Author’s response to reviews


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Version: 2
Date: 1 February 2015

Author’s response to reviews: see over
RESPONSE TO REVIEWER'S COMMENTS

Reviewer's report
Version: 1
Date: 16 December 2014
Reviewer: Neil Martinson

Reviewer's report:
This study reports the prevalence of TST positivity (at least 10mm in diameter) in almost 300 people in a population of 300,000 living in 75,000 households in Rubaga part of Kampala, Uganda. Whilst an interesting finding, the manuscript needs more detail.

Major Compulsory Revisions
1. Some detail must be provided, albeit brief on how many households were sampled and why so few people had a TST. Referring to reference 18 is insufficient as that published paper does not detail who was selected for TST testing. Moreover, there is at least one discrepancy between that paper and this (population size of Rubaga).

Response: 4494 households were sampled but the only participants who were eligible for tuberculin skin testing were those who reported chronic cough and those who were randomly selected as chronic cough controls. The specific discrepancy in population size addressed from 300,000 to 400,000 in text.

2. Please explain why no clear measures of TB infection such as a TB case in the household either diagnosed by the parent study or recently treated, was included as a covariable.
Response: The measure of TB infection was TST positivity as defined by induration of >=10mm. As reported in the primary study, there were 39 active TB cases of whom 28 (20%) were TST positive. 27 of the participants had previous history of TB, 13 met criteria for TST and 12 had TST readings, of whom 5 were TST positive (>=10mm induration). There were 14 people in current TB treatment but none of them received TST because it would be irrelevant to do it.

3. Similarly what about those who coughed?
Response: Participants who reported any cough but did not meet the definition for chronic cough (>=2 weeks) were not eligible for TST placement as per primary study criteria.

4. Definitions of covariables are required: married v unmarried is likely in reality not clearly demarcated, with several shades of gray between these two categories. Why employed people are lumped together with students, yet Catholics and Protestants remain separate?
Response: In the study, if someone reported that they were married we considered them as married. The question was asked as:
What is your Marital Status? The following responses were provided.
• 1: Married  2: Separated / Divorced 3: Widowed 4: Never Married 5: Refused to Answer

For the analysis we re-categorized the responses into 3: currently married, previously married (widowed + separated/divorced due to small numbers) and never married

Response: We intentionally combined students and employed people based on a common exposure characteristic which we conceived as “leaving a home on a daily basis”. Conceptually this implies being exposed to TB from sources outside of the home; in the general community within individuals’ social network or at the workplace home.

5. Why is there no diagram or figure? Suggest a graph of TST by age and gender may be more interesting than table 3 which could be easily combined with Table 2.

Response: Figure included showing TST by gender and age in text. The prevalence of LTBI was higher in males than females in the 15-24 and 25-34 age categories respectively, and similar in both males and females older than 35 years.

Minor compulsory revisions
1. Rethink the tables: Table 1 and Table 2 contain similar data. Table 2 and 3 could be amalgamated.

Response: Table 1 and 2 revised in text and 2 and 3 combined.

2. You should detail and address limitations of the study clearly. Not just report strengths.

Response: This was a secondary analysis of cross-sectional study initially collected to answer a different primary research question. By design, this analysis is limited in that we could only answer questions based on the available data. For example, we could not account for the potential effect of household clustering in our results because the participants’ identifications were not linked to households from which they were sampled. We expect that the clustering effect could have led to a slight overestimation of the effect of covariates on the primary outcome (LTBI). Additionally, information on chronic cough was self-reported therefore subject to recall bias; this may have resulted in misclassification and exclusion of some participants who could have been eligible for TST therefore resulting in the underestimation of the prevalence LTBI.

Level of interest: An article of limited interest
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests
Reviewer: Kristen Little
Reviewer's report:

Major Compulsory Revisions:

1. The authors do not describe the methods used to select the underlying study sample. More information on sample selection is important to understanding how representative the sample is, and for assessing the analysis methods used. The current statistical analysis utilizes a logistic regression model, which does not account for potential clustering at the household level (or weighting, if needed based on the initial sample selection method).

Response: In the underlying study, 5,102 participants were selected using a multi-stage sampling approach. A simple random sample was used to select five of the 13 parishes using a computer-based random number generator and sampling frame from the Uganda Bureau of Statistics. Weighted proportions-to-village population sizes were calculated to estimate the number of participants to be recruited from each village. This was done to account for the variability in crowding. We identified the first house from a defined central point such as road or drainage junctions in each village and enrolled a convenience sample of persons at home.

2. The manuscript does not include the number of individuals who participated in the underlying study, the number who did/did not receive TST, and the number whose TST was read. This information is lacking in the current manuscript and needs to be added. In addition to information on the proportion of the underlying study population receiving TST, a comparison of the characteristics between those receiving/not receiving TST to examine how representative the individuals receiving TST are of the underlying study population is needed.

Response: 5,102 individuals participated in the underlying study and 290 participants were eligible for TST testing. Of those 283 had their tests read and 7 participants did not have the TST read because they were untraceable within 48-72 hours window of TST reading. Of the untraced participants, 4 were male and 3 were female.

3. The multivariable logistic regression model presented by the authors includes only 2 covariates—age group and employment status. This model excludes other well-known confounders, most notably HIV infection, which was available in the dataset and was evaluated in the univariate portion of the analysis. Even if HIV infection (and other potential confounders including smoking status, chronic cough, sex, etc.) were not statistically significant, the authors should provide further justification for not including them, or add them to the model. An explanation of other potential confounders (history of TB diagnosis or treatment, close contact diagnosed with TB, ART status, diabetes, etc.) that were not available to the study should be mentioned in the limitations section.
Response:
- In a series of multivariable analyses, we considered HIV status, smoking, marital status, chronic cough and sex as potential confounders based on previous studies and biologic plausibility but none of them were included in the final model because they were not found to be confounders in our analysis. Therefore, we decided to maintain the final model with two covariates; Age and employed persons or students (individuals leaving home daily for work or school) based on a measure of model goodness of fit, the Akaike Information Criterion (AIC).
- Sex was not included in the final model because much as previous studies have shown it to be a universal confounder we did not find sex to be a confounder or independent predictor for this study.
- Only 9 (3.2%) participants who reported to be on ART
- We did not have information on close contact diagnosed with TB and diabetes which is a limitation to this study.
- We did not find any previous study showing chronic cough as a risk factor however, we know that it is a marker for TB disease.
- We looked at covariates using a stepwise regression model, and noted variables that had a significant association with LTBI at <0.05

Minor Essential Revisions:
4. The authors should explain how they determined that an induration of 10mm or more constituted latent TB among all participants (irrespectively of HIV status), and any strengths/limitations of this cut-off. Literature should be cited to justify this cut-point, especially articles from HIV-infected populations or in low-resource settings.

Response: We chose the conventional $10 \geq 10$ mm cut-off to define a positive TST for our risk factor analysis, given that our analysis using TST $\geq 5$mm produced similar results as $10 \geq 10$ mm cut-off moreover only one participant had TST $\geq 5$mm.

4. Details on study definitions should be included in the methods section. An explanation on why age was categorized into 3 different levels should be included, as well as the definition of “chronic cough” and the method used to determine HIV status.

Response:
- Age was categorized into 3 different levels based on previous published literature done to assess the prevalence of LTBI among Healthcare workers in Uganda (kayanja et al, 2005), also as a proxy for social networks.
- Chronic cough was defined as self-reported cough of $\geq 2$ weeks at the time of the survey.
- Method used to determine HIV status was rapid testing, more details have been included in the main body of the manuscript.

Discretionary Revisions
6. The authors conclude that their results indicate the need for workplace screenings for latent TB. While this may be the case, a model controlling only for age and employment status may be subject to a number of unmeasured confounders. Further, the logistic regression model does not account for clustering by household. After accounting for
unmeasured confounders as well as household clustering, these results may be
different. Given these limitations, the authors may need to temper or qualify their
conclusions and recommendations. Consideration of the cost of LTBI screening and
treatment should be referenced if the authors do recommend workplace-based
interventions.
7. The authors do not describe whether or not active TB was excluded from the study
population testing positive on TST. Were further TB diagnostic tests performed on any
of these individuals? Is it possible that a portion of the TST positive study sample
actually had active TB disease?
Response: The main aim of the primary study was to identify individuals with chronic
cough that had active TB disease; therefore sputum smear microscopic testing was
performed. Of 140 participants of were TST positive, 28 (20%) had active TB.
8. Was HIV status determined via self-report or HIV testing? If self-reported HIV status
was used, how might this have affected the results?
Response: HIV status was by rapid HIV testing and not self-reports
9. It would be helpful if Table 1 included a comparison between those receiving and not
receiving TST from the underlying study population.
Response: The comparison between those who received TST and those who did not
receive TST is not provided because we consider it not to be very informative since the
sample in which TST was done is a subgroup analysis.
10. Sentence 1 in the strengths and limitations section should be re-worded for clarity,
and the setting to which these results could be generalized to should be better
described (e.g. not just an urban setting, but an urban Ugandan setting, or an urban
African setting, etc.)
Response: This suggestion has been included in the main body of the manuscript

Level of interest: An article whose findings are important to those with closely related
research interests
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests