from the head of the house (as indicated in methods section) all the suspects gave consent before administering the questionnaire. There were no refusals.

Comment 5. The study describes limitation in terms of transport of specimen for culture but methods section does not describe the transport system and any potential issues. This is important as it would help readers decide if this led to any underestimation of rates.
Response: Now we indicate in the text “FNA samples were kept at -20°C till transported in cold box by postal system to Armauer Hansen Research Institute (AHRI) in Addis Ababa for culture.”

Minor Essential Revisions
Comment 1. Following edits in can help improve tables for better understanding:
   a. Add ‘n’
Response: Accepted
   b. Alignment of numbers
Response: Accepted
Comment 2. Line 221 should correct the duplication of word “tried”.
Response: The duplicate is deleted.
Comment 3. Please give Confidence intervals as range eg “35.7-94.2” rather than “35.7,94.2”.
Response: Now the confidence intervals are presented as recommended.
Comment 4. The data for the study is not definitive (based on study design and number of cases), therefore please replace the word “essential” in conclusion with “recommended”.
Response: In the text now we indicate “Screening of TB lymphadenitis particularly for family members who have contact with chronic coughers is recommended.”

Discretionary Revisions
Comment 1. Please provide the statistics for EPTB prevalence in line 167.
Response: We now mention in the text that “Ethiopia reports the third highest number of extrapulmonary TB globally (50,417) [3].”
Reviewer 2: Elizabeth L Corbett

We appreciate the reviewers for their constructive comments which we have used to improve the quality of the paper. We have accommodated the comments line by line. We have made editorial revisions to avoid spelling and grammatical errors.

Reviewer's report

Review of Abebe et al Tuberculosis Lymphadenitis

This is a well-written manuscript describes a prevalence survey for tuberculous lymphadenitis as part of a demographic surveillance site interview round in Ethiopia. This is interesting and novel, especially given the high proportion of tuberculosis that is extrapulmonary in Ethiopia (for reasons that are currently unclear). The study is clearly described and well written.

My main concern is around the approach to identification of individuals with lymphadenopathy, where it is not entirely clear to me exactly how adenopathy was identified -- through interview only (I.E. asking individuals if they had noticed lumps and bumps themselves) or whether there was also examination routinely.

Major compulsory points

Comment 1. The phrase used in the manuscript to describe the initial case finding step ("any adult with lumps in the neck, arm pits or groin up on interview": abstract and page 4 second para) is insufficient to allow the reader to understand the exact procedures used, and the phrase itself is also not grammatically correct.

This needs to be clarified and described in more detail.

Critically, were all participants systematically examined for lymphadenopathy? Or was the first case finding step instead a question about palpable nodes? Clearly one would expect more lymph nodes to be identified on systematic examination than interview. If interview was used, then the authors need to discuss this as a limitation in the discussion.

Response: As indicated in the methods section interview was used to identify the suspects. Now we indicate in the limitation section that “However, our study was not without pitfalls. We probably underestimated the prevalence of tuberculous lymphadenopathies because individuals were not systematically examined for
lymphadenopathies and culturing of the samples were delayed due to transport problems.”

**Minor essential revisions**

Comment 2. Fine-needle aspirations were taken from any enlarged lymph nodes. Only about a fifth of the enlarged nodes found were tuberculous. The current manuscript describes only the tuberculous diagnoses, whereas it would be of considerable interest to know all diagnoses made.

**Response:** In the result section now we indicate that “Other diagnosis of the lymph nodes include: reactive lymphadenitis (57), pyogenic lymphadenitis (6), benign mesenchymal neoplasia (6) and non-specific lymphadenitis (5).“

Comment 3. The subsequent case ascertainment appears to be slightly problematic, with relatively few culture-positive aspirates from those diagnosed through cytology. The cytological features used to diagnose TB are listed in the methods, but not detailed for the cases. Again providing this additional detail would add value to the manuscript and credibility to the findings.

**Response:** We have added now details of the cases in the result section. Accordingly it indicates in the text that “the microscopic features of FNA cytology of the TB lymphadenitis showed epithelial histocytes with giant cells in 8 cases, epithelial histocytes with caseous necrosis in 2 cases and caseous necrosis alone in 3 cases.”

Comment 4. Line 189 “This is mainly because pulmonary TB is more fatal than….” Would be better expressed as “has a higher case fatality rate than”

**Response:** Accepted and modified as per the suggestion of the reviewer.

Comment 5. Limitations need to include discussion of the sensitivity and specificity of the method used to identify lymphadenopathy

**Response:** In the discussion now we indicate that “The strength of our study was that it has tried to address the neglected component of TB at community level. However, our study was not without pitfalls. We probably underestimated the prevalence of tuberculous lymphadenopathies because individuals were not systematically examined for lymphadenopathies and culturing of the samples were delayed due to transport problems. Moreover, the methods that we used for the laboratory diagnosis of lymph node TB are not the most sensitive and specific. We did not use PCR which do have
high sensitivity in detection of lymph node TB [31]. These all limitations in combination may have resulted in under estimation of the lymph node TB prevalence in communities living in Gilgel Gibe research site.”
Reviewer 3: Solomon A Yimer

We appreciate the reviewers for their constructive comments which we have used to improve the quality of the paper. We have accommodated the comments line by line. We have made editorial revisions to avoid spelling and grammatical errors.

Reviewer's report:

General Comment

This study investigated the burden of TB lymphadenitis, an area that has not been explored very much in most high burden countries. I agree with the authors that it is perhaps the first community based study focusing on the prevalence of TB lymphadenitis in rural Ethiopia. The study is very well conducted and will serve as baseline information for future studies. The writing is good even though there are some typographical errors that need to be corrected. I suggest authors to address the flowing points in order to improve the manuscript.

Major Compulsory Revisions

Background

Comment 1. Many of the abbreviations used are not spelled out the first time they were used in the main text. Please check the entire manuscript and make sure the necessary corrections are made.

Response: We accepted the reviewer’s comments and corrected accordingly.

Methods

Comment 2. Line 75- in relation to selection of study area; were there other justifications for choosing the study site other than being a field research site?

Response: The basic reason why we choose the site was because there was a well characterized population at the site as a result of continuous registration of vital statistics. There were no other reasons considered to select the site.

Comment 3. Methods, line 82 says “the total number of adults …was 30,040”. Is this number referring to the total permanent eligible population of the “filed research area”?

Response: Yes. At the time of data collection there were 30,040 residents aged 15 years and above in the study area.
**Comment 4.** Methods, line 132 - authors claim that “new TB cases identified were immediately referred to the nearby health facility for treatment”. What mechanisms were emplaced to make sure that all those referred patients went to the health center and got treatment?

**Response:** There were regular data collectors for vital statistics at the site. They accompanied each and every TB patient to go to a nearby health center.

**Results**

**Comment 5.** Line 137-138, you mentioned that one kebele was completely removed from the analysis due to incomplete data. I was just wondering to what extent the data were incomplete to result in complete exclusion of that kebele from the analysis?

**Response:** The FNA samples collected on site were lost during transport to Jimma University. As a result there were no laboratory data that we could analyze from data collected from that specific kebele.

**Comment 6.** You have not mentioned if there were some households/individuals missed or refused to participate in the study from the other kebeles. Did you have such observations? If so, what were the proportions? You need to clarify these important points.

**Response:** As indicated in the methods section we were making repeated visits (up to three times) to a household in case we did not find the heads of the households or the houses were closed. This helped us not to miss a single household. During the data collection we did not encounter a household or an individual that refused to take part in the study.

**Comment 7.** In table 2 and Table 3, you have not analyzed “sex” and “age” together with other variables. Why did you prefer to exclude these variables from the analyses? I think it is important that these variables are also included in the analyses.

**Response:** We now included age and sex in table 3 (previously table 2). We did not include in table 4 (previously table 3) since the variables analyzed in the table were lymph node characteristics only.

**Comment 8.** I could not see the distribution of TB lymphadenitis cases identified in each kebele. Probably another table showing the distribution of cases, including
prevalence and confidence intervals per site would be helpful to have more understanding of the epidemiology of the disease in the study area.

Response: The distribution of TB lymphadenitis per each kebele is now presented in table 1.

Comment 9. It would also be important to provide map of the study sites so that readers can have a better picture of the study area.

Response: The map of study area is now included as figure 1.

Discussion

Comment 10. Line 164-165 reads “the proportion of extra pulmonary TB among all TB cases varies from country to country”. This invites authors to provide more information. Please give some country specific examples. Also line 167 reads” Ethiopia reports the third highest number of extra pulmonary TB globally”. Please give an appropriate citation for this information.

Response: Now we indicate in the text that “Of the 22 high burden countries the highest proportion was reported from Cambodia (34.2%) and the lowest from China(0.69%) [3]”.

Comment 11. Line 196-201, you discussed that you found more TB lymphadenitis cases among women than men and compared it with other studies “(18-23)”. However, “sex” and age did not show significant difference in the frequency of TB lymphadenitis in your study. I think you need to be cautious when comparing your findings with other studies that reported significant difference. I suggest you consider revising your discussion here.

Response: We agree with the reviewer and revised the portion of the article. In the text we now indicate that “Studies have reported that women were more likely to be positive for TB lymphadenitis compared with men [20-25]. Moreover, it has been suggested that in male dominated communities, where women experience poorer living conditions, young females generally notice differences in their appearance earlier than males [26]. In our study, however, the rate of TB lymphadenitis was not significantly different between the two sexes. Our previous finding from the study area on health seeking behavior also did not find a difference in gender [27].”

Comment 12. The discussion of your finding, increased risk of TB lymphadenitis among
patient with a history of contact with chronic cougher, is placed towards the end of the discussion. As this is one of the most important findings of your study, it should have been discussed further up in the discussion section.

**Response:** We now discuss about contact history in 5th paragraph.

**Comment 13.** With regard to the limitation of the study, you only mentioned about the problem of “delayed culture of samples”. Would there be other limitations to your study apart from the one you mentioned? For example, you have not used PCR in your study which might have helped you pick up some more cases. Could that also be considered as a limitation to your study? What about in terms of generalizability of your study? I think you have some more points to discuss as limitations to your study.

**Response:** We agree with the reviewer and modified the limitation part of our discussion. Accordingly it is now indicated in the text that “The strength of our study was that it has tried to address the neglected component of TB at community level. However, our study was not without pitfalls. We probably underestimated the prevalence of tuberculous lymphadenopathies because individuals were not systematically examined for lymphadenopathies and culturing of the samples were delayed due to transport problems. Moreover, the methods that we used for the laboratory diagnosis of lymph node TB are not the most sensitive and specific. We did not use PCR which do have high sensitivity in detection of lymph node TB [31]. These all limitations in combination may have resulted in under estimation of the lymph node TB prevalence in communities living in Gilgel Gibe research site”.

**Minor Essential Revisions**

**Abstract**

**Comment 14.** Abstract, lines 1 and 31- “cross sectional”, better to write it as “cross-sectional”.

**Response:** Accepted

**Comment 15.** Abstract, line 29- the word “therefore” should be followed by a comma.

**Response:** Accepted

**Comment 16.** Abstract, line 35- be consistent in spelling out abbreviations. “AFB” is not spelled out.

**Response:** Accepted and now it is spelt out as acid fast bacilli.
Comment 17. Background, line 6 - “...total number of TB cases, is about 34%” please remove the comma.
Response: Accepted

Comment 18. Methods, line 74, your listing of Woredas “Sokoru, Omo Nada, Tiro Afta and Qarsa” should be written in Italic.
Response: Accepted

Comment 19. Methods, line 91, I suggest you remove” (MB and AB)”. You do not have to name them as you already have mentioned that FNA was performed by study pathologists.
Response: We accepted and removed the MB and AB from the text.

Comment 20. Methods, line 97, you spelled out FNA after it was already used. Please correct that!
Response: Accepted.

Comment 21. Methods, line 103- “MB and AB” again mentioned here. Please remove it! It is not necessary.
Response:

Comment 22. Results, line 143- “On the basis of FNA” should be followed by a comma.
Response: The phrase was used to express the AFB microscopy from FNA sample. We now revised and indicated in the text as “ AFB microscopy from FNA samples, -----”.

Comment 23. Results, line 151- “... age group 35-44(99.4 per 100000 people)”. Space and comma are needed i.e. 35-44 (99.4 per 100,000 people).
Response: Accepted

Comment 24. Discussion, line 170- reads “in this study... was established when FNA...” FNA should be followed by a comma.
Response: We accepted and removed the MB and AB from the text.

Comment 25. Line 206- 208, reads “This suggests...HIV either Mycobacterial strains...or host factors play an important role...community”. Please add the word “may” between “factor and play.”
Response: Accepted.

Comment 26. Line 221, “The strength of our study was that tried it has tried...” Please delete the word tried” as it a repetition of the same word.
**Response:** Accepted.

**Comment 27.** Table 1, make sure that the title is complete! “100000”, please put comma in between, and add “Gilgel Gibe, south west Ethiopia”

**Response:** We accepted the comments and made the corrections accordingly

**Comment 28.** Table 1, Third column, is it lymphadenitis or lymphahadenopathy? Please make corrections accordingly, also please spell out “OR” and “CI” at the end of the table.

**Response:** We accepted the comments and made the corrections accordingly. OR and CI are now spelt in the table legend as Odds ratio and confidence interval respectively.

**Comment 28.** Table 1, please close the brackets for confidence intervals for the last 2 categories of age groups.

**Response:** Accepted.

**Comment 29.** Table 1 please put space between the OR and the brackets where you have the confidence intervals.

**Response:** Accepted.

**Comment 30.** Table 2, please put space between the figures and brackets where you have the percentages and confidence intervals. Also spell out “COR” “USD” at the end of the table.

**Response:** Accepted.

**Comment 31.** Table 3, please put space between the figures and brackets where you have the percentages and confidence intervals. Also please close the bracket corresponding to the first category under the variable “number of lymph nodes”, third column.

**Response:** Accepted.