Author's response to reviews

Title: Longer hospital stay is associated with higher rates of tuberculosis-related morbidity and mortality within 12 months after discharge in a referral hospital in Sub-Saharan Africa

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Ref.: Response to the Reviewers’ comments on the manuscript entitled: “Longer hospital stay is associated with higher rates of tuberculosis-related morbidity and mortality within 12 months after discharge in a referral hospital in Sub-Saharan Africa (MS: 2104297450121631)”

Dear Editor,

Thank you very much for considering our manuscript for publication in your journal and please, extend our gratitude to the reviewers for their useful comments. Their very constructive critics, comments and suggestions have significantly improved the quality of the manuscript.

Please find attached to this letter the point-by-point response to the reviewers’ comments and do not hesitate to contact us with any further questions and for any further information.

Yours Sincerely

Nicola M. Zetola
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Reviewer: Shaheen Mehtar
Reviewer's report:

The English and spelling needs attention. The sentences are long and complicated, leaving the reader confused and therefore the sentences have to read several times to glean the meaning.

We have edited the manuscript with full attention to spelling and improving clarity.

The authors say medical wards (methods 1.1), - how many medical wards? or how many beds? Only the admissions were mentioned- clarity is required.

As recommended by the reviewer, we have clarified the text as follows: “This study was conducted at two medical wards (one for males and one for females) comprising a total of 100 beds.”

1.2- authors mention three tier TB-IPC yet only talk about two; there is no mention of the ventilation system in place in the text but is casually mentioned in Fig 2 as two fans being present. This has a significant impact on dispersal of aerosols and some attempt to measure the airflows or movement of air would have been useful.

We appreciate pointing out this omission. In this revised version of the manuscript we added the following text in the methods section: “1.2.2. Environmental controls. Each bay has five windows and two ceiling fans for ventilation.” We also agree with the reviewer that measures of airflow would have been useful and we plan to include such a measure in a future study on this topic.

There is no assessment regarding the period between suspected or proven TB and treatment being started while in hospital- the duration of exposure would have been helpful.

As the reviewer implies, other studies have found an association between longer times to treatment initiation with worse clinical outcomes. Controlling for such variable could have been helpful in our analyses. Unfortunately, due to the retrospective nature in which outcomes were collected, we were unable to obtain accurate data in that regard. In this version of the manuscript, we acknowledge this as a limitation.

However, the main focus of the study is to describe the incidence of TB within one year after hospital discharge. Mortality due to TB among those patients is reported as a secondary, mostly descriptive, outcome. Nevertheless, data from other studies in the same population of TB patients indicate that time to initiation of treatment is normally distributed and likely similar among patients with poor clinical outcomes when compared with patients with good outcomes. We have no reason to believe that in this particular samples, differences were in time to treatment initiation were a significant contributor to mortality.

1.2.2-N95 respirators instead of masks

This change has been made.

2. Second sentence. I do not understand what the authors are trying to say- clarity required

We have clarified the text which now reads: “All data were consistently collected at the same time of the morning and evening to ensure standardized procedures, as well as timely and accurate collection of data on relocated patients.”
ATT- no explanation given

We have modified the text to define ATT as an abbreviation of antituberculous treatment.

The method the data was collected on follow up depends on 100% entry into the TB register which is known not to be always complete. Some of the information was therefore not available. No effort was made to contact the patient yet the acquisition of TB was assumed to be from the hospitalisation irrespective of the interval.

This is certainly a limitation of the design and discussion of this issue has been expanded in the appropriate section. However, in the context of such limitation, we maximized our efforts to obtain accurate data. We examined records at the hospital, TB clinics, and the Botswana National Tuberculosis Reference Laboratory in addition to the National TB Program’s TB registry.

Despite this, we agree that some TB cases might have been missed. Thus, our study indicates the “minimum” TB incidence after hospitalization, suggesting that the problem could be of even higher magnitude. We have expanded the discussion of this important issue. We have also updated the limitation section to address the possibility of TB acquisition from a different source than the hospitalization.

In the results there were 34 cases of pneumonia yet only 20 were accounted for, what happened to the other 14?

We have modified the text to clarify that the no evidence of TB was found in the records of the remaining 14 patients who died with an initial diagnosis of pneumonia.

There was no indication on follow up when were the patients found to have TB. Was there an infectivity curve? Was it randomly acquired from the community? How do the authors know it was from the healthcare facility without doing epidemiological molecular studies? The data is not coherent and appears flawed. The data is associated with lying next to someone with TB but not how long it took to become infected.

Without TB strain genotyping is impossible to determine whether the “new” TB episodes were due to health care acquisition. Although the association of incident TB with longer hospitalization time and proximity to TB patients suggests that a high proportion of these incident TB cases were due to nosocomial acquisition, our results describe an association between hospital stay and post-discharge TB incidence but cannot establish causality. This is now clearly discussed in the revised version of the manuscript.

However, our study is one of the first ones describing the very high one-year TB incidence and TB mortality among patients admitted to the hospital in settings with high prevalence of TB. Thus, our results strongly suggest that such patients deserve closer follow up and higher level of suspicion for TB, regardless of the cause of this high TB incidence.

Also, there is no mention of supershedders or whether HIV pos patients with TB were presented a higher risk of producing TB bacilli.

Factors associated and the clinical/public health role of “super-spreaders” is of major importance. However, their identification would require the use of molecular methods which were not available in this study. Future studies should certainly look into this issue.
Our study focusses on transmission and not on the effect of HIV over the index case. Our study assumes that HIV and non-HIV patients would be equally likely to transmit the disease if they have the same burden of bacilli. Thus, we present the bacillary burden of disease (as indicated by microscopy) but did not stratify it by HIV status.

The authors need to go back and review some of the findings. Then a clearer explanation for what possibly happened should be revisited.

As suggested by the reviewer, we have thoroughly reviewed the findings and clarified our interpretation of the findings in the revised manuscript.

Reviewer: Suzanne Verver

This elegant paper describes the risk of TB and TB related mortality one year after hospital admission and factors associated with it. It is one of the first papers on these subjects and uses creative and innovative ways to show the association. The paper highlights the relevance of TB infection control in hospitals and need for focus on ambulatory care. Discussion shows very important recommendations. It has a wealth of data and by trying to show all, some important details seem to be deleted.

Major Compulsory Revisions

1. In the objectives a 4th one should be added: to determine association between exposure during hospital stay and TB incidence and mortality during follow-up; since this is focus of analysis.

We appreciate the reviewer’s recommendation. This 4th objective has been added as suggested.

2. Methods para 2.1 and 4 use different definitions for TB. One seems to be for index cases, and one for cases diagnosed during follow-up. Why did author not use the same definitions?

We actually did use the same definition for the index case and for TB cases identified during follow-up. To clarify this point, we added a paragraph 2.2 subtitled, “TB case definition” which describes the definitions used during both time points.

3. In the analysis section calculation of person-time should be described. I assume person-time is from date of discharge till 12 months later, but cases are only counted for 9 out of 12 months. I wonder whether person-time should be reduced to 9 months. If not, reason should be made crystal clear.

We have added text to the analysis section describing our method for calculating incidence rates. We agree that person-time of follow-up should be consistent with the 9 months of observation during which incident TB cases are counted (since TB cases identified in the first 3 months were considered cases undiagnosed during the hospitalization). This explanation is now explicitly included in the Methods section.

4. It seems some associations are given in results text while detailed numbers are missing. Maybe due to lack of space some tables were omitted; but they are necessary to convince readers.
a. Before multivariate, also univariate odds ratios should be given; probably in an adapted table 3. Table 3 should also have a line of totals. The methods and results refer to association for mortality; but associations for mortality are not given.

The analysis for associations with mortality was underpowered and not very contributing to the overall message and conclusions of the study. In this version of the manuscript, we have deleted the references to the association analysis for mortality.

We fully acknowledge that authors sometimes present tables that compare one by one an outcome with multiple individual factors followed by a multivariable analysis that adjusts for confounding. If confounding is present, as is the case in our study, the one-way comparisons are simply intermediate steps that offer little useful information for most readers. Given the large amount of data already being presented in this manuscript, we would request to omit presenting these intermediate steps as they might mislead certain readers without a strong statistical background or distract readers from the most important results and the focus of the study. However, if the Reviewers or the Editors feel strongly about the need to include such data into the tables and text, we will be happy to provide them.

b. There should be more clear division between dependent and independent variables. It seems that in table 3 dependent and independent variables are different from table 4 and 5. For example in table 3 exposure index seems dependent, while in table 4 and 5 it is dependent. When this is on purpose please give reason.

As the reviewer indicates, this division adds clarity to the manuscript. They were combined in the same table primarily due to space issues (to decrease the number of tables). As indicated by the reviewer, we have divided Table 3 into two, clearer Tables.

Prior Table 3 was a descriptive table that presented the main exposures of interests (i.e. hospital days, days in cohorting and exposure index) and the outcomes (i.e. TB incidence and mortality) by patient subgroups. Tables 4 and 5 are analytical tables with the TB outcomes as the dependent variable. We have added text in the Results section to clarify this point.

c. Methods para 5: statistics: Fisher’s exact or Wilcoxon-rank-sum test: results are not given. Use of ART is evaluated as confounder, but results are not given (except description). Smear positive 1+, 2+, 3+ and chest x-ray results are evaluated as severity of disease but no association results given. Maybe for all of these OR changed less than 10%, but that should be indicated in results.

We have removed the reference to Fisher’s exact and Wilcoxon rank-sum tests from the Methods section. We also added the following to the Results section: “Use of ART at baseline, smear microscopy grade and chest X ray results were not found to be confounders in multivariable models and, therefore, removed from the final models.”

d. Results last para, last sentence: ‘particularly resistant TB’: these results are not given.

This text has been removed from the Results.

e. Why is days spent in cohorting bay not in table 4 and 5? It is described in abstract that this measure is compared to total hospitalization and ‘number and proximity to TB index case’ and that ‘performance’ is similar. In discussion it states: ‘similar level of associations’. From table 3 it seems cohorting bay was probably not significant (although no OR given); while total hospitalization and ‘number and proximity’ were
significant. So the performance was actually different. Can you clarify? Rather than performance or association, better to specify as adjusted odds ratios (if that is what you mean).

We appreciate the reviewer’s recommendation and fully agree with it. In this version of the manuscript data is presented more consistently across the tables. In this version, Table 3 contains results for 3 key variables: Average No. of days admitted, Average No. days in cohorting, and Average exposure index. For consistency, we have remove the “days adjacent to index case” from Tables 4 and 5. For simplicity and clarity, we present the results of the results from the model with the best fit based on their AICs (out of the 3 potential models)

f. Discussion states: ‘without reaching a plateau’. Curves are not shown. Can they be put in online supplement? Or delete this sentence.

We deleted this text as suggested as was a left-over from prior versions in which such analysis was present.

5. Table 3: how can the TB related mortality be higher than the overall mortality in the rows for CD4 count and diagnosis of PTB during admission?

We very highly appreciate the detailed comments and analysis provided by the reviewer. This inconsistency was due to an oversight during the manuscript preparation. While the analyses were accurate, the results were presented accidentally inverted. This has been corrected in the new version.

6. Table 5: column 3: strange that an OR of 1.0 has p of <0.01? I assume this OR means increased odds for each day extra? Maybe useful to explain in methods or results and add decimals where appropriate.

Indeed, the results presented represent the increased odds for each extra day spent at the hospital. As recommended, this explanation is clarified in the methods and result section and the decimals were added were appropriate.

Minor Essential Revisions

1. The annual rate of TB cases during follow-up mentioned in the abstract (3712/100,000) should be repeated in main text. Since number of person-years is much less than 100,000; this gives false idea of precision. Maybe better to use 4/100 pyrs. Further it does not seem to agree with table 3? In table 3 probably ‘per 100,000 pyrs’ should be ‘per 100 pyrs’?

We thank the reviewer for the suggestion as it certainly makes the TB incidence easier to interpret. The use of 100,000 person-years was used just to follow the conventional report of annual TB incidence in populations. We have changed the rate estimate to be per 100 person-years as suggested and added the total incidence rate in the Results section.

2. Abstract states: number and proximity to index case. These seem 2 different measures. You mean ‘composite measure of exposure combining number and proximity to index case’.

We thank the reviewer for pointing out this oversight. We have revised the abstract as suggested.
3. Background last paragraph, first sentence: ‘have been extensively studied’. This needs a reference for TB.

As suggested, we have added appropriate references have been added to the revised manuscript.


This has been fixed.

5. Methods paragraph 2: which environmental factors were collected and how have they been used in analysis? Maybe not used, so can be deleted?

We have deleted this text in the revised manuscript. Although those variables were examined during early stages in the analyses, there were not found to be useful. We believe environmental factor are major contributors to TB transmission and our finding (lack of association) were due to the data collection techniques used during this study. We decided to keep them out of the overall text to prevent confusion and misleading readers unfamiliar with the topic.

6. Methods para 2.1 versus 2.2: in 2.1 cultures are not mentioned while they are given in 2.2. Does hospital not have culture results but clinic may have them? Or they usually become available after discharge? Or maybe this is just an omission in para 2.1? Similar does para 2.3 refer to smears and cultures?

We have revised these paragraphs to improve consistency and clarity.

7. Para 2.4: what happened if x-ray readers disagreed on severity?

The following text has been added, “Final decision on severity was determined via consensus among the three specialists.”

8. Para 3: what is the difference between those loss to follow-up (=untraceable?) and those not seen but assumed to be alive? In the results it seems 8.6% was lost to follow-up (which is fantastic that they are so few in such complicated study); but there are many more who are assumed alive and have no TB.

We were able to find some record of patients after discharge, whether they developed TB or not, for all patients except the 77 who were categorized as untraceable.

9. Results last para, last sentence: history of prior TB infection. Do you mean ‘TB disease during admission’?

No, we meant history of TB prior the admission. This text has been deleted since it was not a significant predictor of post-discharge incident TB.

10. Table 1: Some categories do not add up to 1094. Rest is unknown? Please indicate so, or correct. Check other numbers.

As recommended, a row showing missing data has been included where appropriate and the presented results have been checked for full consistency and accuracy.

11. Table 4 and 5: add n for each column. Add a line between variables ‘total days admitted’ and ‘days of adjacent exposure’.
Tables 4 and 5 have been revised as suggested.

12. Figure 2 is very difficult to read; can this please be redone? Some of my questions may be answered when this figure is better readable.

The quality of Figure 2 has been improved within the figures included in the manuscript. A larger and clearer version of the Figure is also included as an extra attachment to facilitate any formatting requirements.

Discretionary Revisions

1. The authors collected an enormous amount of data and maybe the paper should be split in 2 papers; one on factors during hospital stay (focusing on objective 1), and one on the follow-up period (which is the main focus on this paper). Alternative; objective 1 in itself can be deleted, since this is just information collected to analyse the association between exposure and TB incidence (that I referred to as objective 4 above). This may also reduce the description of a lot of data collected that were actually not used in analysis (see above).

We agree with the reviewer and we certainly considered the option of presenting the data in two manuscripts as opposed to one. However, we felt that keeping Objective 1 in the same manuscript was important (if not necessary) as exposure is relatively meaningless without correlating it with a “harder outcome” such as TB incidence. In addition, data regarding nosocomial TB exposure is scarce in the literature and significantly adds in the understanding of the “full picture” of the under-recognized consequences of hospital admissions in settings with high TB (and HIV) prevalence.

2. In order to shorten these parts may be deleted:

a. Para on Xpert in introduction (since this is repeated in discussion)

This section has been removed from the Introduction.

b. Methods para 4: Sentence on tuberculin (this is isolated statement)

As suggested, these sentences have been deleted.

c. Details of diagnosed cases in methods para 4 (since not used in analysis)

Similarly, these sentences have been deleted.

d. Table 2 not relevant for message of the paper.

The above-mentioned text and table 2 have been deleted as recommended.

3. Para 5: ‘Finally....’. This can be labelled as sensitivity analysis?

While the two approaches to modelling our data might be considered sensitivity analysis, sensitivity analysis is more commonly used to explore whether the results of a disease model are robust to varying assumptions. Therefore, we chose not to use this terminology for our study.