Author’s response to reviews

Title: Investigation of Household Contacts of Pulmonary Tuberculosis Patients Increases Case Detection in Mwanza city, Tanzania

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REVIEWER #1

Reviewer Comments #1 on Manuscript Revisions for INFD-D-17-00741

Overall Impressions:

The revised manuscript provides a much clearer, more concise message that is both important and reads well. The major issues and comments have been adequately addressed, and only the following minor issues remain for consideration and inclusion.

Response: Thanks for the complement
Abstract:

• Methods: please include the cadre of the health care worker who did the home visits, as well as add “standardized TB screening” to the statement: “Contacts were traced by home visit by (cadre?) and data were collected using a standardized TB screening questionnaire.”

Response: We have amended that accordingly.

Introduction:

• Line 19 on page 2; 2nd paragraph of introduction: you don’t need to define the abbreviation TB (“tuberculosis (TB)”) again as this has already been defined in the first sentence of introduction. Thus, it is okay to just use “TB.”

Response: We have amended that accordingly.

• Page 2: abbreviation for World Health Organization (WHO) – the full name is introduced in second paragraph and can add the “(WHO)” at that point. Then in the fourth paragraph, you can simply write “WHO” and not need to write out the full name there.

Response: We have amended that as suggested by the reviewer.

• Page 3, lines 2-4: The first sentence in a fragment. Better phrasing would be “A systemic review and meta-analysis of 41 studies showed that screening household contacts increased new case findings by 4.5%. Therefore, we hypothesized that…”

Response: We have amended that as suggested by the reviewer.
Methods:

• First paragraph of page 3 (first paragraph of methods): it would read better if you first introduced the dates and sites of the study; and then introduced the ‘how’ of how the retrospective review was done. For example, “retrospective study was done on newly bacteriologically confirmed cases of TB between (insert dates) at (insert sites)” then transition to how the data was collected via the registry books, home visits, etc.

Response: We have amended that accordingly

• Somewhere in Methods also need to write the cadre of the person making these phone calls and/or home visits (e.g. TB nurse, physician, counselor, community health care worker, etc).

Response: We have amended that accordingly

• In Methods, you need to explicitly state and explain to the reader why both clinical diagnoses of TB and EPTB cases were excluded and not included in your study. There is a not-insignificant number of clinically-diagnosed and EPTB cases both worldwide and within Tanzania. It is okay that your study specifically focused on only bacteriologically confirmed pulmonary TB, but it must acknowledge in the methods (and/or limitations) the reasons why clinical pTB and EPTB were not included (and the inherent limitations of that action).

To help put this into context using the 2016 WHO TB country profile for Tanzania (page 157 of the WHO report):

• Of all cases notified (62,180, which as you state is already under-diagnosing and missing 100,000+ cases), the % bacteriologically confirmed among pulmonary is only 53% per the report. Thus for pTB, if you narrowly only look at bacteriologically confirmed, you are missing 47% of pTB cases (i.e. the clinically diagnosed pTB in Tanzania is nearly one half of all cases!). That is a huge, significant proportion of pTB in Tanzania that is clinically diagnosed.
In the same report, pulmonary TB makes up 79% of reported TB cases in Tanzania; thus 21% of cases of TB in Tanzania are EPTB.

Thus, with your narrow definition of bacteriologically confirmed pTB in Tanzania, you are at the risk of missing 21% of TB cases (EPTB), and of the remaining 79% of TB cases that are pTB, you are at risk of missing nearly half (47% clinically diagnosed pTB) as well that may exist among household contacts. That adds up to a large proportion of other TB (EPTB, clinical pTB) that your study is potentially missing during its contact tracing efforts.

Again, targeting only bacteriologically confirmed pTB was how the study was designed and how the data was collected/reported, but the authors need to address this big gap/limitation either as part of methods, in the conclusion or both; and provide as strong a justification for those choices as possible.

Regarding your reply, you wrote: “We decided to look for bacteriologically-confirmed TB because we wanted to be sure that we diagnose TB and report bacteriologically confirmed. So when we tell the increment benefit of active case finding we are certain. The sensitivity of clinical diagnosis is low.”

As a teaching point on terminology: actually the sensitivity of clinical diagnosis for TB is quite high, but its specificity is quite low. If you think of sensitivity as the phrase “Of all those with TB disease, XX% are positive test/criteria.” Thus for clinical symptoms or symptom scoring (which is non-specific) it can be quite sensitive for TB…it just risks over diagnosis of TB when non-TB pathogens cause the same clinical symptoms. So for all those with pTB, upwards of 80-90% will have clinical symptoms meeting the definition of clinical pTB (i.e. clinical symptoms/scoring is highly sensitive). The challenge is that symptom-based diagnosis is not highly specific (“Of all those without TB, YY% will have a negative test/criteria”). This is because there are many people without TB who can have symptoms of chronic cough, fever, weight loss, etc for other non-TB reasons.

If you PubMed search “Validity of Keith Edwards scoring system for diagnosis of pulmonary TB” you’ll find numerous studies specifically looking at these TB scoring systems. Results are variable, but in general, sensitivity is 80-85% while specificity is notably lower (60-70%). There is a decent amount of additional published literature assessing the sensitivity/specificity of clinical symptoms/scores; the general consensus of the scoring systems (clinical diagnoses) are
that while they are not perfect, they can be very important and useful (especially in areas without easy access to advanced diagnostics) due to good sensitivity at the expense of specificity.

- It doesn’t affect the manuscript was written, but just to help raise awareness of the importance/utility of clinical diagnosis of TB (especially in HIV+ and children, where microbiologic confirmation is more uncommon)

Response: Thanks for the educational contributions. We have put this consideration into the study limitations

- In responses, you mention: “We regret that we did not capture the data of those refused to be visited and those who were not reached by phone.” That is important information for your reader to know, and I would recommend including similar phrasing on page 3 lines 37 (e.g. you could just add, “and the study did not collect and report data on those excluded based on refusal of participation, could not be reached, or could not produce sputum”)

Response: We have amended that as recommended by the reviewer.

- Page 3, lines 58-60: first sentence mentions one spot and one morning sputum (and similarly mentioned above in lines 26-27). Then the next line mentions spot being collected during first and second visit. Thus, it seems that every contact had 3 sputums collected (one spot from first visit, one morning from instructions during first visit, and then a second spot during second visit). Is that correct? Or was it only two samples (one spot and one morning)? Needs clarification so that reader can understand exactly how many sputums (and how each collected) for each enrolled contact.

Response: We collected two sputa, one spot and one morning. We have amended that for clarity.

- Page 4, Line 4: acronym BMC TB laboratory used. Need to define “BMC” above when introducing full name of Bugando Medical Centre.

Response: We have amended that as recommended by the reviewer.
• Page 5, line 3: would recommend removing “visible” and just say with “signs and symptoms of TB.” The term “visible” is not commonly used in the literature, and would exclude common TB symptoms such as fever.

Response: We have amended that as recommended by the reviewer.

Results:

• Page 5, lines 11-12, please change wording to: “Upon following of these cases, 456 household contacts met eligibility criteria and were enrolled into the study.” Because you don’t have any data on the # unable to be reached, refusing or unable to produce a sputum, the way it is currently written conveys the message that there were 456 household contacts total of those contacts (but the reality is that there were only 456 contacts that were fully eligible per your study definitions, and there could be more contacts present, but who didn’t meet eligibility criteria).

Response: We have changed it as suggested by the reviewer.

• Page 5, line 21: please change to “Among the 456 household contacts,…”

Response: We have changed it as suggested by the reviewer.

• Page 5 line 21-23: please use “M.tb-culture positive” and “AFB-smear positive” for the correct terminology for these tests

Response: We have changed it as suggested by the reviewer.
• Page 5 line 31, updated heading to “Predictors of bacteriologically-confirmed pulmonary TB among household contacts”

o Similar, in text of this section, add “among household contacts” so that your readers know you are referring to predictors among the 456 household contacts (and not the original 93 TB index cases)

Response: We have changed it as suggested by the reviewer.

Discussion:

• Page 5 line 60: slight typo, and need to add “..that people with good nutrition…”

Response: We have changed it as suggested by the reviewer.

• Page 6 line, 5: slight typo, and need to add, “..predisposes them to an infectious contact than any other person…”

Response: We have changed it as suggested by the reviewer.

• Based on the statistically significant associations you found (e.g. meals and marriage), does your team have any recommendations that could be built upon those findings. Many studies in the Discussion section might list, “based on these associations, more attention to XYZ should be made,” or “programs targeting XYZ should be integrated into TB services, health policy, etc”. They are interesting findings, and would be interesting to hear what the study team makes of these, or how they recommend these findings be used to improve clinical practice or policy.

o An important part of any “Discussion” section is to synthesize the results into meaningful actions, recommendations and next steps. And I would highly recommend you synthesize the findings from the data into suggestions/recommendations for Mwanza, LZ, Tanzania or beyond!
Likewise, in the treatment cascade of any disease (such as TB, HIV, etc), case finding is an important first step...but it needs to be followed by linkage to care, treatment initiation, treatment success/adherence, treatment completion/cure, and then prevention. If desired, your team could mention as a next step that the importance of active case finding cannot stand alone on its own, but must be effortlessly integrated into the TB treatment cascade of linkage, initiation, etc. While your study didn’t specifically look at that, future studies need to (to ensure all the great successes from active case finding aren’t lost if additional steps to link the patient and initiate TB treatment are not done; otherwise there is the risk that the active case finding was all done for naught).

Response: We have added a phrase on the recommendation as part of the conclusion.

- For limitations, please also mentioned issues discussed above about missing cases of clinically diagnosed TB and EPTB

Response: We have considered that into the limitation

- Also for limitations, did the study continually/longitudinally follow any of the household contacts?

  o Standard of practice for contact tracing is to follow household contacts for 6-12 months post-exposure to the contact, since the majority of progression from TB infection to disease occurs within the first 12 months of exposure. Thus, while you may have had ‘healthy, sputum negative’ contacts during the time of the study, perhaps 3-4 months later they developed pTB. Would be important to mention this either as a limitation, or a ‘next step’ to emphasize to your audience that active contact tracing isn’t a onetime thing, but is a continuous process of follow up over 6-12 months after a TB exposure.

Response: We have considered that into the limitation

- In your responses, you mention that HIV testing was not done in the study, thus removed from intro and discussion (“The HIV status of household contacts was not tested. Fund for research was not adequate to accomplish this. We regret that this is a missed opportunity.”).
While these reasons are understood, in this day and age, and in countries with high TB and HIV prevalence (such as Tanzania), it is impossible to talk or write about TB without any mention of HIV (and vice versa).

Thus, I would highly recommend at least a mention of the relationship of TB and HIV, their synergistic relationship, and how one epidemic drives the other. And a mention that examining HIV was outside the scope of this study, but remains critically important for any intervention targeting TB.

TB efforts worldwide have been trying to gain momentum and attention to the TB epidemic, and as your manuscript provides a nice opportunity for this, it would be a disservice to great TB efforts like this one in Mwanza, to not at least give a brief mention (e.g. as limitations) of the importance of HIV testing in anyone with TB disease, presumptive TB, or household contacts of TB.

Response: We have added a phrase in the introduction and put a statement in the study limitation section.

Conclusions:

• Can you please explain your analysis method and data source for the statement of active case finding providing a detection rate 20 times high than passive diagnosis?

I think there may be some confusion in that you are comparing the findings from your study (which looks at active case finding among household contacts of confirmed pTB) to the overall incidence rate of TB in Tanzania (per 2016 WHO report the incidence rate is 306 cases of TB for every 100,000 citizens of Tanzania; or the total TB disease burden per year per the entire population). That figure 306 per 100,000 people is not a passive case finding rate, it’s the estimated yearly incidence rate of TB (e.g. in Mwanza, for every 100,000 people living in Mwanza, 306 of them developed TB disease). It does not give any information on passive case finding.

I don’t think the comparison – if I am correct in my interpretation – is a valid one. You can simply remove the “20 times” statements, and just talk about how the yield of your effort was quite good (contact tracing 100 people lead to 7 new cases, which is very important message to share).

I am unaware of any published data on passive case finding yield and numbers in Tanzania, but would be very interested to read if you have a reference. Grossly looking at the WHO 2016
report, you could assume very broadly that if every reported TB case in Tanzania was found passively (which is not true, but could be the assumption). If that was the case, then 62,180 cases were found passively of the estimated 164,000, which would mean that passive case finding identified 38% of all TB cases in the general population. But since your study is looking at yield among household contacts and the WHO statistic is looking at the general population in Tanzania (and not only household contacts), I do not think these two statistics can be compared in that manner.

I look forward to the team’s response and clarification on the matter; as perhaps I am also mis-reading or mis-interpreting the data presented.

Response: We have removed the phrase delineating the incremental yield of 20 times compared to passive case finding as suggested by the reviewer.

- I would consider removing the last sentence about phylogenetic analysis from the conclusion. While the epidemiology of disease outbreak is a crucially important topic, it’s beyond the scope of the paper and hasn’t been mentioned or discussed prior in the paper. So it seems a bit tacked on and non-sequitur as the final sentence of the entire paper.

Response: We have removed the phylogenetic analysis part as suggested by the reviewer.

Tables/Figures:

- Figure 1:

  As you mentioned previously, you were unable to track/quantify the numbers unreachable, refusing and/or not producing sputum. I would suggest adding an asterisk to this figure to share that important information (“We regret that we did not record these people. We regret that these data was not collected besides their remarkable importance in this study.” Or similar phrasing)

Response: We have added the statement as suggested by the reviewer.
George Praygod (Reviewer 2):

Abstract

Discrepancy of the yield of contact tracing reported in abstract and in the results section (7% vs 6.4%)

Response: We calculated the yield and got 6.4%. Since these are the people, they are discrete we concluded by saying seven out of a hundred.

Methods and Results

Most of the methodological issues queried in the first review have not been adequately addressed. This include the following:

-Since this is cross-sectional study, the readers will be interested to see if these results are representative of the Mwanza city situation. The authors should justify why only a few TB clinics in Mwanza city were involved in selection of index TB cases as this has a potential to produce findings which are only applicable to parts of the city.

Response: We recruited index cases from four TB clinics of Bugando Medical Centre, SekouToure Regional hospital and Nyamagana district hospital. These hospitals attend a bigger number of patients from Nyamagana and Ilemela districts which makes the city of Mwanza. So we thought that the contacts derived from these index cases represents the city of Mwanza (Not the Region of Mwanza). We have amended the title to read the Mwanza city. However there might be some bias so we considered that in the limitation of the study.

-The selection of household contact is not well explained. If the TB index household had more than one contact, how many contacts were selected and how was the selection done? If some people living with TB index case were not at home at the time of the visit, how was this handled?
In other words, are the household contacts selected in this study representative of all the household contacts in Mwanza city? Also, it would be nice to say how many contacts were invited and how many consented to be included in the study for readers to rule out bias. This will help readers to judge if the contacts sample drawn can be taken to be representative of TB contacts in Mwanza.

Response: If the TB index household had more than one contact, we enrolled all contacts. If some people living with TB index case were not at home at the time of the visit, we followed them on the next days so as they are enrolled into the study.

We are not sure by hundred percent if the household contacts selected in this study representative of all the household contacts in Mwanza city. So we added a phrase delineating this as the limitation in the study limitation section.

On the other hand, we regret that we did not count how many contacts did not consent so as to rule out bias. We have as well phrase this into the study limitation.

-It seems that the study inclusion criteria were not the same for adults and children (which is fine). Adults were only included if they provided at least one sputum sample, but children were included even when they did not produce sputum (this is understood because it is not easy for children to produce sputum). I think authors need to include the section on inclusion and exclusion criteria so that it becomes clearer for readers as to how potentials participants were included.

Response: All participants who were included into the study if they were able to produce the sputum. We stated the Methodology the criteria for being enrolled and excluded "The household contacts who were able to produce the sputum sample were enrolled into this study while those who were not able to produce sputum were excluded".

-In lines 36-44 (page 3), it is not clear what nurses collected and how they collected the data. We see what was collected in the results section, but would be nice to include this information in this part of your manuscript so that people can judge and see if the data collected is valid. For example, how the nurses ascertain that contacts had weight loss, were smoking or lived more that
I km from health facility. I would be nice to described how weight loss and smoking status were determined (ever, past or current). Authors should how data included in the analysis were collected.

Response: At the time of home visits, the study TB nurses administered questionnaires to only those who provided spot sputum samples, to obtain the socio-demographic, baseline information, and predictors of bacteriologically-confirmed pulmonary TB. The predictors investigated were symptoms of pulmonary TB (cough, fever, weight loss, excessive night sweats and hemoptysis), current smoking, house size, distance to health facility, number of people living in the house and number of meals taken per day. Later, the house parameters were measured using a tape measure.

The smoking status that was asked was current, the weight loss was determined by the patients perception based on loosening of clothes or belt, or by previous weight measurement by the participants themselves. The distance from home health facility was estimated, since the location of the health facilities are all known.

Discussion

Lines 58-60: explanation given on why people who eat less than 3 meals a day have more TB is not adequate and should be expanded.

Response: We have expanded the this discussion

Section on limitation should be expanded. For example authors should include possibility of bias in contact tracing and confounding

Response: We have included that in the study limitation